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POLY(*N*-ISOPROPYLACRYLAMIDE): EXPERIMENT, THEORY AND APPLICATION

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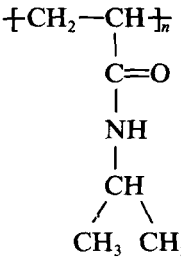
1. INTRODUCTION

Over the past few years, poly(*N*-isopropylacrylamide) (PNIPAAM, **1**) has been appearing in the literature with increasing frequency. As Fig. 1* illustrates, growth has become rather explosive.



(1)

Historically, the first publications pertaining to PNIPAAM quite logically dealt with the synthesis and polymerization of the corresponding monomer,

*The ChemAbstracts online search (CAS) (done 8/7/91) was based on the search of 25189-55-3 (polymer registry number) OR 2210-25-5 (monomer registry number) OR (polymer? and *N*-isopropylacrylamide) using the CA and CAOLD files. The papers located by this search are not exactly identical to those discussed in this review; several citations were excluded as a result of not possessing a unique connection with PNIPAAM, being concerned with unrelated aspects of the monomer or just about polymers in general. In addition, several papers were located that were overlooked in the CAS search. Of course, the number for 1991 is incomplete and was still increasing at the time of this writing.

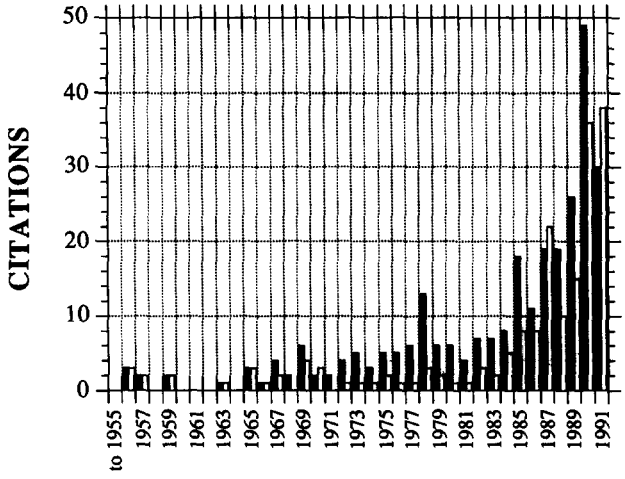


FIG. 1. Literature citations of PNIPAAM: (■) CAS search results; (□) references in this review.

NIPAAM.[1-4] *N*-isopropylacrylamide[4] was stated to be an effective rodent repellent! Subsequently, the main impetus for using PNIPAAM has been its novel thermal behavior in aqueous media. It has become perhaps the most popular member of a class of polymers that possess inverse solubility upon heating, a property contrary to the behavior of most polymers in organic solvents under atmospheric pressure near room temperature. Its macromolecular transition from a hydrophilic to a hydrophobic structure occurs rather abruptly at what is known as the lower critical solution temperature (LCST). Experimentally, this lies between ca. 30 and 35°C, the exact temperature being a function of the detailed microstructure of the macromolecule. Early research focused on this transition as a theoretical curiosity; however, more recently this speciality polymer has been applied in very diverse end uses as the potential to apply this transition as a switching device has been recognized.

As illustrated in the table of contents, on the molecular level, PNIPAAM has been used in many forms including single chains, macroscopic gels, microgels, latexes, thin films, membranes, coatings, and fibers. Moreover, a wide range of disciplines have examined PNIPAAM, encompassing chemistry, physics, rheology, biology, and photography. As a result, many papers fail to cite previous work on PNIPAAM from ignorance or narrowed focus; the literature has thus also been plagued by redundancy.

Consequently, this review will aim to serve as a summary of the work reported in the open literature on PNIPAAM from the perspective of polymer science from its first appearance in 1956 to July, 1991. The synthesis and characterization of its various incarnations will be discussed. The gamut of experimental techniques used to observe the LCST will be presented; known applications of

TABLE 1. Free radical synthesis

Solvent	Initiator	References
Methanol	AIBN	5
Benzene	AIBN	6–10, 19, 20, 25
Benzene/Acetone	AIBN	11–14
THF	AIBN	15, 19, 20
Benzene/THF	AIBN	19, 20
t-Butanol	AIBN	16, 22–24
Dioxane	AIBN	26
Benzene	Benzoyl peroxide	17, 21
Chloroform	Lauryl peroxide	18

PNIPAAM will be interspersed including those disclosed in patents, where appropriate. A survey of work with other aqueous LCST polymers is also included. It is hoped that this review will serve as further motivation for cross-fertilization between and within theory, experiment and application of PNIPAAM and related polymers.

2. SYNTHESIS

Poly(*N*-isopropylacrylamide) (PNIPAAM)[5–86] has been synthesized by a variety of techniques; free radical initiation of organic solutions[5–26] and redox initiation in aqueous media[19,20,27–37] have been the most widely used techniques. Novel results have been observed using ionic initiators;[38,40,41,85] radiation has also been applied somewhat in constructing PNIPAAM systems.[68–73] By substituting comonomers,[15,26,34,35,46,47] diverse labels and functional groups have been introduced. When the comonomer is difunctional, subsequent crosslinking leads to gelation. These gels are macroscopic structures[30,42–59] or microgels/latexes,[60–67] the latter typically made possible by polymerizing the monomer as an emulsion.

This section will summarize various approaches to synthesizing PNIPAAM, tabulating the systems and discussing salient findings. Thorough comparisons of the resultant molecular weight distributions will not be done since the exact conditions are quite numerous and not directly comparable. Moreover, the diverse measurements of molecular weight are probably not equivalent. What this section will reveal is the various ways of obtaining PNIPAAM to allow design of the proper system for a given application.

2.1. *Single chains*

2.1.1. *Free radical initiation in organic solution* — Table 1 summarizes the various initiators and solvents that have been used in free radical PNIPAAM in organic solution. Temperatures varied from near 50°C to as high as 75°C. The

TABLE 2. Redox synthesis

Initiator	Accelerator	References
APS	sodium metabisulfite	27, 32
APS	TEMED	19, 20, 33–36
KPS	sodium metabisulfite	28, 31
KPS	TEMED	29, 30, 37

reactions were typical textbook free radical polymerizations.[87] Variations in monomer and initiator concentration resulted in diverse molecular weights as expected; in one case these two variables were used to create a set of molecular weight "standards" by relying on low conversion to minimize the polydispersity (PD) somewhat.[5] Alternatively, Fujishige claims to be able to obtain[14] a set of effectively monodisperse polymers spanning 10^5 to 10^6 in molecular weight by fractionating a single polymer sample using a mixture of acetone and *n*-hexane. However, neither of these studies used GPC to determine the breadth of the PD of the resulting samples. Therefore, insufficient support exists for their calculated Mark–Houwink coefficients; this work will be discussed in a subsequent section (Section 3.1.4). In a more recent paper, Fujishige[13] claims that his approach yields polymers with a PD of 1.3. While this value of PD is useful, it is not good enough for theoretical correlations.

Another variable that markedly effects the resulting molecular weights of free-radically polymerized macromolecules is chain transfer. Hoffman and coworkers[19] utilized the greater propensity of propagating PNIPAAM chains to undergo chain transfer to solvent during synthesis in THF compared to synthesis in benzene to create a series of polydisperse samples ranging in molecular weight from 2000 (pure THF) to 250,000 (pure benzene) by polymerizing in various mixtures of these solvents. Snyder and Klotz[21] manipulated chain transfer agents such as butyl mercaptan to create a series of PNIPAAM oligomers useful in studying the effects of molecular weight on hydrogen–deuterium exchange. In these oligomers, sulfur was removed by reducing with hydrogen and Raney Nickel. The resulting polymer properties are thus not perturbed by the endgroups being vastly different in structure relative to PNIPAAM itself. Thus the well known ability to control the molecular weight distribution of polymers by variation[87] of solvents and/or external chain transfer agents during synthesis operates in the usual manner with PNIPAAM.

2.1.2. *Redox initiation in aqueous media* — Redox polymerization of NIPAAM typically uses ammonium persulfate (APS) or potassium persulfate (KPS) as the initiator and either sodium metabisulfite or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) as the accelerator.[19,20,27–37] Table 2 summarizes the associated references showing all the possible pairings of initiator and accelerator. In addition, the solutions are usually buffered to constant pH;[19,20,28,31–37] in the

absence of buffer, much greater PD is obtained.[28,29,36,37] In one such polymerization, a very accelerated rate of polymerization was noted[36] which clearly could be the cause of such a phenomenon. Although some researchers have tried[37] to perform theoretical calculations using polydisperse samples in their experiments, these systems are not very suitable for explaining basic solution phenomena. In particular, variations in LCST behavior, as measured by differential scanning calorimetry (DSC), have also been observed[36] at high PD and may significantly effect conclusions.

One of the earliest papers on PNIPAAM, published in 1957 by Wooten and coworkers,[27] is the most detailed analysis of the effect of buffers on the redox polymerization of NIPAAM. The system uses APS and sodium metabisulfite as the initiation system. It is interesting to note that although some papers state the initiator as sodium bisulfite, actually the two species are in equilibrium with each other and with a number of other species in aqueous solution.[88] An asymmetric polymerization rate maximum is found at pH 6.5, dropping to zero at pH 3. The inherent viscosity of the polymer is independent of pH below 6.8 and increases at higher pH. While APS concentration has little effect on the rate or viscosity, the bisulfite ion concentration, which drops sharply above pH 6.8, is a mirror image of the viscosity. At such high pHs, bisulfite is converted into sulfite ion, which is claimed to have a lower chain transfer activity and therefore is the cause of the changes observed in molecular weight.

Alternatively, the Hoffman research group[19,20,34,35] uses a complicated buffer based on normal saline and sodium phosphate (10 mM) at pH 7.4 for the redox synthesis of PNIPAAM. As will be discussed in more depth later (Section 3.1.2), whether one polymerizes NIPAAM in organic or aqueous solution affects polymer properties[36] as demonstrated by DSC analysis. This may be due to the fact that it is much harder to dry a polymer that has been in contact with aqueous media than one synthesized in organic media; moreover, hydrolysis in water may occur and result in pendant acid groups.

2.1.3. *Ionic polymerizations* – A very different type of PNIPAAM results if ionic initiators are employed in the synthesis. In 1959, Shields and Coover[38,85] reported the use of "metal alkyl/transition metal halide catalysts" to produce crystalline PNIPAAM. This material is insoluble in aqueous solution as well as in all other typical polar solvents for amorphous PNIPAAM. In addition to the polymer possessing an expected higher density of 1.118 g/cm^3 compared with 1.070 for the amorphous sample, crystallinity was further demonstrated through X-ray diffraction. A melting point of 170–200°C was cited as determined by polarized microscopy compared to 100–125°C (actually closer to the range of and more appropriately called the glass transition temperature[18,39]) for the amorphous PNIPAAM. The authors suggest that 1,4-polymerization through the nitrogen group (by Michael addition) may have occurred; this is supported by the work of Kennedy and Otsu,[40] who suggest a mechanism of

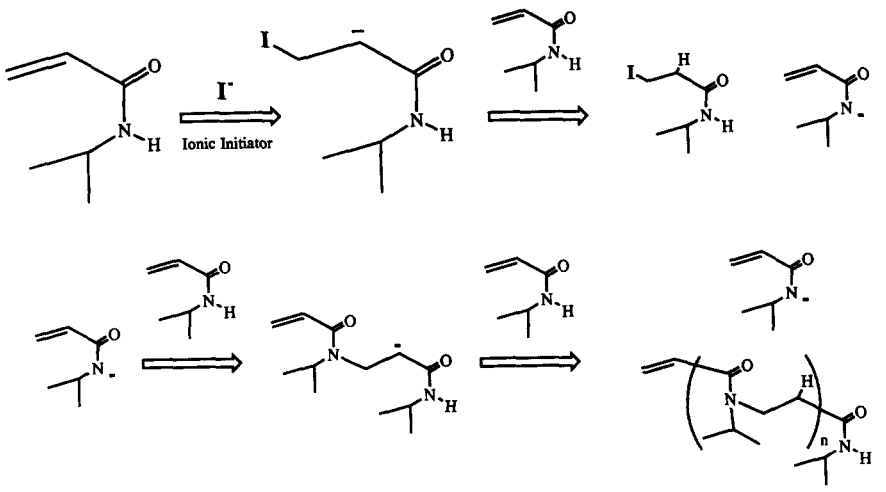


FIG. 2. Mechanism for hydrogen transfer polymerization.

hydrogen transfer polymerization (Fig. 2).[87] In addition, they[40] mention work involving an anionic polymerization of NIPAAM[86] initiated by *n*-butylithium that results in a polymer with a melting point of 129°C. This polymer was insoluble, and infrared spectroscopy showed evidence for hydrogen transfer polymerization in this case as well. No additional characterization has been reported on these types of polymers which are probably somewhat more stereoregular than free-radically synthesized PNIPAAM as well as being isomeric to it. The lack of a hydrogen on the nitrogen would thus appear to shift the hydrophilic/hydrophobic balance to insolubility in water by decreasing the ability of the polymer to hydrogen bond.

NIPAAM has not been polymerized by any "living" method thus far; such a method would be very desirable since it should be an effective source of polymers exhibiting molecular weight distributions narrow enough for theoretical studies. Group transfer polymerization[89] has been done on *N,N*-dimethylacrylamide to directly produce a polymer of polydispersity 1.43; however, apparently, no one to date has succeeded in protecting and deprotecting the active amide hydrogen of NIPAAM.

From a different perspective, small amounts (ca. 6%) of NIPAAM have been copolymerized with ethylene[38] under standard batch (1360 atm. 130°C), ionic Ziegler–Natta conditions for making polyethylene. As a consequence of the hydrogen bonding that results in the copolymer incorporating NIPAAM, the product has a greater tensile and impact strength while maintaining transparency. In addition, melt flow properties were also modified.

Thus, ionic polymerization methods produce PNIPAAM with vastly different bulk properties relative to free-radical and redox techniques, it is interesting to

TABLE 3. Macroscopic gel synthesis

Initiator system*	Solvent	Crosslinker†	References
APS/TEMED	water	MBIS	42–44, 47–48, 49–52, 55
BPO/*N,N*-dimethyl-*p*-toluidine	DMSO	MBIS	44
Cobalt 60	water	MBIS	44, 49
t-Butyl peroxyoctanoate	dioxane	EDMA	45, 48
AIBN	DMSO	MBIS	46
KPS/TEMED	water	MBIS	6, 42, 53
APS/sodium metabisulfite	water	MBIS	53–54, 57
TEMED, KPS	water	MBIS	56

†MBIS = *N,N'*-methylenebisacrylamide; EDMA = ethylene glycol dimethacrylate.
*APS = ammonium peroxydisulfate; KPS = potassium peroxydisulfate; TEMED = *N,N,N',N'*-tetramethylethylenediamine; BPO = benzoyl peroxide; ALBN = azobisiobutyronitrile.

note that a "non-LCST" PNIPAAM exists that may be a useful control or reference; furthermore, it has potential for application in novel composite structures with PNIPAAM possessing an LCST.

2.2. *Crosslinked poly*(N-*isopropylacrylamide*)(*PNIPAAM*)

2.2.1. *Macroscopic gels* — The same polymerization methods used to synthesize single chains are also used to produce PNIPAAM gels; these gels are readily obtained by the addition of a crosslinking agent to the recipe (Table 3). *N,N'*-methylene-bis-acrylamide (MBIS) is the overwhelming choice for this component. This is probably a consequence of its structural similarity to NIPAAM in addition to its established use in polyacrylamide gels for electrophoresis. Table 3 indicates that redox initiation in aqueous media is the most popular technique for creating gels. Polymerizations are typically done in micropipettes,[42,43,55,57] although the gels have also been alternatively synthesized between glass plates with spacers.[49] In one case, flat sheets were created by polymerization onto specially-treated polyester.[58] In many of the systems, other comonomers (Sections 3.4 and 4.1.3) are added to achieve desired properties.

It was previously mentioned[36] that different shaped DSC endotherms are observed for single chains prepared by redox-initiated polymerizations as opposed to those observed when using thermal free-radical initiation. Even more dramatically, Hirotsu claims that whereas the PNIPAAM gel phase transition observed is slightly discontinuous when TEMED is used as the accelerator in a redox-initiated polymerization, an apparently continuous transition is detected when sodium metabisulfite is used instead.[30,42,55] Where volume transitions have been measured by other research groups, the use of TEMED does yield a polymer with a discontinuous transition[6,29] with one exception where the transition was reported to be continuous[47] prior to a subsequent photoionization. However, in contrast, when Freitas and Cussler used[53,54]

sodium metabisulfite as the accelerator, they only observed very sharp volume changes at the LCST. When ionic sodium acrylate is added as a comonomer, the transition of the PNIPAAM copolymer switches from continuous to discontinuous[30] according to the Tanaka group.[57] It may be inferred that the amount of ionic groups introduced by the initiator and differences among the various experimental techniques employed for observing the transition account for the discrepancies among the various research groups.

Free radical polymerization in DMSO[44] results in gels that exhibit a smaller change in dimensions when they deswell above the LCST compared to results with corresponding redox systems. These gels also possess[46] continuous volume transitions until photoionized. The most anomalous report of PNIPAAM gel synthesis[52] employed the "standard redox technique", yet it yielded PNIPAAM homopolymer with an LCST near 42–45°C instead of in the range of 30–35°C as reported by all other groups. The authors note and attribute this discrepancy to differences in either composition, molecular weight or crosslinking. However, other investigations have shown that molecular weight[7,33] and crosslink density[44] do not have such a significant effect on the transition temperature. As both comonomers (Section 3.4) and additives (Section 3.3) have a substantial effect on the LCST of PNIPAAM, it would appear that unknown impurities were trapped during this particular synthesis. Thus more controlled experiments under identical conditions need to be done in order to ascertain the role of the mode of synthesis on the nature of the gel LCST transitions, and especially the origins of their discontinuity.

The macroscopic shape of the PNIPAAM may be cylinders, sheets, or fibers; the last has been prepared by spinning a 5% solution of a 5:1 NIPAAM/*N*-methylolacrylamide copolymer followed by crosslinking through the methylol groups. Since the comonomer is crosslinkable[59] it is probably incorporated for increased dimensional stability. When solutions are spun into saturated aqueous sodium sulfate, the polymer precipitates as a result of being in a medium in which its LCST is below the processing temperature (see Section 3.3.2). Afterwards, the resulting fibers are wound up and vacuum-dried at 150°C to crosslink. These swell in water at 25°C, but subsequently shrink by 40% when transferred to water at 50°C. Upon cooling the fibers in air to 20°C, they reversibly return to their original (swollen) dimensions. Thus it is possible to make macroscopic gels with LCST phenomena not only with "molds" such as pipettes and glass plates but also by other standard polymer processing methods.

2.2.2. *Microgels and latexes* — Gel beads can be manufactured by a wide variety of techniques. Creation of such particles then permits the alternative use of quasi-elastic light scattering for theoretical studies of the volume transition;[60] moreover, unique fluid properties also result when these particles are suspended in aqueous media.[63,64] Synthetic techniques (Table 4) employed are typically still the aqueous redox methods[60] described above (Sections 2.1.2 and 2.2.1) but with

TABLE 4. Microgels and latexes

Initiator system	Crosslinking agent	Polymerization Medium	Swollen Size (μm)	References
APS/TEMED	MBIS	sorbitan monolaurate/water	0.4	60
APS/TEMED	MBIS	water in paraffin oil	100–1000	61, 62
KPS/sodium metabisulfite or 4,4′-azobis(4-cyanovaleric acid)	MBIS	various surfactants like Triton 770 aqueous emulsion	0.2–0.5	63, 64
Oleophilic peroxide	various	ethyl acetate emulsion polymeric suspending agents	ca. 100	65
KPS or 2,2′-azobis(2-amidinopropane). HCl	MBIS	surfactant-free water	1	66, 67

*Abbreviations same as in Table 3.

a change in the physical geometry of the "polymerization reactor". Instead of homogeneous reaction medium such as in bulk or solution, a heterogeneous medium is created by polymerizing the NIPAAM within the surfactant micelles of an emulsion. More highly organic emulsion-type systems with ethyl acetate as a second solvent have also been reported;[65] these use poly(vinyl alcohol) to suspend monomer while stirring. Although solids content is usually low, greater than 10%[63,64] solids can be employed when inter-bead interactions are desired in addition to intra-particle forces at the LCST.

Alternatively, inverse suspension (water-in-oil) polymerizations have been done by injecting aqueous polymerization mixtures into paraffin oil.[61,62] In such a case, stirring is more important in determining the physical product dimensions than with the surfactants cited above. In the latter case, the size and shape of the micelles defines the microgel particles. Stable surfactant-free latexes[66,67] have also been created by thermal initiation of low solids (2.5%) aqueous solutions. While choice of methods ultimately depends on desired properties (Table 4), avoiding surfactant is an added bonus, since detailed studies have shown that the LCST of PNIPAAM is greatly perturbed by their presence. Such data is reported in the Section 3.3.3 and certainly should be useful in selecting the optimum recipe for specific properties.

2.3. *Other synthetic schemes*

2.3.1. *Radiation polymerization* – Another synthetic technique that has been applied in the synthesis of PNIPAAM is radiation polymerization; either cobalt-60 gamma rays[68-72] or an electron beam[73] have been used as the energy source. For example, solid state polymerization of a variety of *N*-substituted acrylamides has been demonstrated[68] using a cobalt-60 gamma ray source under a nitrogen atmosphere[68] or under vacuum.[71] Solution polymerizations have also been thus initiated;[69,70] the use of solvent with low chain transfer constants such as benzene and various acetates resulted in polymers with an order of magnitude higher, molecular weight (10^6 versus 10^5), compared to those synthesized in ethanol or chloroform, which have relatively higher chain transfer.[69] In contrast to the ionic polymerizations (Section 2.1.3), radiation polymerization results in polymers which exhibit LCST behavior[70,71] since most radiation-initiated polymerizations occur with free radicals as the propagating species rather than ions.[87]

Radiation has also facilitated grafting NIPAAM unto substrates of biological interest,[71,72] motivated by the subsequent thermal control of the hydrophilic/hydrophobic balance of the resulting surface. Using gamma rays, Uenoyama and Hoffman[72] grafted PNIPAAM onto silicone rubber substrates for model implants, hoping to be able to retard biological response. Alternatively, Okano and fellow researchers[73] used a 25 Mrad electron beam to graft NIPAAM from

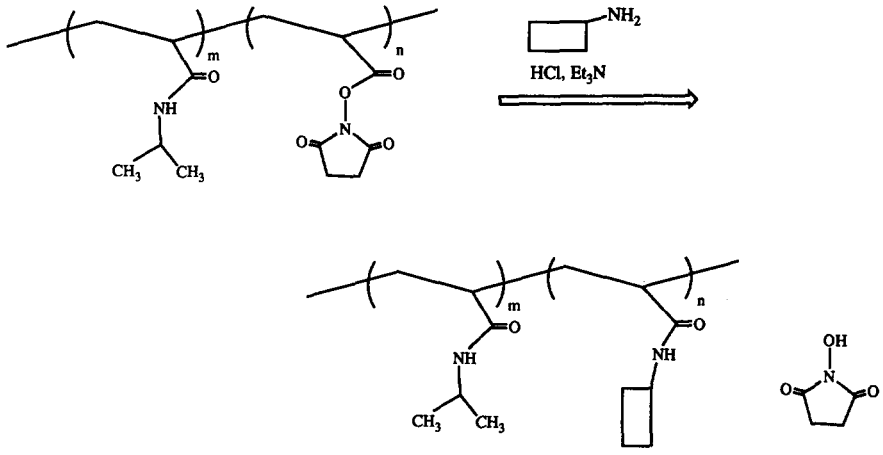


FIG. 3. NASI scheme for synthesizing functional PNIPAAM.

isopropanol solution onto polystyrene tissue culture dishes. By "switching" the resulting surface to a hydrophilic state by lowering the temperature below the LCST, far more cells detached than when cultures were made in control dishes. Thus radiation polymerization is a viable technique for producing LCST-active PNIPAAM.

2.3.2. *Functionalized PNIPAAM* – Both single chains and various crosslinked gels of PNIPAAM have been synthesized with small amounts of comonomers to introduce labels to monitor the behaviour of the macromolecular chains,[74,75] to hydrophobically modify the polymer,[26,76–78] and to incorporate biological activity.[15,19,20,49] In these cases it is often desirable to use as little comonomer as possible in order to minimize perturbation of the probe's environment (Section 3.1.4) and of the polymer's conformation (and hence the LCST), both effects usually being a consequence of the added hydrophobicity of the comonomer (Section 3.4). The most basic technique is the simplistic, direct substitution of the desired comonomer into the same reaction medium used to synthesize the homopolymer;[26,74–78] if the comonomer does not have any functional groups that can easily chain transfer or inhibit the propagating polymer chain, polymers of similar molecular weight distribution to the homopolymer are obtained. This leads to much improved experimental control. Photoresponsive PNIPAAM chains[25] or gels[46,47] are among those synthesized by the direct copolymerization with active comonomers.

The second approach to functionalization has been to create a versatile PNIPAAM by copolymerizing it with *N*-acryloyloxysuccinimide (NASI). As

shown in the schematic in Fig. 3, this method, first developed by Whitesides and coworkers, allows the production of many copolymers with similar molecular weight distributions from a stock solution[79] upon subsequent reaction with amino-functionalized molecules. Kodak has since commercialized the comonomer. Hoffman has used this process to conjugate antibodies[19,20] and enzymes[49] to PNIPAAM. Winnik has more recently adapted the NASI method to produce fluorescently-labelled PNIPAAM for aqueous solution studies[22-24] by using naphthalene and pyrene species with pendant reactive amino groups. Molecular weight distributions were shown to be unaffected by the chemical transformations and polymer purification processes through using a GPC with tandem UV and refractive index detectors.[24] Winnik also uses excess isopropylamine to convert unreacted units to the same structure as the rest of the backbone.[23] This latter approach thereby allows different levels of functionality with the same stock polymer and also allows creation of an ideal homopolymer control when only isopropylamine is added to the NASI-modified PNIPAAM.

Using a related approach, Nguyen and Luong[15] have copolymerized glycidyl acrylate with NIPAAM. This unit can also be post-reacted with amino functionality present in proteins. The other logical scheme of directly modifying PNIPAAM by polymer reactions has not been extensively explored; fluorescein isothiocyanate has been reacted onto PNIPAAM at a level of 5 groups per chain, but the experimental method was not reported.[80] More recently, Bord and Winnik[90] have directly modified polyacrylamide with hydrophobic absorbers such as xanthenol and dibenzosuberenol; however, a much lower degree of modification was found possible with PNIPAAM due to increased steric hindrance.

On the other end of the spectrum, gross changes in polymer properties have been made by the introduction of large amounts of comonomer. As will be discussed (Section 3.4.2), by changing the type of substituted acrylamide used, solubility is seriously perturbed.[34,35,81] Very preliminary mechanistic studies suggest that random copolymerization occurs.[34,35] This is an expected consequence of the similar structures of the monomers. These conclusions are somewhat supported by the vast studies on many types of comonomers related to NIPAAM by similar synthetic techniques.[10] Polaroid workers have reported copolymers of NIPAAM with acrylylglycinamide[82] as yet another comonomer which particularly results in novel properties as a consequence of both homopolymers possessing different types of thermodynamic transitions.

In a very different approach to those above, Okano *et al.*[83] have created interpenetrating networks (IPNs) or PNIPAAM and a polyethylene oxide–polydimethylsiloxane copolymer. A PNIPAAM gel was formed by the "standard" AIBN-initiated free radical polymerization but with ethylene glycol dimethacrylate (EDMA) as the crosslinker. By using a trifunctional isocyanate derivative for a mechanistically differing stepwise crosslinking of the other polymer, it was possible to carry out both reactions simultaneously. The result-

ing properties of this novel system will be discussed later (Section 4.3.2.1). In still another alternative manner of combining PNIPAAM with another polymer, redox polymerization has also been applied to graft NIPAAM onto nylon capsules.[84]

Thus diverse pathways exist to creating PNIPAAM polymers. In the following sections, their structures and properties will be correlated. In addition to a summary of general conclusions, novel effects achieved by fine-tuning the microstructure will be discussed.

3. SINGLE CHAINS IN SOLUTION

3.1. *Solution properties of the LCST*

The behaviour of a polymer in a given medium reflects the balance of like and unlike interactions among its own segments and the surrounding molecules.[91] In the case of aqueous solutions, the solvent–solvent interaction in water is particularly strong as indicated by its partially ordered structure.[91–97] Indeed, the eccentric physical properties of water[92] control the conformations and the subsequent reactions of biological macromolecules that are responsible for life on Earth.

Ordering of solutes such as PNIPAAM in aqueous solution results from specific orientations required to hydrogen bond[93] with the already somewhat arranged water molecules. This becomes especially important when water molecules must reorient around nonpolar regions of solutes, being unable to hydrogen bond with them. These have been claimed to be clathrate-like structures.[92] This latter phenomenon, known as the hydrophobic effect,[94,95] results in a decreased entropy upon mixing (negative ΔS). At higher temperatures, the entropy term dominates the otherwise exothermic enthalpy of the hydrogen bonds formed between the polymer polar groups and water molecules that is the initial driving force for dissolution. Once the free energy change (ΔG) becomes positive upon mixing, the consequence is phase separation above a lower critical solution temperature (LCST) such as exists in the case of PNIPAAM. If the concentration of the polymer is high enough, this replacement of polymer–water contacts with polymer–polymer and water–water contacts is manifested by precipitation.

With such a perspective, we will proceed to discuss the solution behaviour of PNIPAAM. However, caution must be used since the description given above is rather crude; indeed, the origins of the general phenomena of hydrophobic effects and hydrogen bonding in water are still being debated.[98–101] Hopefully, the findings obtained with PNIPAAM can contribute to increased understanding of the basic nature of aqueous media.

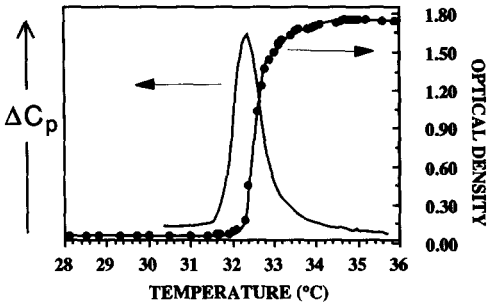


FIG. 4. Cloud point and DSC measurements of the LCST of PNIPAAM chains (0.4 mg/ml).

3.1.1. *Cloud point* — The earliest* report of the LCST of poly(*N*-isopropylacrylamide) in the literature was in 1967 by Scarpa *et al.*[102] They reported inverse temperature solubility and subsequent precipitation of a 2% solution at 31°C. Near the end of 1968, Heskins and Guillet[32] published a study much more frequently cited by researchers; again, simple visual observation of macroscopic phase separation upon heating was among the employed techniques. This rather simple method of determining the LCST is commonly known as the cloud point method.[103] Various researchers have somewhat quantified the method by using a standard UV-VIS spectrophotometer,[11,23,34–36,81,104] the main difference among them being the selected wavelength of observation. Fixed wavelengths such as 500 nm[11,36] or 600 nm[34,35] or computer-averaging turbidity from 400 to 800 nm[23,104] has been employed. The wavelength of the measurement determines the minimum size of precipitated particle detected; nonetheless, for binary aqueous solutions of PNIPAAM, there seems to be no particular advantage to any particular wavelength in the UV-VIS spectrum. However, as will be discussed below (Section 3.3), when certain additives are added to the system,[11,35,36] the precipitated aggregate's size can be equal to or less than that of the wavelength of the light used, leading to clear, "turbid" solutions. Therefore, the observation of an LCST may be a function of the wavelength chosen. Consequently, it may be very difficult to assign an LCST based on cloud point measurements,[36] and more precise dynamic light scattering[105] must be used to observe the precipitation process.

Nonetheless, measuring cloud points is the simplest, most convenient method of determining the LCST. Heating rates are typically ca. 1°C/min[11,22,36] and results are not very concentration-sensitive,[11,23,81] provided the solutions are not

*Actually, the inverse temperature aqueous solubility of PNIPAAM as well as that of its monomer were reported in the commercial literature of American Cyanamid Company[300] in March, 1963! However, they did not observe the abruptness of the transition, but merely noted the gradual decrease in solubility with increasing temperature. I thank Dr Lloyd Taylor for bringing this to my attention.

too dilute. Figure 4 illustrates a typical cloud point curve. Although Fujishige[11] and coworkers claim that the cloud point curves for PNIPAAM ranging from molecular weights of 50,000 to 8,400,000 are superimposable, it has been more clearly illustrated[36] that the molecular weight distribution does affect the transition temperature. Moreover, a PNIPAAM sample of weight average molecular weight of 10,700 (by light scattering) exhibited a much broader cloud point curve than higher molecular weight samples.[36]

Taylor *et al.*,[106] using dynamic light scattering, briefly reported that when PNIPAAM phase separates, it is rather difficult to observe two layers. Heskins and Guillet[32] reported complications in their attempt to assemble a phase diagram in which they relied on centrifugation as the technique for analysis; given the former group's observations, it is no surprise that Heskins and Guillet were unable to consistently quantitate the amount of precipitated polymer.

That the phase diagram is indeed rather flat,[81] that is, that the LCST is rather independent of polymer concentration over a wide range, is better confirmed by using DSC as will be discussed in the next section. Thus cloud points may be simple to measure, but the nature of the precipitation process is certainly not entirely straightforward. This particularly becomes important when measuring the LCST of PNIPAAM solutions in the presence of additives (Section 3.3).

3.1.2. *Differential scanning calorimetry* – Heskins and Guillet[32] were the first to report that an endotherm can be observed at the LCST upon heating aqueous solutions of PNIPAAM. Their measured transition heats varied with concentration; this was attributed to the energy required to break hydrogen bonds between polymer and water molecules. However the instrument they employed (Perkin Elmer DSC-1B) was not sensitive enough for precise measurements; an instrument such as that typically used in biological studies[107] is required. The latter type of calorimeter has recently been extensively utilized to observe PNIPAAM solutions.[36,108] Schild and Tirrell[36] (Fig. 4) have demonstrated that the transition is detected by DSC (MicroCal MC-1) is in excellent agreement with results from cloud point measurements. Transitions were found to be independent of heating rate at $\leqslant 30$°C/hr; typically, studies employed 15°C/hr for a consistent reference. Characteristics (height, width, peak position) of the endotherms were also found to be independent of concentration for at least the range 0.4–4.0 mg/ml in accord with the flat phase diagrams others have reported.[11,81] Most interestingly, large differences were found to exist in the shape and height of the endotherms between polymers of different molecular weight distributions, although all the endotherms have a similar enthalpy (ca. 6.3 kJ/mol) which is typical for hydrogen bond interactions.

While Fujishige and coworkers[11,12] cite a similar enthalpy for aqueous PNIPAAM, they supply absolutely no details of their measurements. In contrast, they claim that their samples (all $M > 50{,}000$) have the same LCST,

whereas Schild and Tirrell[36] observe the expected decrease in LCST with increasing molecular weight.[109] Taylor and Cerankowski,[81] Ito,[10] and the Saito research group[29] also measured enthalpies that are similar to those quoted above. However, none of these groups focused on the peak shapes, which Schild and Tirrell have shown to be sensitive to the presence of salt,[36] surfactants[9] and comonomers.[74–76] Moreover, these researchers have shown that the observation of an endotherm for a polymer possessing an LCST in water is general and detectable for other polymers such as hydroxypropyl cellulose, poly(vinyl methyl ether) and poly(propylene oxide)glycol.[36]

3.1.3. *Light scattering* – Experiments using light as a probe offer information on the size, shape, and interactions of macromolecules.[110,111] Much more structural information is available than can be obtained with the simple turbidimetric, cloud point measurements discussed above (Section 3.1.1). Initial studies employing more sophisticated light scattering apparatus concentrated on determining weight average molecular weights of PNIPAAM.[5,32] Heskins and Guillet[32] reported that the apparent molecular weight increased 4.5 times upon increasing the temperature from 25°C to 33°C, and suggested a simple aggregation phenomenon was present. More recent measurements[11–13,30,106] have employed dynamic as well as static light scattering to much more dilute solutions to attempt to detect a coil-to-globule transition.[109] In this case at the LCST, instead of intermolecular polymer–polymer bonds replacing polymer–water interactions, because the neighboring chains are so distant, intramolecular polymer–polymer bonds form, thereby collapsing the chain. Theoretically, one would ultimately attain a hard sphere ($R \sim N^{1/3}$).

The earliest attempt to apply quasi-elastic light scattering (QELS) was that of Taylor and associates[106] briefly reported in 1982. They simply observed an increase of the diffusion coefficient above the LCST, reflecting a decreased radius. Quantitative results were not presented and a stable suspension as mentioned above (Section 3.1.1) was observed. More recent work by the research groups of Hirotsu[30] and Fujishige[8,11–13] utilize far more dilute concentrations in order to obtain greater detail and observe chain collapse before the chains can aggregate.

Hirotsu and coworkers[30] applied QELS to a 27 μg/ml PNIPAAM sample of $\bar{M}_w$ of ca. 13.6 million in order to attempt to observe the coil to globule transition. They observed a collapse from 1000 Å to 600 Å upon heating through the LCST, assigning this portion of the transition to an intramolecular process. The correlation function could not be fitted to one exponential, which they claim suggests that there are other contributions in addition to the hydrodynamic diffusive mode. This collapse was detected at 34°C; subsequently, at 39°C (no heating rate reported), a sudden increase in the transmitted intensity was observed. Hence, qualitatively, the mechanism they suggest for the LCST is a collapse of single chains followed by their aggregation. Thus, as water–polymer

hydrogen bonds become less favorable relative to polymer–polymer and water–water interactions, the PNIPAAM monomer units first interact with their nearest neighbors on the same macromolecule, followed by association with surrounding chains.

At semi-dilute concentrations (2.7 mg/ml), Hirotsu and coworkers suggest[30] that their observation of a critical divergence of corresponding fluctuations (relaxation rate) is similar to the collective diffusion associated with the transition observed in PNIPAAM gels. This is of interest and will be discussed later (Section 4.1.1) to illsutrate the universality in behavior with single chains and gels.

In a preliminary report,[11] Fujishige claims that both dynamic and static light scattering can detect PNIPAAM collapse at the LCST. With a 12 μg/ml solution of an 8.4 million molecular weight sample, analogous results to those of Hirotsu[30] were obtained; a similar interpretation, namely, a collapse temperature lower than that for macroscopic phase separation, was suggested. In a subsequent paper,[12] Fujishige and coworkers report much greater detail; they were able to distinguish between the radius of gyration (R_g) measured by static methods and the hydrodynamic radius (R_h) found by QELS, and apply "blob theory" in the same manner as Chu and coworkers have done in attempts to detect a coil–globule transition for polystyrene in cyclohexane cooled through its UCST.[112] Samples of molecular weights between 1.63 million and 25.2 million are employed and for the first time, the authors report the polydispersity of some of their samples (1.3–1.4). These were obtained by fractionation and should be even narrower to truly apply theoretical analysis to the system. Nonetheless, from their detailed analysis, they claim that R_g/R_h decreases more rapidly than in the case of PS in cyclohexane to a value very close to that expected for a true globule. The theoretical implications of these results will be discussed shortly (Section 3.2). Fujishige[9] has also done extensive light scattering studies of PNIPAAM solutions below the LCST in conjunction with viscometry to ascertain the shape of the PNIPAAM chains in water (Section 3.1.4).

From a somewhat different perspective, Saito and coworkers[37] attempted to confirm spinodal decomposition in aqueous solutions of PNIPAAM. However, they employed a sample with $\bar{M}_w$ = 2.3 million and $\bar{M}_n$ = 0.29 million. With such a broad molecular weight distribution, it is barely conceivable to assign significance to these results even if the LCST is at its minimum theta value.[109]

3.1.4. *Viscometry* — The first studies of the viscometry of PNIPAAM in aqueous solutions were once again reported by Heskins and Guillet[32] in 1968. The intrinsic viscosity was seen to decrease with increasing temperature, yet the $\bar{M}_v$ was observed to become larger. Calculations were done with data from sedimentation experiments as well to conclude the polymer was more like a flexible coil than a rod below the LCST.

There has been criticism[13] of this work as it involved a single broad molecular

TABLE 5. Mark-Houwink-Sakurada coefficients for PNIPAAM

Solvent	Temperature (°C)	a	References
Water	20	0.93	5
Water	20	0.50	14
Water	20	0.51	13
Water	25	0.97	5
Dioxane	20	0.50	113
Methanol	25	0.64	5
THF	27	0.65	14

weight sample of PD = 3.4. Greater understanding of the polymer's structure in solution is obtained through using the Mark-Houwink-Sakurada[110,111] equation:

$$[\eta] = KM_v^a$$

the basic tool in determining the shape of polymer molecules in solution. If the value of the exponent (a) is 0.50, then one is observing a random polymer chain in theta solution where there is effectively a Gaussian distribution of monomer units. The value of a increases for practical purposes to 0.6–0.8 when the polymer is stretched out in a good solvent with excluded volume interactions. Higher values of $a(> 1.0)$ exist when the polymer is rod-like. Ideally, the polymer samples used to calculate a are monodisperse, and in the case where this is not possible, $\bar{M}_w$ is inserted rather than $\bar{M}_n$ as it is closer to the true value.

Given this introduction, the results of such investigations are listed in Table 5. It appears that PNIPAAM is an expanded coil in organic solutions with the exception of dioxane.[113] However this value was determined by the one-point method, which is not very reliable.[110] In aqueous solution, there is sharp contrast between the results of the research groups of Chiantore[5] and Fujishige.[13,14] The former group concluded that PNIPAAM is highly expanded, approaching a rod-like conformation, and have even shown how PNIPAAM is more expanded than other substituted polyacrylamides. Chiantore and coworkers claim this derives from PNIPAAM possessing both bulky side groups and the ability to hydrogen bond.[114] However it should be noted that samples were derived from separate syntheses taken to low conversions to avoid excess polydispersity, but only $\bar{M}_w$ was measured: there was no real measure of PD.

In his preliminary report, Fujishige[14] determined a based on fractionated samples; however, he did not report a PD for any of the samples. Moreover he also utilized $\bar{M}_n$ (from osmometry) in his calculations, which is less accurate than using the weight average value.[110,111] He also claimed to see an anomalous effect at slightly elevated temperatures closer to the LCST: the appearance of a tiny fibrillar suspension along with break points in the intrinsic viscosity plot are explained to be the result of shear-induced phase separation. An attempt to confirm this phenomenon[115] was unsuccessful; furthermore, one can easily fit (by

linear regression with correlation coefficients > 0.99) straight lines through the data points in the plots that Fujishige claims possess break points. Indeed, in a much more thorough paper that followed, his research group[13] ignored this earlier finding entirely. However, they do confirm that the PNIPAAM chains are near theta state ($a = 0.51$) at 20°C, this time using $\bar{M}_w$. Still, the theta state, as defined by the second virial coefficient being zero, is not attained until 30.59°C, a value very close to the LCST as expected. They have done a similar study on poly(*N*-isopropylmethacrylamide)[116] where they conclude that the addition of α-methyl group leads to chain expansion relative to results with PNIPAAM.

Concentrated solutions (10–25%) of PNIPAAM have been reported to be elastic, displaying spinnability and the Weisenberg effect.[17] It was noted that polyacrylamide does not exhibit such phenomena at similar concentrations. Instead of a simple precipitation above the LCST, the solutions became turbid and gel-like. No further detailed studies have been reported in the literature involving single chains at these concentrations, though it should be noted that hydrophobically modified PNIPAAM (< 2 mol% *N*-hexadecylacrylamide) was qualitatively observed[115] to reach such conditions at much lower concentrations than the homopolymer as expected from related studies with modified polyacrylamides.[117,118] Moreover, the addition of sodium dodecyl sulfate (SDS) and other surfactants to PNIPAAM also results in rather viscous solutions[17,115] as has been reported with other aqueous polymers.[119] These two systems will be discussed below in terms of other measurements of their behavior (Section 3.3.3 and 3.4.1), but it is interesting to note that either approach enhances polymer–polymer interactions resulting in viscoelastic solutions. This should be of significance in applications where controlling the amount of added polymer and obtaining desired rheological response at lower polymer concentrations is desired.

3.1.5. *Fluorescence* – The general application of fluroescence as a probe to characterize the polarity, mobility, and other properties in diverse media has been described.[120,121] Various molecules can be used in free solution or covalently bound to ascertain details of polymer solution behavior. The first application of fluorescence methods to studying solution behavior of PNIPAAM appears in the thesis of Breton[113] in 1982. 1-Naphthyl methacrylate was copolymerized with NIPAAM at ca. 4 mol%. More excimer was observed in aqueous solution versus in methylene chloride and decay parameters of the fluorescence were also different. Thus there appears to be promoted hydrophobic association between the pendant naphthyl groups in water. A concentration dependence of photophysics was observed in water, but the obvious experiments of changing temperature and introducing additives were not explored.

In 1989, Binkert and coworkers[80] published a brief report involving introducing fluorescein isothiocyanate onto PNIPAAM using ca. 5 labels per chain;

TABLE 6. Fluorescent-labelled PNIPAAM

Fluorophore	mol.%	References
Fluorene	0.05	74
Fluorene	0.42	74
Pyrene	0.06	74, 75, 127
Pyrene	0.36	75, 127
Pyrene	0.50	22–24
Pyrene	5.0	22, 23
Naphthalene	3.7	24
Pyrene/naphthalene	0.27/2.0	24
Pyrene/naphthalene	0.74/2.9	24

however, the synthesis and characterization of this system were not divulged. Time resolved fluorescence depolarization experiments appeared to show an abruptly increased relaxation time at the LCST (observed cloud point) reflective of a decrease in local mobility and a decrease in anisotropy; the latter effect was attributed to increased energy transfer between labels. Both these effects are claimed to be the result of collapse of the polymer from an expanded chain to a dense globule, but this is just speculation and cannot be commented on as the concentration used in the experiments is not given!

Most recently, much more detailed investigations have been done on fluorescence with PNIPAAM by two research groups: Winnik and coworkers,[22–24,26,77,78,122,123] and Schild and Tirrell.[8,9,74–76,124–128] Both polymer-bound[22–24,26,74,75,123,127,128] and free fluorescence probes[8,9,26,76–78,122,124–128] have been applied in studying binary solutions of PNIPAAM[22–24,126,128] as well as solutions of hydrophobically-modified PNIPAAM[26,76,78,124,128] and solutions of PNIPAAM in the presence of additives.[8,9,74,75,125,127,128] Whereas both groups have investigated hydrophobically-modified PNIPAAM, the Winnik group has extended its binary solution work on HPC[104] to PNIPAAM whereas Schild and Tirrell have focused more on the effects of cosolutes. This section will discuss binary solutions, while hydrophobically-modified PNIPAAM[26,76,78,124,128] and solutions of PNIPAAM in the presence of additives[8–9,74–75,125,127–128] will be discussed in separate sections (Section 3.41 and 3.3).

The contrasting approaches of the two research groups are reflected in the difference in the amount of fluorescent labelling of PNIPAAM as shown in Table 6. Schild and Tirrell prefer a minimum amount of attached fluorophore so as to closely approximate homopolymer behavior[74,75,127] and rely on measuring changes in fluorescence intensity. Interestingly, slight shifts in the LCST peak by DSC are observed as well as a more dramatic change in shape of the endotherm between the labelled and non-labelled PNIPAAM. However, as will be discussed below, this had no effect on interpreting results as LCST curves with additives for labelled and unlabelled PNIPAAM of similar molecular weight show superposition of the transition temperatures.

Thus, whereas none of the fluorescent PNIPAAM samples Schild and Tirrell[74,75,127,128] used exhibited a pyrene excimer emission spectrum, all of the Winnik group samples exhibited such phenomena.[23,24] As the earlier work done by this research group with hydroxypropyl cellulose (HPC) has shown, dramatic changes in solution behavior can consequently occur, including "double-LCST" phenomena.[104] Thus pyrene (5%)–PNIPAAM had limited solubility, and cloud point curves were rather diffuse.[23] Moreover, while the pyrene dimers of the 0.5% pyrene sample dissociated above the LCST, those of the more heavily labelled PNIPAAM persisted; these chains are proposed to exist as single molecule micelles as was found for PNIPAAM copolymers with long alkyl-chain comonomers discussed below.[26,76,77,78,122,123,128] While having excimers present allows greater flexibility and information in experiments, one should be cautious in generalizing conclusions to homopolymer solution behavior.

Nonetheless, Winnik obtains interesting findings with these polymers in binary solution. Although it was difficult to distinguish intra- and intermolecular interaction with just pyrene-labelled PNIPAAM, it was clear that excimer formation does not occur in methanol as the "hydrophobic effects" were suppressed.[23] Fluorescence quenching experiments[22] were done on these polymers using water soluble ethylpyridinium bromide and nitromethane. Below the LCST, quenching exists but the Stern–Volmer equation could not be fitted to the data, showing that the process was not diffusion-controlled. Nonetheless it was clear that the polymers partition into a water-poor phase above the LCST as they are protected from quenching under such conditions.

Over the past few years, Morawetz[129] has been at the forefront in applying nonradiative energy transfer (NRET) to investigating polymer systems. By labelling two sites in a media with a fluorescent donor and a corresponding fluorescent acceptor, it is possible to calculate the distance between the two probes from efficiency of energy transfer.[130] This technique has been found very useful by Winnik in the PNIPAAM system where it is applied to probe conformational and interchain effects.[24] Using doubly labelled PNIPAAM (synthesized via the NASI methods discussed in Section 2.3.2) with naphthalene donor and pyrene acceptor, it was observed that NRET slowly decreased over the temperature range of 18–31°C. As a result, it was concluded that there is a gradual shrinking of solvated polymer coils into a collapsed state, followed by aggregation into larger particles. Experimentally this last phenomenon was followed by observing disassociation of pyrene excimers as they are solubilized into the separated, less polar phase. Below the LCST, using singly labelled polymers, no NRET was detected, indicating a lack of interchain interactions below the LCST. This was independently confirmed by Schild and Tirrell[74,128] using the fluorene–pyrene donor–acceptor pair with a lower degree of labelling.

In examining binary PNIPAAM aqueous solutions, Schild and Tirrell[126] used

free fluorescent probes: pyrene, 1-pyrenecarboxaldehyde (pycho), 2-(*N*-dodecyl-amino)-naphthalene-6-sulfonate (C12NS) and ammonium 8-anilinonaphthalene-1-sulfonate (ANS). All successfully monitored the LCST by displaying abrupt shifts in their emission spectra as they moved from water to the precipitated PNIPAAM-rich phase above the LCST. The micromolar amounts of each probe used did not perturb the LCST from its probe-free value as measured by cloud point or DSC. This fact, and the observation that their spectra below the LCST are identical to that of each probe in polymer-free solution, indicate that PNIPAAM itself does not have any hydrophobic binding sites, unlike HPC[104,131–133] or the hydrophobically-modified PNIPAAM detailed below (Section 3.4.1). Further evidence for the absence of interactions was obtained by observing no NRET between fluorene-labelled PNIPAAM (Table 6) and free pyrene below the LCST.[74,128]

3.1.6. *Other characterization* – The solution behavior of PNIPAAM has been investigated by other assorted techniques. That first paper on the solution properties of PNIPAAM cited above involved the utilization of infrared spectroscopy (IR) and pH measurements to observe slow hydrogen–deuterium exchange.[21,102] These initial studies attempted to use PNIPAAM as a model for a non-α-helical polyamide.[102] It was estimated that one-third of the N–H groups were not bound to carbonyl groups. PNIPAAM was found similar to comparable small amides in regard to many details of the interaction but the minimum rate constant for the exchange was found to be one hundred times smaller. This was attributed to a change in self-dissociation constant of water in the neighborhood of the pendant residues from its value in bulk solvent. The follow-up study[21] established that this local environment first begins to exist in even trimers of PNIPAAM. Thus this work seems to support the view that the structure of water is different around a solute as compared to the bulk aqueous medium.

Offering contrast to the investigative methods so far described is the empirical approach of "solubility parameters". Standard group contribution techniques[134,135] yield very similar values for all types of polyacrylamides, thus showing how poor such methods are in predicting actual solution behavior. This has been pointed out[23] to be particularly true for aqueous media as the solubility parameter for PNIPAAM has been quoted as 13–14 and that of water is 23.4. The solubility parameter method would then predict nonsolubility for all polyacrylamides. Three-dimensional parameters are frequently cited,[134,135] but it would be best to rely on the studies aforementioned rather than on this sort of sketchy empiricism.

Surface tensions of dilute aqueous solutions of PNIPAAM have also been measured.[8,9,128,136] They were found to be independent of molecular weight (600,000–6,200,000) and concentration, and to decrease from 47.8 mN/m to 41.9 mN/m upon heating through the LCST.[136] Hysteresis exists and was suggested to result from preferential adsorption to the Teflon rod used.[136]

Standard Wilhelmy and du Nouy methods on a slightly lower molecular weight sample than the lowest used above yielded a surface tension of ca. 40 mN/m and independence of concentration for at least an order of magnitude on each side of 0.4 mg/ml.[8,9,128] Such surfactant-like properties are not unique to PNIPAAM among aqueous polymers, having been reported for hydroxypropylcellulose (HPC);[137] moreover, knowledge of their existence aids in assembling theoretical models[8,9] as it aids understanding the mechanism of interaction with added "conventional" surfactants.

Proton NMR has also been applied to PNIPAAM single chain solutions. Although Tanaka mostly focused on applying this technique to gels (Section 4.1.1), his group did note comparatively that[138] single chains possess different spectra than those of gels. Although lines are in the same positions as with gels, they are much narrower as would be expected from the greater mobility of single chains compared to gels. Another contrast was that spectral line shapes did not change with increasing temperature until the LCST and at that point, equilibrium was reached much more rapidly than with gels. Kubota and coworkers[139] have also examined PNIPAAM chain solutions with ^{1}H-NMR, measuring relaxation times as a function of pressure. Both T_1 and T_2 exhibit discontinuous transitions at the LCST. Values for T_2 were found to change under pressure; however, the LCST was reported as almost independent of pressure. This again is unlike the case for PNIPAAM gels where Cussler and coworkers[140] have seen a sensitivity to swelling.

3.2. *Theory*

From the studies of PNIPAAM solutions discussed above, it appears that below the LCST, PNIPAAM exists as isolated, flexible but extended coils in dilute aqueous solution. Whereas light scattering[12,13,30] does not show any conformational change below the LCST, early viscometry[32] and NRET results by Winnik[24] concluded otherwise. As Winnik mentions, part of the discrepancy may be attributed to the fact that NRET examines a much smaller size scale; nonetheless, the promotion of interactions by the added hydrophobicity of the attached fluorophores cannot be entirely ignored.

At the LCST, it appears that the individual polymer chains collapse prior to aggregation. This clearly would be more probable with more dilute solutions. Subsequently, scattering increases and a cloud point exists which is coincident with a calorimetric endotherm. Finally, a second phase of lower polarity is formed that is suspended in the water-rich phase.

Many theories have been advanced to explain the LCST phenomenon in PNIPAAM single chains and gels. They will be discussed in Sections 3.2 and 4.2 and related to experimental data cited above to assess their validity. Conclusions regarding the overall picture will be discussed after reviewing the theory of PNIPAAM gel transitions (Section 4.2).

When Heskins and Guillet[32] performed their classic study, they attempted to explain their observations using a modified version of the Flory–Huggins lattice solution theory for polymer solutions. By "plugging" in their enthalpy and points from their phase diagram, they concluded that the driving force for the transition was the greater entropy present in two phases versus inhomogeneous solution. They mention the fact that the water is often "ice-like" (more ordered) about hydrophobic groups (the *N*-isopropyl) as well as the fact that alternatively the ordering may be due to the hydrogen bonds between the polymer (amide) and water. Heskins and Guillet speculate that both these effects may influence results.

Although the application of the Flory–Huggins model to such nonrandom mixtures is invalid and their experimental approach using a polydisperse sample has been criticized,[13] the general requirement of a negative excess entropy of mixing for an LCST[81] has been derived mathematically from thermodynamic principles. Moreover, as the observed endotherm is in the range of the enthalpy of hydrogen bonds, it might be expected that changes in such a state drive the transition. There has been much debate as to whether "hydrophobic effects" or "hydrogen bonding effects" are dominant in general in aqueous solutions[87–89] and in the particular case of PNIPAAM. As the former are caused by changes in hydrogen bond interactions, these effects clearly cannot be independent.

Qualitatively, Schild and Tirrell[36] have surmised that the formation of hydrogen bonds between PNIPAAM and water that is the basis for solubility is also a hindrance due to the specific orientations required. Indeed, they cite Walker and Vause[93] whose theoretical models adequately describe LCST phenomena in general as resulting only from changes in preferences for hydrogen bonding. However hydrogen bonding cannot be the sole cause of the LCST as polyacrylamide is soluble at all temperatures in water. Yet from the fact that less (more) hydrophobic poly(*N*-alkyl acrylamides) have higher (lower) LCSTs than PNIPAAM, one can suggest that the LCST of polyacrylamide in aqueous solution is simply above the boiling point. Nonetheless, the experimental results discussed in the next section support that a facet of the classic "hydrophobic effect" is operative as well.

Winnik[23] concurs in her brief but qualitative description of the LCST that both effects mentioned above are important. In contrast, Fujishige[11,12] and Saito[6,29,141] advance that the driving force is entirely "hydrophobic interactions". The latter gel theory[141] will be discussed later (Section 4.2); the former is an application of "blob theory"[109] previously used for UCST predictions of single chain collapse by merely flipping the temperature axis. Such a theory considers only single chains rather than the entire system.

At the other extreme, Matsuyama and F. Tanaka[142] and the Prausnitz research group[143] attribute the LCST entirely to hydrogen bonds in their more mathematical (less experimentally-based) theories. The former pair apply mean-field theory to fit a single coil–globule transition. They attribute their inability

to use a single fitting parameter at all temperatures to the fact that they accounted only for polymer–solvent interactions and not for intramolecular bridging and intermolecular aggregation.

Prausnitz,[143] in contrast, develops a quasichemical partition function to extend conventional lattice theory. Each molecule/polymer segment is permitted to possess three energetically different types of contact sites: hydrogen bond donor, hydrogen bond acceptor, and dispersion force. The four resultant exchange energies are hydrogen bonding between like molecules, hydrogen bonding between unlike molecules, weak attractions between hydrogen bonding and nonhydrogen bonding species, and attractions between nonhydrogen bonding units. With three adjustable parameters, the authors are still only able to fit experimental results[32] remote from the critical point. They rationalize this as due to simplifications in assuming the exchange energies are temperature-independent as well as not accounting for nonclassical fluctuations in composition that occur near the critical point. They also apply their theory to gels, and in Section 4.2 we will continue our analysis as there has been greater debate between opposing viewpoints[108] in that arena.

Given this background of the origins of the LCST of PNIPAAM, results on more complex systems will now be described. Variations discussed below should optimally provide a feedback mechanism to extend understanding of the basic nature of the transition. Then it will be easier to determine which theory adequately describes the LCST.

3.3. *Additives*

In many of its applications, PNIPAAM is mixed with not only water but also various cosolutes that are being delivered, removed, or are present as otherwise inert substances relative to the application's main function (Section 3.5). However, any of these cosolutes may interfere and perturb the LCST if they bind to the polymer or substantially change the water structure. Therefore, basic studies of their influence on the solution behavior of PNIPAAM are motivated not only by the theoretical problem of competitive interactions, but also by commercial utilization. Furthermore, if interactions are on a molecular level, then such investigations should be relevant to PNIPAAM gels (Section 4.3) and coatings (Section 5) as the basic nature of the interaction should persist. The simplicity and convenience of the techniques such as cloud points, microcalorimetry, and fluorescence then have even more to offer as the foundation upon which other systems can be understood.

The behavior of a polymer in solution reflects the balance of the interactions between its segments and the solvent molecules.[91] As Fig. 5 indicates, one can imagine a triangle of interactions involving somewhat arbitrarily classified mechanisms[96] of polymer binding and solvent perturbation. Thermodynamics[91] dictates that components whose hydration spheres are incompatible with that of

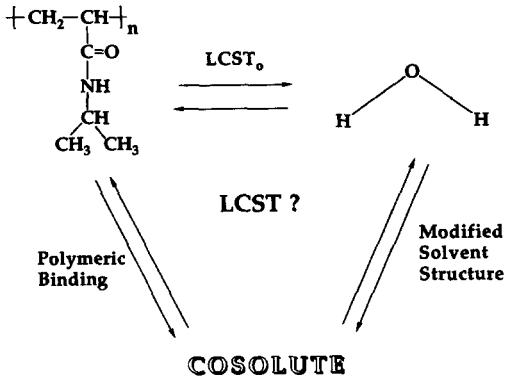


FIG. 5. Triangle of interactions in ternary PNIPAAM systems.

PNIPAAM will depress the LCST. However, it has been stated that if the activity of the third component is about the same in both separating phases, its presence will elevate the LCST.[81] Some generality[81] has been observed in the effects of third components on the LCSTs of synthetic polymers such as PNIPAAM and on diverse phenomena such as helix–coil transitions, gelation, protein denaturation, and the solubility of small molecule nonelectrolytes. Being able to relate findings to these other fields provides even greater motivation for these investigations.

3.3.1. *Solvents* — The simplest additive one can add is a solvent. Theoretically, the problem should be able to be treated by the same models (Section 3.2) used for binary systems if the solvent is another low molecular weight, essentially nonionic liquid like water. PNIPAAM is soluble in many organic solvents as long as they are capable of hydrogen bonding. Among those reported are acetone, methyl ethyl ketone, chloroform, dioxane, ethyl alcohol, methyl alcohol, and tetrahydrofuran (THF).[14] In all of these cases, no LCST is observed: PNIPAAM is soluble to the solvent's boiling point. As discussed above in the viscometry section (Section 3.1.5), the few experiments that have been done indicate that the Mark–Houwink–Sakurada coefficient in such solvents is consistent with values typically obtained for good solvents.

In general, one would naively expect that adding a second better solvent to aqueous PNIPAAM would raise the LCST, extending the solubility range. Schild and Tirrell[33,128] have shown that this is not true for a number of organic solvents mixed with aqueous solutions of PNIPAAM. Instead, cononsolvency (or antagonistic solvency) has been observed; for example, certain mixtures of methanol and water (obviously considered a solvent below the LCST) behave as nonsolvents at a given temperature below the LCST of the polymer in water alone. This phenomenon has been observed for a number of other polymers in nonaqueous systems[33] and thus the phenomenon is not unique to PNIPAAM.

However, as the effect is not observed for PVME[32] in water/methanol, and instead its LCST continuously increases as the "better" methanol solvent is added, use of a given solvent pair is not sufficient for cononsolvency and the solubility observed depends on the identity of all three species.

Microcalorimetry showed a decrease in enthalpy (ΔH) for the LCST transition as the corresponding cononsolvent was added to water.[32] This indicates that the nonaqueous solvent reduces either the number or the strength of polymer–water contacts. Preferential adsorption of methanol to the polymer chain would result in a decrease of ΔH since the strength of the hydrogen bonding of the polymer to the second solvent is likely to be lower. Alternatively, water–alcohol complexation would also reduce the interaction of polymer and water.[32] Winnik and coworkers[16] have also reported cononsolvency with PNIPAAM in water/methanol mixtures and have decided that the latter proposal is reasonable, citing archaic theories of methanol being bound in clathrate cages of water. Both groups also cite an analogous observation of a "cononsolvent" effect in gel swelling which will be discussed in Section 4.1.2. As derived, the theory presented for gels requires the free energy of the methanol–water interaction to be negative, whereas in actuality its experimental binary value is always positive. Therefore, Winnik and company[16] conclude that the addition of PNIPAAM enhances the attractive interaction for water and methanol.

Schild and Tirrell[32] recognized the analogy to gels as well, having also observed the cononsolvent transition with single PNIPAAM chains and aqueous DMSO. This system was reported much earlier to result in a "re-entrant transition"[43] for the corresponding gels. Schild and Tirrell[32] also demonstrated the necessity of there being a positive interaction parameter between water and methanol based on Flory–Huggins spinodal calculations. However, they also realized that such a model, like the gel model, is a mean-field model and is worthless in describing systems where molecules and interactions are not randomly placed and oriented. Moreover, given the concentrations of the solutions involved, the resulting conclusion that a single polymer segment can modulate the interactions of ca. 5000 solvent molecules and change their interactions from repulsive to attractive is implausible. Schild and Tirrell conclude that any mechanism to explain the transition in both single chains and gels must thereby involve local polymer–solvent interactions.[32] Such collapse transitions based on local concentration fluctuations have been proposed by de Gennes.[144,145] These require the two solvents to be near their own binary critical point and this is probably true for methanol and water as their interaction parameter is large and positive. It is certainly true of THF/water where a known LCST has been reported at ca. 72°C.[146] Moreover, it is even stated that the effect is seen clearly even far from the critical point at 25°C. This then makes effects on the polymer LCST plausible and indeed Schild and Tirrell observe cononsolvency when THF is added to aqueous PNIPAAM.[32] The theory of de Gennes predicts that when the correlation length of the concentration fluctuations of the better

solvent approaches the size scale of the chain, the polymer is solubilized within these better-solvent-rich domains, resulting in collapse as a consequence of the constrained environment. De Gennes also predicts a chain re-expansion and this may be somewhat related to the experimental observation[32] of a sudden re-solubilization of PNIPAAM above a critical amount of the nonaqueous solvent. Further study is needed to demonstrate the entire model de Gennes has formulated, but this hypothesis certainly is more realistic than mean-field and "ice" models.

Interestingly, a study related to those above was earlier published by Saito and coworkers.[29] They added various alcohols to aqueous PNIPAAM and detected depressed LCSTs, but failed to complete the phase diagram, semantically limiting themselves by calling the alcohols additives. Moreover, they even did the same experiments with PNIPAAM gels in water/DMSO which were reported six years beofre,[43] and if one analyzes their plot, similar results can be observed. However, in neither of these cases did they realize they were observing cononsolvency. Thus, they failed to comprehend the true meaning of their observations. This is one of many examples where limited experimental design and narrow knowledge of the literature has led to incomplete conclusions. This review's intent is to alleviate such problems that result when work is done on the same polymer for diverse reasons by workers in different fields unaware of the others' existence. Further details concerning cononsolvency will be discussed in the gel section (Section 4.1.2).

3.3.2. *Salts* – Eliassaf[17] reported that 6M LiCl precipitates PNIPAAM from dilute aqueous solution at 30°C. In a more detailed investigation, Schild and Tirrell[36] have examined the effects of a number of salts on the LCST of aqueous PNIPAAM. They observed that the well-known Hofmeister series seems to hold in terms of the effectiveness of a series of salts in depressing the LCST; however, the data on the shapes of the endotherms was rather enigmatic. As Monji and Hoffman[147] point out, such salts and other cosolutes can often interfere with applications of PNIPAAM such as their immunoassay reported in Section 3.5.2. These simple experiments therefore have a practical value in product design.

3.3.3. *Surfactants* – The interactions of nonionic water soluble polymers with surfactants have been recently summarized;[119] they are a subject of both theoretical and industrial interest. The earliest report concerning interactions of PNIPAAM with surfactants was by Eliassaf[17] with sodium dodecyl sulfate (SDS); he briefly reported that 1% SDS increases the viscosity and prevents the precipitation of PNIPAAM even in boiling solution. Schild and Tirrell[8,9,127] have done systematic studies on aqueous mixtures of poly(*N*-isopropylacrylamide) and sodium *n*-alkyl sulfates, ranging from methyl to as long as *N*-hexadecyl. For SDS, they found a continuous increase of the LCST with increasing surfactant concentration, elevating it above the boiling point below 1% SDS, consistent

with the earlier report. However, they also observed that the precipitated particle size decreased below that of the wavelength of visible light at far lower concentrations. Blinkert and coworkers[105] have used dynamic light scattering to follow this change in the state of aggregation, calling it intermolecular solubilization as opposed to intramolecular solubilization, the term they assign to the fact that the LCST increases.

Schild and Tirrell[8,9,127] have gathered extensive evidence for understanding the system by using various measures of SDS aggregation. They demonstrated using various fluorescent probes, including free pyrene,[120,121] that the micellization of SDS is promoted by the presence of PNIPAAM. Through the study of an entire series of sodium *n*-alkyl sulfates, they concluded that the concentration at which the surfactants form micelles in aqueous PNIPAAM, the critical aggregate concentration (CAC)[119] decreases relative to the critical micelle concentration (CMC) in water alone as the *n*-alkyl chain length is increased. This effect is observed only when the chain length is at least *n*-pentyl; the shorter chain length surfactants do not aggregate. When added to PNIPAAM, these latter amphiphiles depress the LCST just as salts do. However, the longer-tailed surfactants elevate the LCST after initially depressing it (acting as salts before they bind). The concentration at which the elevation of the LCST occurs is coincident with that at which the surfactants form micelles. Hence, it is proposed that surfactants bind to PNIPAAM at this CAC and, through their ionic repulsion, cause the polymer to become more soluble. By fitting experimental results to an adaptation of the theoretical model of Nagarajan and Ruckenstein for polymer–surfactant complexation, this hypothesis is clearly supported.

Schild and Tirrell[75,128] also determined the essentially identical CAC using the 0.06% pyrene labelled PNIPAAM as demonstrated in Table 6 as well as with other free and amphiphilic fluorescent probes. This technique of using free, polymer-bound and surfactant-bound pyrene was especially valuable when determining the interactions of PNIPAAM with other surfactants. In each case, the necessary experimental control of *redetermining* the LCST curve of the labelled PNIPAAM as a function of added surfactant was done to verify that the two reference states are equivalent.

Having demonstrated that hydrophobic effects enhance interactions with the sodium *n*-alkyl sulfate series, Schild and Tirrell[75,128] then turned to various cationic and nonionic headgroups, using surfactants of similar C_{12} tail length as a control. The benefit of the polymer-bound pyrene is that it resolves ambiguities in systems where the measured CAC equals the CMC with free pyrene, that is, pyrene molecules not covalently attached to any of the species in the solution. In these cases, it is unclear whether PNIPAAM binds the added surfactant at the CMC, at concentrations greater than the CMC, noncooperatively (as monomers), or not at all. Therefore, in these systems where the CAC in the presence of PNIPAAM was measured to be essentially equal to the critical micelle concentration (CMC) (through the use of free pyrene), the polymer-bound

probe was able to distinguish the nature of the interactions. For PNIPAAM and dodecyltrimethyl-ammonium bromide (DTAB), surfactant binding occurs near the CMC; in the case of PNIPAAM and Triton® X-100, interactions appear to exist above the CMC. Finally, micellization was unaffected by the presence of PNIPAAM in the case of Zwittergent® 3-12. These results confirmed the general validity of the proposed theory for nonionic polymer–surfactant complexation; experimental results concurred with theoretical predictions. The only exception is the Zwittergent® 3-12 system, with which the model was not supposed to be valid[75] due to the nature of the dipole interactions in the headgroup. LCST measurements were also done on each system; generally, higher surfactant binding resulted in a greater elevation of the LCST of the polymer. Schild and Tirrell[128] have also studied a number of other surfactants in this manner including worm-like micelles and double-tailed amphiphiles that form vesicular membranes; the latter will be discussed in Section 5.2.2.

Specialized fluorescence probes have also been applied to extend the understanding of the interactions of PNIPAAM with surfactants. Fluorescent amphiphile (C12NS)[125] cited above (Section 3.1.5) has been directly interacted with PNIPAAM, thereby avoiding ambiguities associated with the use of exogeneous probes. The elevation of the LCST of PNIPAAM was observed to occur at the concentration (CAC (T = 24.5°C) = 20 μM) at which C12NS formed aggregates. This was reflected by a blue shift in the emission spectrum of C12NS from 430 to 424 nm, similar to the case where C12NS is directly added to SDS micelles. More detailed experiments were done which also showed that the precipitated polymer phase solubilizes C12NS below its CAC.

Schild and Tirrell[74,128] also applied fluorescence probes to perform NRET investigations between fluorene-labelled PNIPAAM (Table 6) and various pyrene derivatives illustrated in Fig. 6. NRET was observed between fluorene-labelled PNIPAAM and these amphiphiles; a greater degree of interaction was detected for the quaternary ammonium amphiphile (C11PN+, I) as compared to that observed for the zwitterionic sulfobetaine-based one (II). Such a relative ranking of binding had already been demonstrated[74,75,128] using unlabelled polymers and surfactants with free probes as well as with labelled polymers and unlabelled surfactants. Thus three methods yield the same conclusion. Moreover, in the case of the quaternary ammonium amphiphile, pyrene excimers are induced by the addition of the PNIPAAM. This is further indication of the formation of C11PN+ aggregates (at least dimers) attached to the PNIPAAM chain. Such proximity would then allow NRET to occur and increase the probability of C11PN+ contact to form ground and excited-state dimers.

Interaction of poly(*N*-isopropylacrylamide) (PNIPAAM) with two perfluorinated carboxylic acid amphiphiles was also explored in aqueous solution.[7,128] Increasing concentrations of perfluorooctanoic acid (PFOA) first slightly depressed the LCST of PNIPAAM and then elevated it at concentrations greater than ca. 2.5 mM. However, at higher concentrations (> ca. 3.5 mM), the

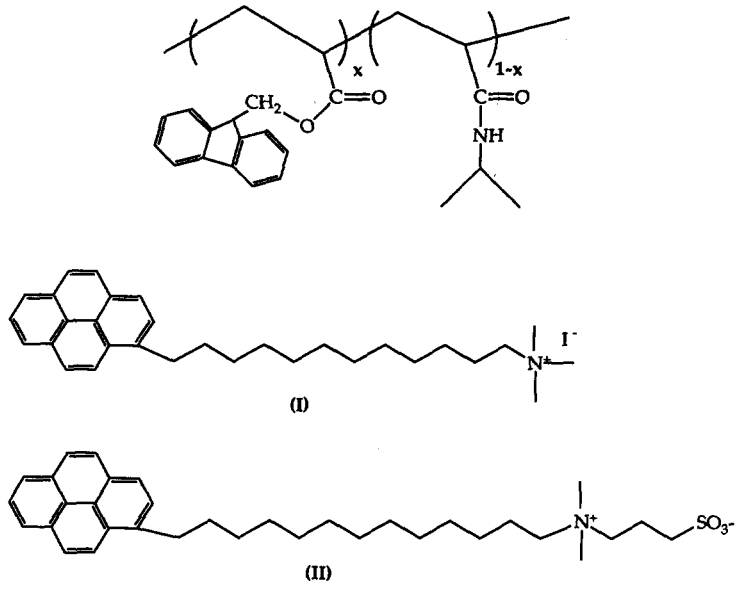


FIG. 6. NRET system for PNIPAAM solution interactions.

transition could not be detected by either microcalorimetry or cloud point measurements. In turn, PNIPAAM appeared to promote the micellization of PFOA as determined by surface tensiometry. Thus the phenomenon appears similar to that observed with hydrocarbon surfactants, although smaller precipitated aggregate sizes than with SDS appear to exist. Consequently, the application of quasi-elastic light scattering as cited above[105] would certainly aid in defining the limits of solubility in this system. Adding heptafluorobutyric acid (HFBA) to PNIPAAM resulted in an even more abrupt transition at the LCST, similar to cononsolvent effects previously observed with PNIPAAM.[32]

Winnik and coworkers[122,123] have reported on the interaction of surfactants with hydrophobically-modified PNIPAAM; these findings will be reported at the end of the following section along with the work of Schild and Tirrell on such multivariable systems.[128] In the course of their investigations, Winnik and coworkers[122,123] neglected the relevant control system of unmodified PNIPAAM itself interacting with surfactants, preferring to focus entirely on the copolymers. However, they do present results for their 5% pyrene–PNIPAAM which can be compared to the much more lightly labelled pyrene-labelled polymers discussed previously. In the case of the 5% pyrene–PNIPAAM, the amount of pendant pyrene is high enough to create excimers; these dimers could be "destroyed" by the addition of surfactants. The CAC reported for added SDS is claimed to be in agreement with the result reported by Schild and Tirrell.[8,9] As mentioned above, Schild and Tirrell[75,127,128] have used many different free and covalently

bound fluorescence probes for the PNIPAAM/SDS system and obtained essentially the same CAC in almost all cases. It appears that even large amounts of attached probe may not affect the result for the Winnik polymer[123] for this particular case, but it should be noted that the transition illustrated is slightly broader, indicating that a secondary binding may be present.

3.4. *Copolymers*

3.4.1. *Hydrophobically-modified* – In the sections on viscometry (Section 3.1.4) and on rheological applications (Section 3.5.1), the significance of hydrophobically-modified polyacrylamides in various applications is discussed. Basic studies in the area performed by Schild and Tirrell[76,124,128] and the Winnik research group[26,77,122,123] have investigated both binary solutions[26,76,77,122,128] as well as systems with added surfactant.[122,123,128] In contrast with the viscometric studies cited above, these studies have all been done using either free or covalently bound pyrene-derivative fluorescent probes.

The first report of hydrophobically-modified PNIPAAM came from Schild and Tirrell[76] in 1989. They were motivated by a report that such a modified polyacrylamide had hydrophobic domains[117,118] and sought to create a thermally-controlled collapse in the hydrophilic region by substituting *N*-isopropylacrylamide for acrylamide. Employing *N*-hexadecylacrylamide (HDAAM) as a comonomer, they discovered that even 1.7 mol % HDAAM in the PNIPAAM copolymer led to insolubility. Two soluble copolymers (0.4 and 1.1 mol %) were synthesized (characterized by ^{13}C-NMR under quantitative conditions) and compared to the solution behavior of homopolymer. The cloud points were only slightly depressed (maximum ca. 2.5°C) but the transition width of the DSC endotherms increased almost 3–4 times. These copolymers were subsequently studied in the presence of fluorescent probes. It was concluded that micelles existed at 0.4 mg/ml; the solubilization sites of pyrene, pycho, and ANS were determined by their ability (or inability) to detect the LCST under the reasonable premise that probes deep in the core of the micelles should not be affected by the LCST.

One year later, Winnik *et al.* reported similar findings of hydrophobic domains for copolymers of C_{10}, C_{14}, and C_{18} *n*-alkyl acrylamide derivatives copolymerized with PNIPAAM[77] at both 0.05 and 1 mol% comonomer. Increasing polymer concentration was observed to decrease the polarity value reported by pyrene as expected, except for the less substituted C_{10} copolymer. This last polymer is thus similar to PNIPAAM homopolymer in its solution behavior. It is interesting to note that these results are probably due to the same type of intermolecular associations explored by Exxon,[117,118] because the decrease in reported polarity is coincident with a steep increase in viscosity at slightly higher concentrations.[128]

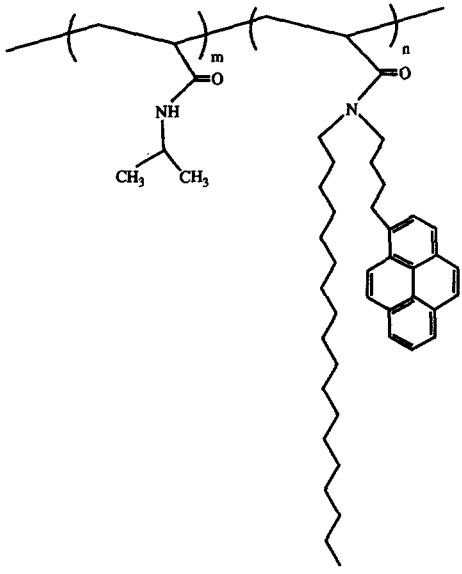


FIG. 7. Fluorescent, hydrophobically-modified PNIPAAM.

Through monitoring changes in the emission spectrum of pyrene, it was possible to detect the LCST;[26] environments of similar polarity were detected for all the modified polymers above the LCST, increasing or decreasing through the transition depending on the polarity of the original solution. These experimental results are consistent with the observations and phase intermixing model of Schild and Tirrell.[75,124,128] Winnik and coworkers also did[26] fluorescence lifetime and depolarization (microviscosity) measurements on these copolymers to support the premise of the formation of polymeric micelles; great shielding from water existed in the examples which contained longer hydrocarbon tails as expected.

A 0.5% pyrene-labelled hydrophobically modified PNIPAAM (Fig. 7) was also synthesized by Winnik *et al.*[26,77] with a C_{18} side group. Excimer formation was not observed in methanol, but it was present and increased asymptotically with increasing concentration in aqueous media, indicating the formation of a higher order structure. Upon heating through the LCST, the excimers were abruptly disassociated. This finding supports their hypothesis that the polymeric micelles are disrupted above the LCST, consistent with the phase-intermixing model of Schild and Tirrell.[76,124] An interesting comparison was then made between the polymer in Fig. 7 and the 0.5% pyrene-labelled PNIPAAM in Table 6. Whereas the covalent pyrene moieties in the hydrophobically modified PNIPAAM exist in the micelles and thus a greater and constant amount of excimer exists below the LCST, the 0.5% pyrene-labelled PNIPAAM decreases in excimer content below the LCST as it responds to gradual changes in polymer

conformation. Consequently, the former polymer detects a more abrupt LCST transition.

The Winnik research group has also applied[78] the intramolecular excimer-forming bis(1-pyrenylmethyl) ether (dipyme) as a probe of these polymers (C_{14} and C_{18}). Microfluidity was concluded to be more comparable to the lower value found in general for vesicles than that for micelles. Additional data obtained demonstrated that the polymer-rich phase above the LCST is more polar and even less mobile than that below the transition.

Once one has studied hydrophobically modified PNIPAAM, it is logical to then interact these "surfactants" with standard surfactants. The Winnik group has interacted both the hydrophobically modified PNIPAAM[122] and pyrene-labelled hydrophobically modified PNIPAAM[123] with SDS, hexadecyltrimethyl-ammonium bromide (HTAC), and two types of neutral glucopyranoside surfactants (OG).

Pyrene was used successfully to detect the binding of surfactants to the C_{10} hydrophobically modified PNIPAAM below the CMC of the surfactants;[122] however, the transition curve was very broad for SDS and HTAC relative to PNIPAAM homopolymer curves, indicating noncooperative binding. For the C_{14} and C_{18} hydrophobically modified PNIPAAM, pyrene could not be used because it reports a similar polarity in their copolymer micelles as it does for the surfactant micelles. Thus dipyme was used because it is sensitive to microfluidity differences as mentioned earlier in this section. The resultant mixed micelles (again much more cooperatively for the nonionic surfactant) were found to be of intermediate microfluidity.

Experiments with the pyrene-labelled hydrophobically modified C_{18} PNIPAAM (Fig. 7) indicated that the addition of surfactant disrupts the polymeric micelles as reflected by the dissociation of excimers.[123] The process was noncooperative for added SDS and cooperative for OG. Thus mixed micelles that form contain far fewer C_{18} chains compared to the original solution structure.

Schild and Tirrell also investigated the interactions of their hydrophobically-modified HDAAM/NIPAAM copolymers[128] with surfactants. They avoided the use of pyrene for the same reasons as the Winnik group;[122] instead, they selected pycho as it was found not to solubilize in the copolymeric micelles but only in those of SDS. Consequently, they were able to detect the promoted binding of SDS to the copolymers below the surfactant CMC. They observed a transition as cooperative as that of PNIPAAM homopolymer with the 0.4% HDAAM copolymer; however, an interesting two-step transition was detected for the 1.1% copolymer. Contrast with the Winnik results[122] could very well be entirely due to the choice of probe. Since pycho is solubilized only by the SDS-type micelles, pycho will be abruptly solubilized as these are created. However as dipyme is soluble in both types of hydrophobic domains, one would expect the transition not to be as sharp. The double transition Schild and Tirrell observed

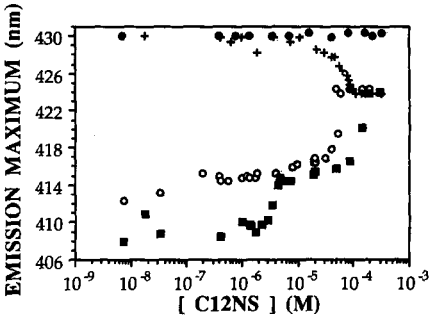


FIG. 8. Interactions of PNIPAAM and copolymers with C12NS. Water alone (●), PNIPAAM (+), PNIPAAM-HDAAM 0.4% (○), PNIPAAM-HDAAM 1.1% (■) at 0.4 mg/ml of each polymer; measurements at 24.5°C.

may be the result of two types of binding, to the hydrophobic domains and to NIPAAAM units.

Whether such a mechanism for surfactant binding is plausible is best shown by investigations of mixtures of C12NS and PNIPAAM copolymer solutions. Whereas the Winnik group fluorescently labelled the polymer to monitor the polymer conformation, Schild and Tirrell[125] use this fluorescent amphiphile (Sections 3.1.5 and 3.3.3) to study the system from another perspective, that of the surfactant. They had previously used C12NS to explore complexation between PNIPAAM and sodium *n*-dodecyl sulfate (SDS)[8,9,128] as well as investigate its direct interactions with PNIPAAM.[39]

Figure 8 illustrates the effects of increasing concentrations of C12NS in the PNIPAAM and copolymer solutions at 24.5°C. With the copolymers, C12NS can first be solubilized in their HDAAM cores, even at the lowest concentrations employed down to the limits of the sensitivity of our instrumentation. The 1.1 mol% HDAAM system clearly affords a larger hydrophobic region (greatest blue shift in spectra) to contain C12NS than that of the 0.4 mol.% HDAAM or the homopolymer as expected. Figure 9 shows spectra for 1 μM C12NS added to 0.4 mg/ml of each polymer; the emission maximum blue shifts from its aqueous value (vertical line) in the absence of polymer as the HDAAM content in the solution increases. At these concentrations, the emission maximum of the homopolymer solution is identical to that in water alone; hence the blue shifts observed are a result of binding to the HDAAM cores and not to NIPAAM units. Both copolymer solutions exhibit abrupt red shifts as the concentration of C12NS attains the range of concentration (20–100 μM) at which the amphiphile binds to the homopolymer. The curves all superimpose near the solubility limit of C12NS.[125] Schild and Tirrell concluded that C12NS binds to two sites, NIPAAM units as well as the HDAAM core. At higher concentrations, the contribution of the emission of the species bound to NIPAAM is larger than that of those bound in the HDAAM core. This probably results from there

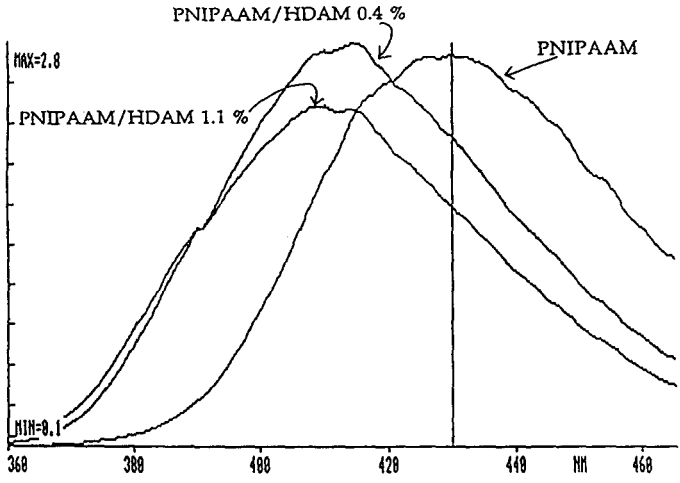


FIG. 9. Spectra for PNIPAAM and copolymers with added C12NS.

being more NIPAAM sites and therefore a red shift is seen as their contribution to the fluorescence dominates.

The model was further tested through choosing a C12NS concentration (0.4 μM) at which the probe does not perturb PNIPAAM or form aggregates.[8,9,125,128] Hence it is employed as a probe, as was done for PNIPAAM/SDS complexation. As Fig. 10 displays, C12NS exhibits a thermal response in PNIPAAM/HDAAM solutions analogous to that reported for pyrene.[76,124] Thus both surfactants solubilize in HDAAM cores when they are present and hence are unaffected by the LCST transition. However, when there is a greater amount of HDAAM, polarity increases upon heating above the LCST due to phase (NIPAAM/HDAAM) intermixing.

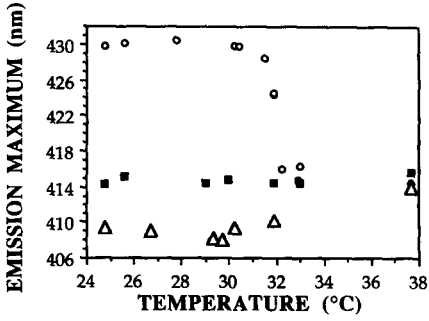


FIG. 10. Following the LCST of PNIPAAM (0.4 mg/ml) polymers with C12NS as a probe. PNIPAAM (○), PNIPAAM-HDAAM 0.4% (■), PNIPAAM-HDAAM 1.1% (△).

3.4.2. *General* – That polymers with both hydrophilic portions possess LCSTs is a rather general phenomenon.[10,34,35,81,148] In a 1975 review, Taylor and Cerankowski[81] cited a broad variety of structures of water-soluble polymers with LCSTs, some of which Schild and Tirrell[36] have subsequently studied with their sensitive microcalorimeter (Section 3.1.2). Moreover, Taylor and Cerankowski[81] claim they have made several hundreds of LCST polymers at Polaroid by following the concept that "as a polymer which is soluble at all temperatures is made increasingly hydrophobic, before complete water insolubility is reached, a range of compositions will be found which will have temperature inverse solubility and the more hydrophobic the increment, the lower the LCST". They stated that these polymers can be created by copolymerization or building hydrophobicity stepwise into or out of the monomer unit. Included in their work is a report of LCSTs of homopolymers of a series of poly(*N*-alkyl acrylamides) which proceed from complete solubility to insolubility as the size of the alkyl side group increases.

Ito[10] has more recently reported a more focused study on poly(*N*-alkyl acrylamides) alone. Some discrepancies exist between the two investigations. The Polaroid group stated that poly(*N*-propylacrylamide) is insoluble, while Ito reports an LCST of 21.5°C for this polymer; Saito's research group[10] has published evidence supporting the latter claim. Ito also reports higher LCSTs for methacrylamide polymers relative to the corresponding acrylamide; although this result concurs with those from Fujishige,[11] it contradicts results from Polaroid.[81] However, all of Ito's poly(*N*-alkyl methacrylamide) polymers have much lower viscosities than the corresponding acrylamide derivatives. As lower molecular weight polymers have higher LCSTs, this may be the origin of some of the discrepancies.

Both Taylor and Cerankowski[81] and the Hoffman[34,35] research group have copolymerized NIPAAM with other *N*-alkyl acrylamides over the entire composition range; typically, continuous changes in the LCST either up or down are observed when the comonomer has respectively a smaller or larger *N*-alkyl group than *N*-isopropyl. However *N*-*n*-butyl acrylamide[34] was found to be an anomaly. After initial depression of LCST upon increasing incorporation into the copolymer, there is a sudden loss in solubility at 40% *N*-*n*-butyl acrylamide, just as occurred at even lower composition for HDAAM (Section 3.4.1). Thus more abrupt transitions appear to occur at longer chain length.

The ability to shift the LCST of PNIPAAM-like polymers from < 0 to > 100°C provides excellent flexibility in tailoring transitions for specific uses. One can "switch off" solubility at biologically relevant temperatures as well as at room temperature. Moreover, the fact that one can obtain the same LCST with a small amount of a very hydrophobic comonomer (say *N*-decyl) or a high fraction of a less hydrophobic comonomer (such as *N*-*t*-butyl) permits further modulation of interactions with cosolutes in the system.

3.5. *Applications*

3.5.1. *Rheological* – We mentioned (Section 3.1.4) that the viscosity of aqueous PNIPAAM solutions is increased by the presence of either hydrophobic comonomers or surfactants. These observations have led to application of such systems for enhanced/tertiary oil recover.[117,118,149,150] Exxon[117,118] has created many hydrophobically-modified polyacrylamides for such an end use; Nagarajan derived his theoretical model[149] for polymer–surfactant interactions adapted above[8,9] (Section 3.3.3), upon motivation by such applications.

More applied studies have been reported using NIPAAM and related copolymers, often with ionic comonomers.[150] The main concern in this field is maintaining sufficiently high solution viscosity in the presence of surfactants and salts.[149,150] Therefore, the basic studies reported above can aid in designing the optimum polymer with the correct response, especially since different salts and surfactants have diverse effects on PNIPAAM conformation. Indeed, Mumick and McCormick claim that PNIPAAM and its copolymers with acrylamide should be useful in drag reduction behavior.[151] Although they report no evidence of such an effect in this preprint, they do show that viscosity and the LCST are perturbed by SDS, urea, and sodium chloride. Disturbingly, they fail to cite any previous work done by any research group with PNIPAAM at all!

PNIPAAM has also been cited as a thickening agent in food and coatings.[26,152] When such polymers have been included as an ingredient in paper coatings, better gloss and ink receptivity were detected relative to that with controls.[152] Applied as a general viscosity-controlling agent, PNIPAAM copolymers have been found to give aqueous solutions whose viscosity decreases with increasing shear rate and falls sharply with increasing temperature.[153] Indeed, hydrophobically-modified polyacrylamides have been patented for their dual role as polymeric surfactants and viscosity modifiers.[154] Thus given the approach of modifying rheology by either adding surfactants to PNIPAAM or copolymerizing internal surfactants by using hydrophobically-modified comonomers, the latter approach may have intrinsic advantages in terms of control of composition.

3.5.2. *Biological* – Hoffman and coworkers[20,147,155,156] have taken advantage of the precipitation of PNIPAAM at elevated temperature to develop an alternative approach for immunoassay technology. PNIPAAM chains were synthesized with NASI groups as previously discussed (Section 2.3.2). These were then conjugated to an antibody; in their case, monoclonal human immunoglobulin (Ig)[20,156] was used. Polymer solutions were subsequently made and mixed with an antigen and a second antibody, the latter conjugated to a fluorophore label. Thus a "sandwich"-type immune complex was thereby formed in solution, covalently attached to PNIPAAM. The solution was then heated above the LCST and separation was carried out as illustrated in Fig. 11. The process was repeated to insure removal of unbound signal. This method has also been

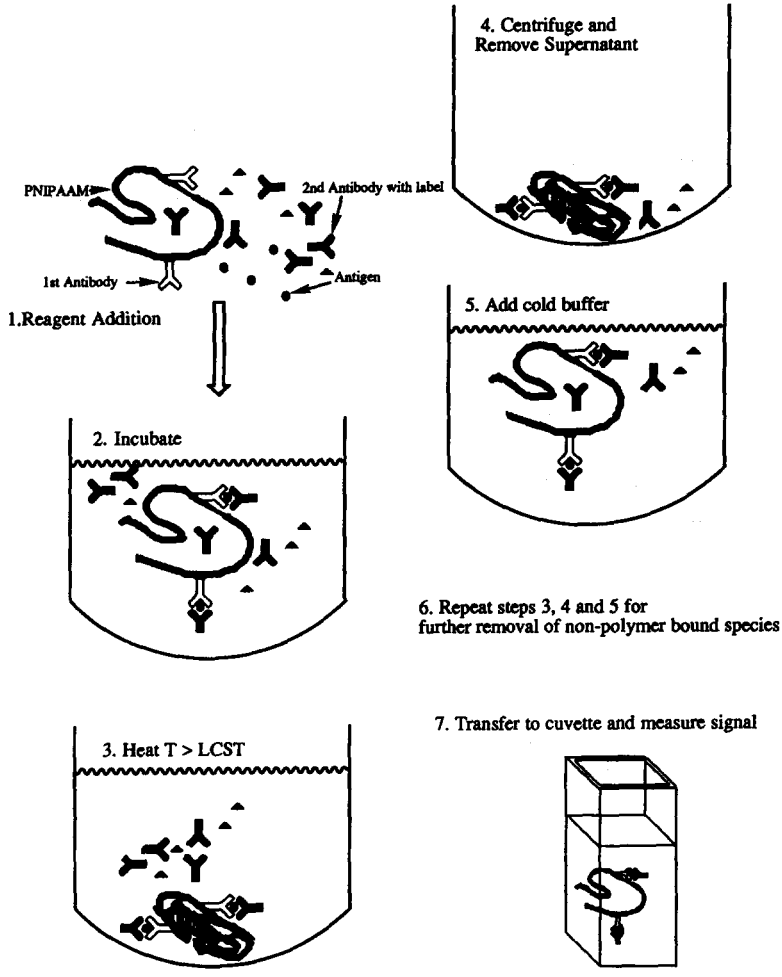


FIG. 11. Immunoassay scheme for PNIPAAM.

extended to mouse Ig and competitive immunoassays have been carried out as well.[147]

Two interesting effects were noted by the researchers.[147] First, they found out that certain materials interfered with the immunoassay process. This effect was due to these additives interfering with the precipitation of PNIPAAM, shifting the LCST. SDS was noted to have a particularly large effect; indeed as noted above, Schild and Tirrell[8,9,127] have found that it strongly elevates the LCST of PNIPAAM. By taking into account that shorter chain sodium *n*-alkyl sulfates[8,9] and other surfactants[75] perturb the solution behavior of PNIPAAM less, as well as choosing the right buffer by accounting for the differential effects of salts,[36]

Hoffman and coworkers could extend the usefulness of their technique and make it more media insensitive.

Hoffman and researchers[20,156] also noted that conjugated polymer (PNIPAAM-Ig) does not precipitate to form turbid solutions; laser light scattering had to be applied to detect the smaller aggregates. Indeed, centrifugation ahd to be used to remove the precipitated complex. As noted previoiusly, above critical amounts of additives such as SDS[8,9] and fluorosurfactants,[7] aggregates smaller than the wavelength of light were also found when solutions were heated above the LCST. Apparently in both cases, particles repel one another. This effect does not appear to be the simple consequence of introduction of charge to the polymers as many other charged surfactants bind to PNIPAAM and do not reduce precipitate size; moreover, a critical concentration appears necessary that decreases as the surfactants become more hydrophobic.[8,9] Nonetheless, this phenomenon deserves greater investigation because of its theoretical and commercial implications. In addition to thermal triggering, additives such as salts have also been used as the "switch" to precipitate the PNIPAAM conjugate.[157] The selection of the best salt (most effective precipitant) would consequently afford less overall perturbation of the materials being separated. Therefore the basic studies[36] previously mentioned have practical application.

Alternatively, Nguyen and Luong[158] adapted PNIPAAM to the standard two-phase partitioning technique used in biotechnology to isolate enzymes. Again the ability to separate the conjugated PNIPAAM by thermal precipitation permits easy enzyme recovery as well as PNIPAAM recycling. As biological systems are so complex with minute amounts of many components, again, being aware of the effects of each additive on the behavior of the PNIPAAM facilitates optimum design of a functional system.

In addition to immunoassays, functional PNIPAAM chains have been coupled with enzymes such as trypsin or cyclodextrin glycosyltransferase.[159] Tests indicate little decrease in enzyme activity following repeated precipitation (LCST manipulated by salt concentration again) and re-solubilization, indicating the suitability of such copolymers as supports for enzymes in homogeneous biocatalysis. Use of PNIPAAM in this manner has also been reported for gels (Section 4.3.2).

3.5.3. *Photosensitive* — Much work has been done by the research group of Irie[160] on manipulating diverse known phase transitions of polymers by attaching photosensitive groups and determining their ability to serve as a switch. Indeed they have copolymerized an azobenzene-based monomer capable of *cis–trans* photo-isomerization with NIPAAM.[25] There is a subtle balance in forces as this more hydrophobic comonomer (relative to NIPAAM) decreased the LCST upon incorporation as expected from discussions above (Section 3.4.2), but when the polymer is UV-irradiated into its more polar *cis*-form, the LCST increases as expected. Maximum elevation of the LCST found was ca. 6

degrees at 2.6 mol.% comonomer. Thus such an optical "switching" device for PNIPAAM precipitation is possible.

Photochemistry has also been examined with PNIPAAM copolymerized with ketones.[113] An increased quantum yield of chain scission was found in water compared with behavior in dioxane. This was attributed to stabilization of an intermediate. Viscosity measurements were used to monitor the solution behavior.

4. CROSSLINKED GELS

Research on PNIPAAM gels evolved rather independently from that on single chains; until very recently investigations have remained separate, even lacking cross-citations, thereby inhibiting the increased understanding of both systems through a lack of exchange of experimental and theoretical findings. The initial impetus for PNIPAAM gel research came from work done on transitions observed with polyacrylamide (PAM).[161] In 1979, Tanaka published[161] data that both PAM gels and single chains possess a collapse transition as one varies the composition of their mixed acetone–water solvent. Later work focused exclusively on gels; it uncovered early ambiguities, establishing that the presence of ionized groups on the polymer introduced either by copolymerization[162,163] or by hydrolysis[164] results in a discontinuous transition as compared to a continuous change in volume when they are absent. A mean field theory was derived[161–164] to explain the observed response. Subsequently, an anomaly was discovered: with NIPAAM substituted for acrylamide, even a nonionized gel exhibits a discontinuous transition in aqueous media, either upon heating or upon addition of DMSO[50] to aqueous solutions. The mean field theory was slightly modified; it was proposed that NIPAAM resulted in stiffer polymer chains than those with AM and thus has the same effect as ionization in extending the gel chains. However, as we discussed in the synthetic section of this review (Section 2.2.1), in retrospect, this finding may be claimed to be coincidental as it has been purported that the selection of the initiator system determines the sharpness of the transition,[30,55] possibly by supplying ionized groups. But even this hypothesis does not seem universally true as mentioned previously. This section will focus on the basic and applied studies of PNIPAAM gels. It will attempt to summarize the salient points as well as to inter-relate these investigations to single chain phenomena.

4.1. *Experiments*

4.1.1. *Binary system* — The various methods of preparing PNIPAAM gels are related in the synthetic section (Section 2.2.1). If a macroscopic product is obtained, it is typically sliced into smaller pieces for more convenient handling; afterwards, it is equilibrated in the desired media at a carefully controlled temperature. A number of techniques have then been applied to observe the

LCST collapse transition of PNIPAAM gels. The first method applied,[50] following the volume change by microscopy, still appears to be the most popular method.[6,29,42,43,55,57] However, weighing gels "drained" on stainless steel screens[53,54] or "blotted" with filter paper[44,49] has alternatively been done to monitor differential swelling; however, one could claim such gravimetric techniques to be less reproducible. Gels have also been sealed in graduated cylinders in their solvent, and then immersed in external baths so that dimension changes could be followed by a cathetometer, an instrument that detects small differences in the height of a column.[54]

If one synthesizes submicron beads, dynamic light scattering can be used to follow the size change.[60–62,165] In one study, ionic gels thus synthesized did not exhibit the expected discontinuous transition that occurs in ionized PNIPAAM bulk gels[60] (see Sections 2.2.1 and 4.1.3). The Tanaka group claimed this was a result of surface inhomogeneities, amplified in small beads where the surface to volume ratio is very large compared with other geometries. Therefore the distribution of different transitions detected is averaged along the surface, and hence appears to be a continuous curve.

The collective diffusion coefficient was found to be discontinuous at the LCST.[61,62,165] Microscopy has found interesting pattern formation on the surface of the beads, explained as a result of a differential swelling response of the inside and outside layers of the gel.[165] Such phenomena depended on whether the shrinking or swelling process was being observed.[61] Spinodal decomposition experiments have also been reported.[166–167] These purportedly show that the gel transition can be fitted by Cahn–Hillard theory as the authors also claimed was possible for single chains;[37] they also demonstrated that poly(*N*-propyl acrylamide) gels[168] spinodally decompose faster than those based on NIPAAM. This was claimed to result from the former polymer's greater hydrophobicity as is also reflected by its lower LCST[6] compared to PNIPAAM. This is an interesting finding that should be independently confirmed.

Very recently, exploring the area of gel kinetics, Kabra and Gehrke[169] have synthesized "fast response" PNIPAAM gels. These are created through initiating polymerization of NIPAAM at a temperature below the polymer LCST in aqueous solution; however, just prior to gelation, the sample is heated above the LCST, yielding a milky latex. The net result is an opaque, porous gel due to the gelation "freezing in" the spinodally phase separated solution. As a result, increased surface area is exposed to the aqueous media. Consequently, the rate of collapse is 3000 times faster, and subsequent swelling is 120 times faster, than that for standard PNIPAAM gels. This technology was reported as an extension of studies done with poly(vinyl methyl ether) (PVME) gels by Hirasa.[169] PVME also possesses an aqueous LCST as will be discussed in Section 6.1.

At the Fall 1991 American Chemical Society (ACS) meeting, Hoffman and coworkers independently presented an improvement on this system. If hydroxypropylcellulose (HPC) is introduced into the reaction mixture and the mixture

is polymerized above the LCSTs of both HPC and PNIPAAM, the precipitated particles (exhaustively extracted afterwards) cause the pores to be even larger. Therefore even faster shrinking rates as well as higher swelling ratios are observed compared to gels created in the absence of HPC. These authors also quote Hirasa as the source of their inspiration. We would like to note that there appears to be no reason why PNIPAAM itself could not be used as the added LCST polymer, perhaps decreasing the necessity of extracting all of the LCST polymer.

Two groups[42,171] have used gel swelling experiments in connection with Flory theory to calculate an interaction parameter (χ) for the PNIPAAM/water system. Both found that χ changes from less than 0.5 to near 1 upon heating through the LCST as qualitatively expected from theory. This provides useful data for theoretical calculations as will be discussed in the next section.

Hirotsu and Onuki[30] have discovered that uniaxial tension increases the LCST of a gel, and makes the transition more discontinuous. The experimental design used was not simple and straightforward, yet this observation is an expected consequence that can also be explained by a Flory-type theory. Further viscoelastic studies[172] have additionally revealed transitions of moduli and Poisson's ratio at the critical point. Even more recently, anomalies in Poisson's ratio near the critical point have been investigated.[173] Other researchers have done more simplistic measurements[171] to estimate an effective crosslinking density for the network.

Two other techniques used to study the gel transition are DSC[29,171] and NMR.[52,138] The former technique obtained equivalent transition temperatures to those obtained with volume measurements, just as DSC complemented cloud point tests for single chains. Moreover, the fact that the enthalpies were similar to those for single chains (Section 3.1.2) suggest analogous driving forces for both systems.

The application of NMR to diverse problems in polymer science has been reviewed; gels have been a particularly interesting application since NMR can probe their mobility.[174] The first NMR study of PNIPAAM gels[52] reported applied solid-state ^{1}H NMR with magic angle spinning. Fast spinning was seen to narrow line widths at constant temperature, a typical finding for this sort of experiment,[174] resulting from the averaging of the various species in the system. Above the LCST, excessive line broadening occurred relative to below the LCST. At 50°C, no lines were visible, indicating that solvent-induced mobility is progressively attenuated with increasing temperature. Thus this is a rather elaborate demonstration of the fact that polymer–polymer contacts are preferred to polymer–solvent contacts above the LCST.

Tanaka and his research group[138] utilized NMR in a different manner for the gel system with more information-rich experiments. Again using proton NMR but without magic angle spinning or any other modifications, they observed very noticeable broadening relative to solutions of free chains. After all the

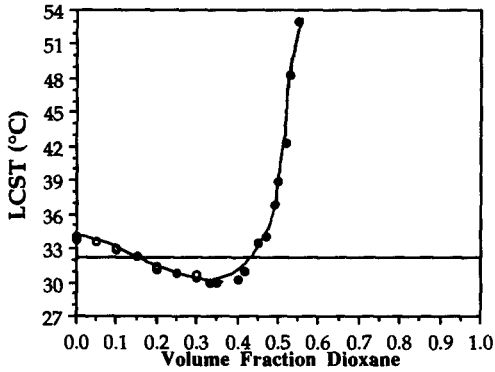


FIG. 12. Phase diagram for PNIPAAM (0.4 mg/ml) in water–dioxane mixtures.

existing peaks "disappeared" upon heating through the LCST, they observed a new broad peak at 7.9 ppm, a finding unlike the first study above. However, Tanaka claims that this peak takes a long equilibration time in order to be detectable. The Tanaka group assigned this peak as the signal from solid polymer; this was confirmed by showing its similarity to the spectra of dried polymer. Relaxation times were also measured; whereas the mobility of backbone protons were not appreciably changed above the LCST, the methyl groups of the *N*-isopropyl group have a large decrease in mobility with increasing temperature. Being that the LCSTs of various poly(*N*-alkyl acrylamides) change with different pendant groups, one would agree that this result is quite logical.

4.1.2. *Additives* – When they first reported the LCST of PNIPAAM aqueous gels,[50] the Tanaka research group also reported and subsequently published in greater detail[43] a "re-entrant phase transition" observed with the addition of DMSO. Upon increasing the volume fraction of DMSO at constant temperature below the LCST, the gel first collapsed and then re-expanded at higher DMSO content. The Tanaka group claimed that the phenomenon was a consequence of the free energy of contact between polymer segments not being a monotonic function of DMSO content. The two solvents' attraction for one another dominates at the middle of the phase diagram, promoting a greater number of polymer–polymer contacts, and hence collapse.

In the single chain section (3.3.1), a phenomenon called cononsolvency was discussed; it can also explain the origins of this gel response. Indeed, dioxane has the same effect on the LCST of PNIPAAM chains: it lowers the LCST to a minimum and then suddenly raises it (Fig. 12).[33] As one can see, at constant temperature as shown by the illustrated horizontal slice, this cross-section is equivalent to a solution becoming precipitated then redissolved as one adds dioxane to an aqueous solution of PNIPAAM. This can also be simply experimentally demonstrated. Therefore there is correspondence between these results

for single chains and the Tanaka result above for gels.[43] Moreover, Saito and coresearchers[29] have done the heating experiment with PNIPAAM gels in DMSO/water and obtained the same qualitative result for the collapse temperature as was obtained with single chains; indeed, looking at their phase diagram at constant temperature, one can also obtain the Tanaka[43,50] isothermal results. However, Saito and coworkers failed to comprehend the significance of their results in view of the literature.

Greater research has been done on the PNIPAAM gels in methanol/water; again, it is interesting to note that the Saito research group[29] simply reports a slight depression of the collapse transition at low methanol content and ignores the observations of previous researchers. Both Hirotsu[42,55] and Tanaka[175] reported 2–3 years earlier that the methanol/water solvent also causes PNIPAAM gels to go through a re-entrant transition; this is evident only when the entire phase diagram is examined. Hirotsu[42] calculated the χ parameters between PNIPAAM gels and alcohols; these parameters are temperature-independent and less than 0.50, supportive of the observation of no collapse transition in these binary systems as opposed to the critical transition in this interaction parameter reported for PNIPAAM gels in water (Section 4.1.1).

In order for this re-entrant phenomenon to still be explained by the mean-field theory that he derived for the binary system, Tanaka[175] concludes that PNIPAAM needs to change the interaction between methanol and water from a repulsive to an attractive interaction. As Schild and Tirrell[33] noted, such a proposal is unreasonable and elucidates deficiencies in this theory as will be discussed shortly (Section 4.2.1).

Thus by introducing the same additives into both gels and single chains, it is possible to gain greater understanding of both systems. Other similarities in responses of PNIPAAM single chains and gels to additives have been observed. It has been reported that SDS surfactant "suppresses" the LCST of PNIPAAM gels[52] at 1%. Below the CMC (0.3%) at 0.1 and 0.2% SDS, the NMR spectra are reported as "to a large extent" resembling those of surfactant-free polymer. Knowledge of the studies of Schild and Tirrell[8,9] would certainly have enabled thse authors[52] to better design their experiments so they would not incorrectly conclude that the LCST is an "off/on" phenomenon, but that the transition temperature is shifted with increasing additive content.

A further comparison is possible with Hirotsu's work:[55] he showed that adding PAM to aqueous PNIPAAM gels also causes the collapse transition. This effect was claimed to result from an *external* osmotic effect: the large PAM chains are assumed to be unable to penetrate the PNIPAAM gel. However, Schild and Tirrell[128] achieved a similar effect with mixtures of single chains of PNIPAAM and PAM (Table 7), indicating that exclusion effects are not a necessary condition for the gel system. Schild and Tirrell observed a 0.4°C depression of the LCST of linear PNIPAAM with a similar amount of PAM as in the gel experiment. Such a polymer-induced coil–globule transition has been

TABLE 7. Interactions of polyacrylamide with PNIPAAM chains and gels

PNIPAAM	PAM Chains	Transition Temperature (°C)
Chains (0.4 mg/ml)[29]	–	34.0 ± 0.1
Chains (0.4 mg/ml)	3.6 mg/ml	33.6 ± 0.2
Gel[53]	–	33.60 ± 0.05
Gel	3.3 mg/ml	33.40 ± 0.05

theoretically and experimentally explored by Tanaka and Ushiki.[176] Interestingly, both sets of observations can also be explained through a much simpler approach using relative interaction parameters and the "$\Delta\chi$" effect discussed by Patterson.[177,178] His general finding is that two chemically similar acrylamide polymers may form a phase separated solution in a solvent to which they have a difference in affinity: polyacrylamide is certainly more water-soluble than PNIPAAM which has a hydrophobic *N*-isopropyl group. The interpretations of Tanaka and Patterson can be considered equivalent; Flory originally treated both single chain expansion and gell swelling as a balance of the free energy of elasticity to that of mixing.[179] Clearly, phenomena are best understood through examining them from complementary perspectives as will be continued to be stressed in the theoretical section (Section 4.2.1). Thus the gel and single chain phenomena both appear to derive from competitive solubilization and not simply from a "mechanical" exclusion effect.

Approaching the study of additives and PNIPAAM from a different perspective, Saito and coworkers[56] measured diffusion coefficients (D) of electroactive potassium octacyanomolybdate by cyclic voltametry in various media. Upon adding free PNIPAAM chians to the solution, the diffusion coefficient of the small molecule was lowered relative to its solution value in buffer alone. When PNIPAAM gel was "coated" onto the electrode, D was decreased even further relative to that in the presence of free chains. The lowest diffusion coefficient was found when the temperature exceeded the LCST of the gel. These results are rather intuitively obvious; nonetheless, they certainly afford a different way to study PNIPAAM.

Multiple solute experiments have been conducted by the Tanaka group.[180] They synthesized a PNIPAAM gel with mechanically entrapped Concanavalin A, which has selective binding affinity for saccharides. Subsequently, they first added the sodium salt of dextran sulfate (DSS) to the system. The gel was thus swollen by ionic repulsion of the species bound inside; consequently, the LCST increased, and the previously discontinuous transition became continuous. This last observation might not be intuitively obvious as "ionizing" the gel has thus far been seen to have the opposite effect (Section 4.1.3); the authors again claim that results are indicative of a nonhomogeneous distribution of the species in the gel which then leads to a distribution of 'local' transition temperatures. By replacing the DSS by a nonionic saccharide through competitive displacement,

the gels deswelled close to their original dimensions. The nonionic complex clearly has less of a perturbation on the LCST of the PNIPAAM, in accord with all the findings previously cited for single chains and gels. Thus it is possible to switch the LCST transition by displacing one additive in a gel with another. This offers much promise for feedback systems in biological applications as will be described (Section 4.3.2).

Tanaka, in collaboration with Kokufata,[181] has even established such a feedback loop using a gel with immobilized enzyme, liver esterase. The LCST was observed to decrease as the enzyme hydrolyzed added ethyl butyrate into ethanol and butyric acid. Thus the *in situ* conversion of additives can also trigger a change in the perturbation of the LCST as the identity of the species changes. Thus whereas in some cases the presence of additives may hinder gel performance, in other systems it serves as the driving force for the application.

4.1.3. *Copolymers* – Whereas NIPAAM has been copolymerized mainly with hydrophobically modified comonomers for use in single chain studies (Section 3.4), ionic groups have been the preferred functionality incorporated for comonomers in gel investigations. The early work of Tanaka with PAM[161,182] demonstrated that introducing ionic groups leads to more discontinuous transitions; this effect was explained as a consequence of increased osmotic pressure through Flory–Huggins theory. These researchers extended such studies with PNIPAAM, copolymerizing with sodium acrylate (SA).[57] Continuous transitions became discontinuous coincident with higher LCSTs and greater swelling. The last two observations are expected to occur as a consequence of the greater hydrophilicity of ionic groups; the origins of the discreteness of the transition have been debated (Section 2.2.1). Re-entrant (i.e. cononsolvent) phenomena with added organic solvents are still detected[43,175] with ionic groups present, indicating no interference with this interaction. NMR by the Tanaka team[138] concluded that ionic PNIPAAM gels are not homogeneous like homopolymer PNIPAAM gels but have both stiff and mobile portions. Thus it appears that there are two independent domains present in a PNIPAAM copolymer gel, as has also been proposed for other ionomeric polymeric structures.[183]

The Prausnitz research group also copolymerized NIPAAM in gels with ionic comonomers; both cationic (2-(dimethylamino)ethyl methacrylate[51] and methacrylamidopropyltrimethylammonium chloride[184]), and anionic (SA) units were used. Their observations of an increased water capacity (increased swelling) and increased critical transition temperatures with greater incorporation of ionic groups concur with similar results from the Tanaka group.[175] However, both cationic gels exhibited only continuous transitions and even the SA-containing gel showed a discontinuous transition only at pH 5. The Prausnitz group acknowledged this discrepancy with the Tanaka results, and suggested that the structural nature of the comonomer may be the deciding factor.[184] They noted

that anionic groups derived from a NASI-type comonomer yielded a gel with continuous transitions, but as mentioned above, the authors there attributed their findings to the small size of the beads.[60] Much larger beads were found to have a continuous transition but the comonomer was also changed to SA in that case so the issue is unresolved.

One must also note that the Prausnitz technique of gravimetric measurements differs from the microscopy done by Tanaka's group.[57] Finally, the Tanaka group never mentions pH in their papers.[57] Prausnitz and coworkers have found the expected results of greater swelling when the degree of dissociation is increased, and hence when the charge is high, respectively at high and low pH for anionic and cationic comonomers. They have also shown that increased ionic strength (even to just 0.1 M) removes the added swelling advantage of ionic gels.[51] Thus they found that the LCST can be shifted in these ionic gels by changing the pH, giving greater flexibility in tailoring properties for particular applications. Moreover, ionic groups are often also useful for incorporation into the gel for specific solute binding as will be mentioned (Section 4.3.2). In contrast, Tanaka has also not reported ionic strength studies.[57]

In an extension of the above work, Hirotsu applied a dc electric field to ionized PNIPAAM gels.[185] Volume changes could thereby be induced, apparently as a consequence of migrating ions. Various field strengths were found to either stabilize the shrunken phase or induce oscillations. Clearly, this makes diverse applications for electronic switching devices feasible.

From the perspective of using nonionic comonomers, other *N* and *N,N'* substituted acrylamides have been made into gels,[6,171,186] in a similar approach as with PNIPAAM (Section 3.4). Quite simply, polymers that possess single chain LCSTs also have gel transitions at similar temperatures when synthesized with a crosslinker present. Collapse was not detected in the *N*-ethyl derivative, but that was simply because the authors heated it to only 60°C, unaware that its LCST is ca. 74°C.[81] The PNIPAAM gel was claimed to have a sharper and greater collapse[138,185] compared to the other polymers tested.

As will be further detailed (Section 4.3.2.1), IPN gels[186,187] have also been made from PNIPAAM. The magnitude of deswelling is decreased relative to results with PNIPAAM by itself as a consequence of the presence of the second network; however, the transition temperature is unperturbed. Thus an "inert" polymeric component appears to have little effect on the LCST itself when not covalently incorporated.

4.2. *Theory*

4.2.1. *Basics* — Theoretical models derived to explain the origins of the LCST of PNIPAAM single chains were presented in the previous chapter (Section 3.2). The best efforts qualitatively surmised that both so-called hydrogen bonding

and hydrophobic effects contribute to the driving force for the transmission. In the realm of gel transition theories,[30,57,108,140,141,143,183,188] much more modelling has been done, with at least as many differences in assumptions, if not more, compared to the single chain work. All of these gel theories basically contain four terms reflecting the changes in free energies of mixing, elasticity, osmotic effects, and specific interactions for a gel in aqueous media. There is little disagreement on the description of osmotic effects which exist when there is ionic charge in the system: Donnan equilibria are consistently used. However, the expressions of the other three contributions to the free energy used vary from theory to theory. The "worst" models use Flory–Huggins theory for the free energy of mixing; this is poor not only because random placement of species is assumed, but also since the lattice is assumed to have no holes, i.e. it is incompressible. Clearly neither of these conditions exist with a gel in aqueous media.

Various theories derived for describing rubber elasticity were used to introduce the elastic term; the earliest Flory theory that some of the authors apply is simply too ideal. It does not hold when the gel is swollen; moreover, the theory also unrealistically assumes that the distributions of chains are Gaussian. Furthermore, the model does not account for the chains being finite or taking up space, thus introducing more physical impossibilities. Some of the models described below apply more sophisticated theories that have been developed but these have additional adjustable parameters, leading to a more tenuous connection with reality.

Finally, where specific interactions between polymer and solvent molecules are defined, there are approaches that assume only hydrogen bonding exists,[143] and those that assume only hydrophobic bonds occur.[141] These are rather arbitrary decisions as one may wonder that by simply changing the names of the mathematical expressions, one may easily come up with the same result for a different molecular force. With such caveats, we will discuss what theoretical studies have uncovered.

The earliest predictions of PNIPAAM gel collapse were from Hirotsu *et al.*,[57] their simplistic approach incorporates the Flory–Huggins mixing term and ideal elasticity into the free energy expression. As Cussler and coworkers noted,[108] this theory cannot predict discontinuous transitions for nonionic gels: this contradicts Tanaka's own experimental results.[50] Furthermore, the best fitting parameters were very different from the ones estimated as physically realistic by the authors.[57] These results are not unexpected considering the comments made previously.

For the two solvent case of methanol and water, both Hirotsu[30] and Tanaka[174] extended their theory by using the single liquid approximation (SLA), which assumes that the solvents are randomly mixed and no selective absorption to the polymer exists. They consequently predict that the change in free energy of mixing (ΔG) of the methanol and water must have been transformed from a

positive (repulsive) value to a negative one as a consequence of modulation of interactions by the polymer. Thus they discuss that various complexes must exist between the components in the media, and conclude that PNIPAAM enhances interactions between water and methanol. However such conclusions contradict the original assumptions for the model: Flory–Huggins approaches require a random distribution of units and cannot describe an ordered system that would result from such complexation. Since when do scientists obtain a conclusion that contradicts the assumptions of the model, and maintain that the conclusion describes the system? Schild and Tirrell[33] also calculated that the same positive ΔG is necessary for Flory–Huggins theory to hold for single PNIPAAM chains in two solvents; however, they did not accept the results, recognizing that it is a physically implausible situation.

As was discussed in the single chain theory section (Section 3.2), Prausnitz and coworkers[143] have developed a theory based on hydrogen bonds in a lattice that permits holes and thus compressibility. This overcomes the deficiencies of Flory–Huggins theory; however, Guassian chains are still assumed, and therefore it is difficult to fit experimental results with a single set of parameters over the entire range of swelling. However, the theory does correctly predict discontinuous transitions for nonionic gels. In a subsequent paper where they discuss results with charged gels,[184] the Prausnitz research group introduced an improved elasticity term based on constrained junctions. This theory actually predicts ionized gels to have discontinuous transitions as well; this is in accord with the Tanaka group's experiments,[57] but not with the Prausnitz group's own observations! (Section 4.1.3.)

Cussler and coresearchers[108,140,188] overcame the deficiency of using a lattice-based mixing term; instead an equation of state approach was applied that also permits compressibility. They derived an interaction energy from the various cohesive energy densities in the system which fit the experimental results. In addition, they noted that neither the Hirotsu/Tanaka[57] nor Prausnitz[143] approaches will predict pressure dependencies of gel swelling they have experimentally observed.[140] But their own model, although sensitive to the fact gels swell under pressure in an attempt to increase entropy, overpredicts this effect. They suggest they can compensate for this result by introducing specific hydrogen bonding interactions into their system.

The Saito research group[141] ignores most of the work so far cited. They assume the mixing term is a viral volume interaction; an elastic expression that accounts for the limits of elongation is also incorporated. However in sharp contrast to the workers above, they claim the entire interaction term is derived from hydrophobic crosslinks:

$$\Delta G = C_a + C_b T + C_c T^2.$$

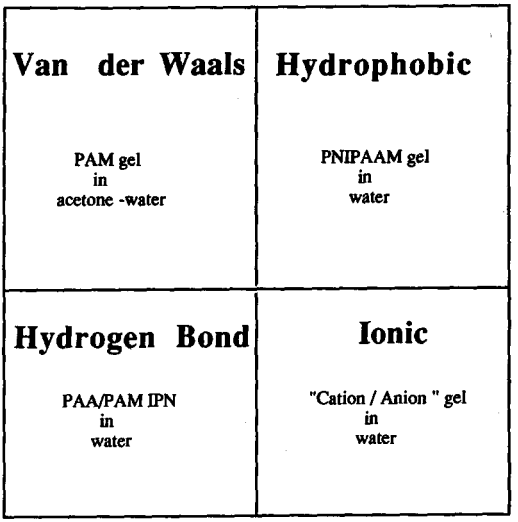


FIG. 13. "Universal" classification of gel transitions.

They then successfully predict continuous transitions that become discontinuous upon ionization, yet use several adjustable parameters to achieve this "victory".

With such diversity among theories, it appears clear that a theoretical explanation of the LCST of PNIPAAM, whether as a gel or as single chains, is far from complete. Better experimental characterization of the networks needs to be done so more realistic elastic effects can be fitted. Mixing terms that account for nonrandom distributions of molecules need to be applied. As for the nature of the specific interaction, the general concept of hydrogen bonding versus what exactly are hydrophobic forces is still being debated. Hopefully, data from PNIPAAM systems can aid in resolving the debate. Even the issue of whether nonionic PNIPAAM gels experimentally and theoretically possess discontinuous transitions is still unclear. As we have been remarking, the effects of initiator residues are unresolved. The proper control experiments comparing nonionic indicators such as AIBN to redox pairs under the same controls need to be done.

4.2.2. *Universality* — Ilmain *et al.* recently presented[189] evidence of a volume transition in a poly(acrylamide) (PAM)/poly(acrylic acid) (PAA) interpenetrating network (IPN).[190] This phenomenon was claimed to be the first polymer gel transition driven independently by hydrogen bonding; moreover, the authors also presented a general scheme with examples (summarized in Fig. 13) of four types of gel volume phase transitions induced by four biologically relevant

intermolecular forces, each of which they stated may be *independently* responsible for the discontinuous transitions. It is highly pertinent to assess the validity, uniqueness, and generality of their findings as PNIPAAM gels were among those discussed, and were classified as being driven independently by hydrophobic bonding in sharp contrast to the proposals above. This attempt at a "unified theory of gel transitions" (Fig. 13) is too idealistic, as will be supported by the analyses below of the assignment of each of the four forces to the four systems. Foremost, it is difficult to believe that the gel transitions in the example systems shown are "purely" derived from the independent forces indicated. Thus although the experimental findings appear to be real and are indeed interesting in their implications, the theoretical explanation for the phenomenon in general lacks sufficient support.

First, one can examine the validity of classifying the PAM/PAA IPN as driven only by hydrogen bonding. Morawetz[191] has done a study of complexation of PAA with a copolymer of acrylamide (AM) and *N*,*N*-dimethylacrylamide in which he assumes the weaker interactions of AM units with PAA are negligible compared to those of the latter acrylamide. In addition, he found that the pH must be at least as low as 3 for interaction of AM-rich copolymers with PAA. Ilmain *et al.* make no mention of pH in their report.[189] Moreover, Morawetz criticizes[191] "zipping mechanisms" such as that proposed by Ilmain *et al.* As we noted,[190] the previous references to this system are not well established, but we can safely assume that complexation does occur.

A further supposedly novel characteristic of the PAM/PAA IPN system is that the swelling is induced by an increase rather than a decrease in temperature, purportedly as a result of breaking the hydrogen bonds of the complex. Klier *et al.*[192] have reported on self-associating networks of poly(ethylene oxide) (PEO) and PMAA. This would be considered a "hydrophobic gel" under the definitions given[189] by Ilmain *et al.* However, it is purported[192] that both "hydrogen bonding" and "hydrophobic effects" are operative: this issue will be discussed below. In their introduction, however, Klier *et al.* reference work by Nishi[193] from the early 1980s concerning PAA/PEO networks that do swell with an increase in temperature. These "hydrogen-bond gels" are essentially a previous example of the "novel" finding of Ilmain *et al.*

In another review "missing" from the paper,[189] Osada[194] describes the general class of chemomechanical systems. Volume changes caused by transitions in polymer association are employed on a macroscopic scale to do work. Here, also, a PEO/PMAA membrane is described that contracts with increasing temperature (from hydrophobic effects) but changes to an expanding system if ethanol is added thereby making "hydrogen bonding effects" predominant. From our previous discussions, we propose that these findings are indicative of the presence of cononsolvency (Sections 3.3.1 and 4.2.1) in the system.

Experimentally, Ilmain *et al.*[189] used urea "to confirm the involvement of hydrogen bonding" and also claim that "urea did not alter the phase behavior"

of a copolymer gel of acrylic acid and *N*-isopropylacrylamide (NIPAAM). First, urea has been claimed just as often to be a "hydrophobic bond breaker".[98,195] Second, given that urea has a large effect on the solubility of linear PNIPAAM chains,[17,29,197] it is difficult to believe that it would not affect a PNIPAAM copolymer gel given the similarity of responses of gels and single chains to additives.[29,33] Thus one cannot use non-response to urea as a proof that hydrogen bonding is the only involved force; moreover, the two molecules do interact. Additionally, Ref. 16 in the authors' own paper[189] states that PAM forms complexes with PMAA (here substitute PAA since we are only discussing the functional group) not only through hydrogen bonding but also through ion–dipole interactions between partially protonated amide groups of PAM and the carboxylic groups of the polyacid.

In regard to Ilmain *et al.* classifying the polyacrylamide/acetone/water system as a Van der Waals gel,[189] several factors must be considered. For example, why is polyacrylamide soluble in water? Dissolution is driven by hydrogen bonding between the amide group and water as has been thermodynamically proven.[198] Removal of the amide group eliminates water solubility: polyethylene is not water soluble! How then is the transition modulated by much weaker van der Waals forces? As for the role of ionic interactions, the authors themselves comment[189] that they observe *discontinuous* transitions only with the presence of osmotic forces due to ionized gels, thereby partially refuting their own claim. The acrylamide system as well[199] was clearly shown to exhibit only continuous transitions when lacking ionized units.

As we stated above, the origin of "hydrophobic effects", that is the aggregation of nonpolar molecules in aqueous solution, is still a debated issue (Section 3.2). Arguments range from returning to the original concept of "like dissolves like",[101] that hydrophobic molecules attract one another, to beliefs that water and hydrocarbons attract one another but that the water prefers hydrogen bonding to itself thereby hindering hydrocarbon molecules from entering the solution.[100] Thus if the hydrophobic effect is a result of the state of hydrogen bonding, then the former force cannot be independent of the latter. Indeed, Israelachvili[200] defines the hydrophobic effect as occurring between "water molecules and molecules like alkanes incapable of forming hydrogen bonds . . ." Furthermore, theoretical calculations use only "pure" examples such as methane molecules since when two or more interactions are simultaneous, one cannot apply simple potential functions.[200] Hence, it seems untenable to claim that polymers containing both polar and nonpolar groups possess transitions driven by a single force; others have concurred with this view.[192]

As Morokuma[201] has emphasized, based on electron density calculations on the origins of molecular interactions, sweeping generalizations as to which energy components are dominant should not be made. Claiming *independent* responsibility for transitions as Ilmain *et al.*[189] have attempted is ill-conceived. Whereas one can concede that in highly ionic systems, such ion–ion interactions

should dominate, from the data amassed in this review, it seems more believable that the PNIPAAM and PAM systems in Fig. 13 are driven by both "hydrogen bonding" and "hydrophobic effects". For the PAM/PAA IPN, while hydrogen bonding clearly exists, it has not been proven to be the sole driving force. Thus, although the work by Ilmain *et al.* is an excellent experimental result to add to accumulated data on the diverse configurations of systems with aqueous transitions, their theoretical efforts are a bit too idealistic.

4.3. *Applications*

The ability to construct PNIPAAM gels of diverse geometries has led to a myriad of applications which exploit the change in gel dimensions to modulate the differential diffusion of species in a medium. Thus it has been possible to selectively remove,[53,54,58,202,207] and deliver[44,45,49,155,179,186,187,208–215] consolutes with thermal-switching control. Industrial separations processes[53,54,58,202–207] will be discussed first (Section 4.3.1), followed by biological operations[44,45,49,155,179,186,187,208–215] (Section 4.3.2). Many of the systems described have already been patented.[63,64,203,206,207] Finally, the ability to assemble gels with a dual photo- and thermal-switch will be presented[46,47] (Section 4.3.3).

4.3.1. *Separations* – The research group of Cussler at the University of Minnesota has been rather prolific[53,54,58,202–204,207] in applied research on PNIPAAM gels, a different perspective from much of the basic research cited above. Figure 14 shows a flow chart of their separation process. Essentially, they realized that if a gel is placed into an aqueous solution with other cosolutes (Step I–II), when the gel swells, very large cosolutes such as macromolecules will be excluded from entering the gel pores by steric hindrance and small consolutes will freely penetrate the network. Therefore, if one subsequently removes the gel (Step III), the solution of large molecules left behind is now more concentrated (the raffinate). The efficiency for such a process is defined as:

$$\frac{[\text{measured increase in concentration in raffinate relative to feed}] \times [\text{raffinate volume}]}{[\text{initial solution volume}]}.$$

Thus if the concentration doubles when the volume is halved, then the efficiency is 100% since the solute has been left behind, entirely non-absorbed by the gel. But if the original and final concentrations remain the same, efficiency has been 0% in concentrating the solute.

Alternatively, if the small molecules (or "clean" water), deemed the extractant, are of interest the removed gel can be placed into a warmed (above LCST) solution to recover them (Step IV–V), effectively carrying out a size separation purification. In any case, this step is performed to recycle the gel for another separation, an advantage since many other separations systems did not succeed commercially because devices had to be discarded after use. Cussler calls his

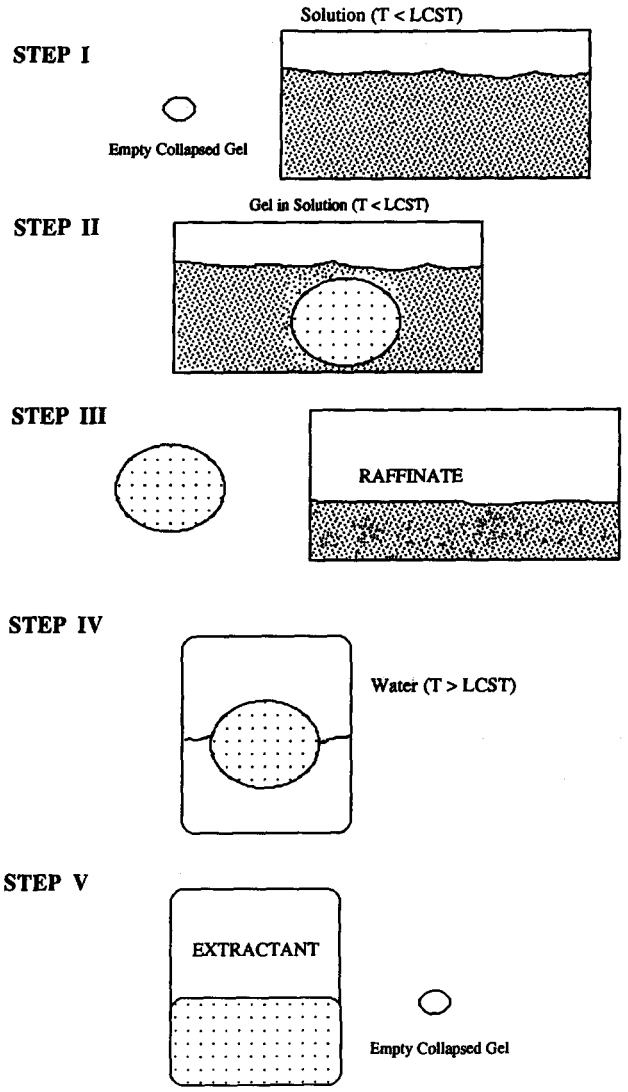


FIG. 14. Flowchart for PNIPAAM gel separation process.

system a "size-selective extraction solvent"; it thus serves as an alternative to ultrafiltration techniques.

Originally, the Cussler group[207] used pH-sensitive hydrolyzed polyacrylamide gels following the Tanaka group[165] that first investigated PAM transitions prior to those of PNIPAAM. In this case, the anionic gel swells at high pH; afterwards, the gel is removed, and recycled by placing in water at low pH. High

TABLE 8. Gels in separation processes[51]

Solute	Molecular weight	Gel efficiency (%)
Urea	60	2
Sodium pentachlorophenolate	240	18
Vitamin B-12	1355	32
Ovalbumin	45 000	97
Blue dextran	2 000 000	97
Poly(ethylene oxide) glycol	400	10
	3 400	30
	8 000	56
	18 500	80
	600 000	96

efficiencies were found for species greater than 3 nm in diameter such as proteins and synthetic polymers that included polystyrene latexes. However, only negatively charged or neutral species could be separated. The fact that cationic proteins such as lysozyme precipitated on the gel was clearly a limitation.

Subsequently, PNIPAAM gel particles were applied.[53,54] As Table 8[53] shows, the efficiency of concentrating the raffinate is again a function of the molecular weight of the species. Thus the gel is a simple filter; as expected, higher crosslinking densities yield increased efficiency. However, as crosslinks are randomly distributed, there is no abrupt cut-off at an exact molecular weight. Additionally, without the benefits of the ionic gel's ability to exclude like-charged solutes through Donnan exclusion in addition to the constraints of gel mesh size, efficiencies are lower for small charged solutes relative to those for the first set of gels.[207]

Nonetheless, these PNIPAAM gel particles have commercial potential as they are able to absorb up to thirty times their dry weight in water.[54] Indeed, such systems have been patented[202] as an inexpensive alternative to ultrafiltration. However, in the cases where the small solutes removed with the gel are valuable, dropping the gels in warm water to recover them inconveniently dilutes them further. Therefore Cussler changed the geometry to flat gel sheets bonded to polyester with a hydrophobic polyethylene coating on the opposite side.[58] Then either by using single sheets or stacking them in a "plate-and-frame" device, handling becomes more convenient. Ports lead to both sides of the latter device's surface; these facilitate charging with solutions and also with water for regeneration.

The Cussler group has additionally patented[203] and published[204] a system for removing low molecular weight contaminants from soy protein. Thus a dried, particulate gel was mixed with a protein extract of defatted soy flakes (isolated under mildly alkaline conditions). It was incubated at 5–10°C until swelling was complete[203] and then the gel was removed. The product isolated from the raffinate was more than 90% protein; the yield was greater than 80%.[204] Soluble

TABLE 9. Various schemes of drug delivery with PNIPAAM gels

Process	Loading	Release
1	T < LCST	T < LCST
2	T < LCST	T > LCST
3	Dried	T > LCST
4	Dried	T < LCST

carbohydrates, minerals and other solution components were removed from the gel by washing it with warm water so it could be reused in this batch process.

Other researchers have patented two other systems that use PNIPAAM gels for removing undesirable materials. Nippon Steel Corp. has developed an approach[205] to remove water from gasoline or fuel oils by adding polymers in the PNIPAAM family as adsorbents. The ability to recycle the materials by heating the gels above their LCST between separation steps reduces expenses. Polymers in the PNIPAAM class have also been crosslinked into fibrous materials for use as a urine absorbent.[206] Incorporated into bed pads, the polymeric composite can be washed and reused in a similar recycling process to those already discussed.

4.3.2. *Biology*

4.3.2.1. Drug Delivery – The application of synthetic polymer systems for drug delivery devices has been of increasing interest, as reviewed recently by Heller.[216] Changes in swelling states of PNIPAAM gels can influence the diffusion of solutes from within the gels to the outside aqueous media.[44,45,49,155,179,186,187,208-211] Several different methods[155] can thus be envisioned: these are summarized in Table 9 and schematically illustrated in Fig. 15. The fact that the LCST of PNIPAAM-type gels can be adjusted to near human body temperature (37°C) by copolymerization and using additives as previously discussed (Section 3.3) further makes them viable for *in vivo* applications. Whereas diffusion processes 1 and 3 in Fig. 15 are proposed to be Fickian,[155] process 2 relies on the pressure generated during gel collapse to squeeze out the drug. Less research has been reported on process 4.

Hoffman and coworkers have developed a process 2 system that delivers vitamin B12, myoglobin or methylene blue.[44,208] A collapsed PNIPAAM gel was incubated in a cold (4°C) solution of one of the preceding "biomolecules" overnight to maximize loading of the PNIPAAM network with "drug". Then release was studied by placing the gel in a solution heated above the LCST (50°C); the diffusion of the "drugs" into the external solution was monitored using UV spectroscopy. Release kinetics showed a two stage process: an initial rapid release is followed by a much slower diffusion of "biomolecule". It was

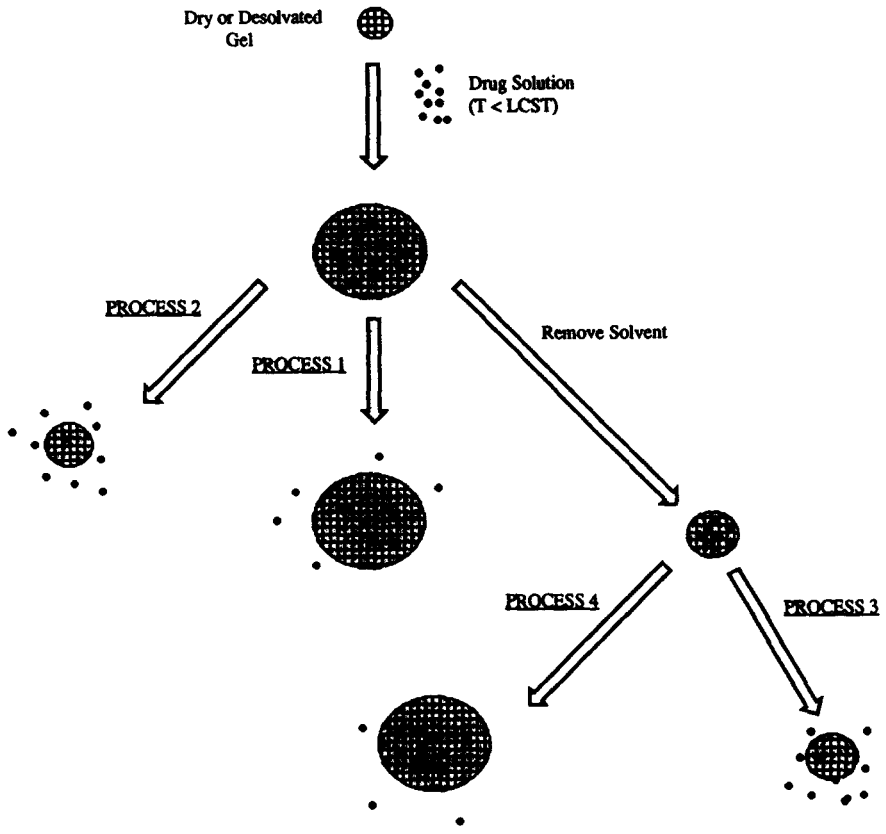


FIG. 15. Various schemes for PNIPAAM in drug delivery.

hypothesized that as the gel begins to collapse, the initial deswelling hydrostatically "pumps" out drug. However a "thick skin" then quickly forms at the interface of the gel with the aqueous solution as this region is the first to contact the solution, and thus to undergo the phase transition. Thus after the initial release of drug, there is increasing retardation in the system due to the closure of surface pores.

Below the LCST, the release is slow and Fickian (process 1) for this system. An Arrhenius plot of the effect of temperature on release rate indeed suggested that there are two distinct activation energies for the gel depending on whether the medium is above or below the LCST.[208] Carboxylic acid groups have also been incorporated into the gel by copolymerizing with methacrylic acid; the resulting gels had affinity for methylene blue cations, and thereby retarded their release.

Okano and Bae have independently developed a rather "opposite" approach

from that of Hoffman for delivering drugs with PNIPAAM copolymer gels.[45] Their system was found to release the drug when the temperature was cold ($<$ LCST), but blocked any release above the LCST. Hence, they were able to obtain pulsatile release by cyclically raising and dropping the temperature about the LCST. As they started with a dried gel, their system can be classified as process 4 for the release during the initial swelling, and then process 1 for the subsequent cycles. They distinguished their results from those of Hoffman by realizing that they were instead using rather hydrophobic drugs (such as indomethacin) that would prefer staying inside the collapsed gel and would only diffuse out when the pores were open. A more detailed study[186] followed that revealed that it is possible to load ca. 20% drug by weight into the gels; such loading did perturb the LCST of the system as expected (Sections 3.3 and 4.1.2). However, the authors did not detail how the LCST changed as a function of drug content after each delivery cycle, merely stating that the LCST was depressed 3–4°C which one might assume to be the maximum/initial effect. As less drug remained in the gel at later cycles, one would expect the LCST to approach its drug-free value.

In addition to doing the rather crude aliquot sampling techniques also used by Hoffman above, these researchers also examined ^{14}C-labelled glucose and insulin diffusion between two chambers of a diffusion cell with the PNIPAAM gel acting as the membrane.[186] Upon analyzing their data, they proposed a similar "surface skin layer" model to that of Hoffman,[44,208] and invoke it to explain why their system has such a rapid shutting-off of the release of the hydrophobic drug above the LCST. Microscopy was done to provide evidence for the model. Their more recent work has focused on copolymers of NIPAAM with alkyl methacrylates.[212] By varying the length of the alkyl chain, the "on-and-off" process could be tailored as desired.

Alternatively, Okano *et al.*[186,187] have developed PNIPAAM-based IPNs (Section 2.3.2). The presence of this second polymer network had little effect on the LCST. The advantage of using IPNs thus is the ability to control only the degree of swelling by the presence of this essentially inert ingredient[187] as was demonstrated by a poly(ethylene oxide–dimethylsiloxane–ethylene oxide)/poly(*N*-isopropylacrylamide) system. This contrasts with results when using copolymerization to tailor the system where both the degree of swelling and the LCST are influenced by composition. This is because the IPN is probably phase separated and hence NIPAAM units have little contact with the siloxane species as opposed to when they are covalently connected in a copolymer. Therefore, IPNs allow greater design control for specific applications. Nonetheless, despite the pulsatile release, the amount of drug released was initially higher the first time the temperature was dropped, apparently due to the release of concentrated drug enclosed in the gel layer by the initial "off" step preparation. Okano and coworkers[213,214] have also directly compared the effects on swelling and solute delivery of copolymers versus IPNs.

Dong and Hoffman[209] have also made a heterogeneous PNIPAAM gel, synthesized by gamma-irradiations of solutions of *N*-isopropylacrylamide (NIPAAM) and bis-vinyl-terminated polydimethylsiloxane (VTPDMS). This network system, is not a true IPN due to grafting between NIPAAM and VTPDMS, but is essentially a crosslinked graft copolymer. Nonetheless, the gel exhibited the same LCST as the homopolymer of NIPAAM, probably due to its block-like nature. The 50/50 gel showed a surprisingly fast rate of shrinking when heated through the LCST. DSC confirmed the existence of a microdomain structure in the gel (the T_g's were essentially their homopolymer values) thus confirming the above-presented hypothesis that when phase separation exists there is no perturbation in the LCST. The gel also swells in ethanol as expected (Section 4.1.2), permitting a high loading of either hydrophilic or hydrophobic drugs by variation of preparative techniques. A novel extension of this work[215] introduced acrylic acid as a comonomer in this system. These gels consequently now also possess pH sensitivity as well as thermal response. The LCST shifts to higher temperature at higher pH due to repulsion between the ionized groups. More importantly, as shown by a detailed *in vitro* study, release of the drug indomethacin occurs at a much higher rate at pH 7.4 than at pH 1.4. The ultimate goal of the project is an *in vivo* system that protects the ingested drug from being prematurely delivered in the stomach, so that it instead reaches the intestines, the desired target. Hence, the pH rate dependence is desired for optimum performance.

Other researchers have developed systems almost identical to those mentioned above.[210] In an even more complex system, Park and Hoffman[211] entrapped *Arthrobacter simplex* cells inside PNIPAAM hydrogels. These cells convert the steroid hydrocortisone to prednisolone. By cycling the gel between two temperatures just below the LCST, it was possible to induce the "hydrostatic pump" effect mentioned above,[44,208] thereby enhancing mass transfer of the reactant into, and product out of, the gel. Conversion was thus increased relative to isothermal temperature trials.

4.3.2.2. Enzymes – Conjugation of PNIPAAM chains to enzymes has been previously discussed (Section 3.5.2). Covalently bonding enzymes to PNIPAAM in gel form has also been done.[49,217-219] Since substrate diffusion is regulated by the gel pore size below and above the LCST, such an approach offers the ability to respectively switch on and off the enzyme. Furthermore, immobilization increases enzyme stability, and enables continuous and long-term operation.[218]

Hoffman and coworkers have demonstrated two different enzyme systems.[49,217-219] In their first attempt, asparaginase was immobilized by introducing it as a comonomer (0.00015%) already linked to the NASI unit.[49,217] Enzyme activity increased at higher temperature as expected from Arrhenius kinetics, but was effectively shut off at the LCST; the Nessler assay cannot work if its

components cannot reach the enzyme site. The critical temperature for this thermal feedback mechanism is the LCST, which can easily be adjusted by adjusting the amount of acrylamide (AM) comonomer. After several cycles of swelling and shrinking, there was no loss of activity; reversibility is thus present despite the enzyme being in a significantly dehydrated gel matrix when above the LCST. On the contrary, enzyme activity increased in each successive low temperature state, indicating some sort of physical or chemical rearrangement[49,217] in gel structure.

The Hoffman research group has also developed a system based on β-galactosidase.[218] They did not immobilize this enzyme covalently in macroscopic gels as above,[47,217] but physically trapped it inside beads of a NIPAAM/AM gel (LCST 37–40°C) synthesized by an inverse suspension polymerization. Batch studies similar to those above demonstrated that the rate controlling step is the diffusion of the reactants. The free enzyme has maximum activity at 50°C; however, the beads have zero activity at that temperature since no reactants can reach the enzyme in the collapsed gel. The greatest activity can be attained by thermal cycling near (and below) LCST (30–35°C). This was verified by an Arrhenius plot: at low temperature, there is kinetic control by the rate of the enzyme reaction (which increases with temperature); at high temperature, activity is diffusion controlled by the entrance of substrate into the collapsing gel. But near the LCST, not only are the gel pores open and the enzyme at work (at its greatest rate below the LCST), but the substrate molecules are thermally diffusing at their greatest rate as well.

The beads have also been packed into a continuous reactor,[218] and the flow rate of the substrate was adjusted in order for the reactants to have an adequate residence time in the beads. This time drops sharply above LCST, causing activity to decrease. This system was also found to be reversible, and was claimed to have potential not only as a bioreactor but also in such exotic applications as artificial organs. Canon[219] has patented a system based on the same concepts the Hoffman group is exploring, but in their use of glucose oxidase they do not rely on the obviously much preferred method of covalent attachment. As mentioned above in Section 4.1.2, Tanaka[181] has also investigated enzymes in PNIPAAM gels. The general concept of controlling reaction rate by selective diffusion is not limited to enzymes; there is potential for immobilizing many other types of catalysts.[217]

4.3.3. *Photoscience* – Two types of applications have been developed with PNIPAAM-type gels in the field of photoscience. First, the scientists at Eastman Kodak[63,64] were interested in temporary barriers that delay the contact of one reactant with another reactant in photographic elements. In particular, they desired such layers to have a negative activation energy such that the permeation of these species requires longer times at higher temperatures. They therefore constructed a polymer consisting of *N*-alkylacrylamide (30–97%, preferably

NIPAAM), a crosslinking agent (3–25%) and other functional comonomers (0–60%) from an emulsion polymerization. This reaction yielded 0.5 micrometer beads which were then coated as desired. The motivation for making the polymer as beads is that if the solution is chilled as it is coated, the beads are then in their swollen state; not only is there consequently less run-off, but such quick setting also aids in maintaining the homogeneity of the layer, and prevents mixing with adjacent layers. Thus one can take advantage of the LCST in the opposite sense: gels are more swollen at lower temperature.

The other adaptation of photoscience to PNIPAAM gels involves using photo-transitions to "switch" the LCST. Two approaches were thus taken[46,47] utilizing photosensitive groups to induce an added driving force to the free energy. In one case,[46] a leucocyanine functional comonomer sensitive to UV irradiation was incorporated at ca. 2% into the gel synthesis. Gel diameters were measured by the standard calibrated microscope technique discussed above (Section 4.1.1). The gel initially has a sharp, but continuous volume change at ca. 30°C upon heating. Upon UV irradiation ($\lambda < 254$ nm), the transition shifts to ca. 32.6°C and is discontinuous, both changes being a result of ionization of the functional group. Moreover, by fixing the temperature at 32.0°C, it is possible to switch between the shrunken and swollen states by irradiating and removing the UV light. The authors believe that such a high-speed system offers promise in optical devices such as optical switches, display units, and three-dimensional holograms.

Alternatively,[47] a biomimetic system was assembled by copolymerizing a light sensitive chromophore, the trisodium salt of chlorophyllin, with NIPAAM. Exposure to visible light from an argon–ion laser (488 nm), in contrast to the other system, depresses a continuous transition at ca. 35°C to 33°C. If 120 mW is used instead of 60 mW, the transition becomes discontinuous at 31.5°C. By increasing light intensity at a constant 31.5°C, it is thus possible to again switch on the collapse, this time at a critical power.

In this latter system, Tanaka and Suzuki[47] suggest that the chromophore dissipates the absorbed light as heat through radiationless transitions, increasing the 'local' temperature of the polymer close to the LCST. Therefore the LCST is depressed rather than elevated as in the leucocyanine system[46] where ionic repulsion is operative.

5. INTERFACIAL, SOLID, AND COMPOSITE STRUCTURES

5.1. *Solids*

Studies of PNIPAAM have focused almost entirely on its behavior in aqueous media; far fewer studies have been done on the polymer in the solid state. However, these findings will be summarized here for completeness of this review; moreover, they may motivate novel applications for such systems.

Previously, (Section 3.1.4), the effects of lateral substituents on the solution behavior of substituted polyacrylamides including PNIPAAM were discussed.[114] Investigations were later extended to attempt to find a relationship between the molecular structures and glass transition temperatures (T_g) of these polymers in the solid state.[220] T_g was found to linearly correlate best with the product of the cohesive energy density and the steric factor, the latter parameter derived from the solution studies.[114] This indicates that both hydrogen bonding and bulkiness of side groups are involved in determining properties in the solid state in an analogous manner to the situation with solution behavior.

As a consequence of their ability to hydrogen bond, NIPAAM units incorporated into nonpolar polymers increase toughness and modify melt flow properties. For example, Mortimer[41] synthesized polyethylene containing ca. 6% NIPAAM as a comonomer; the product was transparent but still had these aforementioned improvements. From a similar perspective, PNIPAAM has been cited in patents for hot melt rewettable moisture-activated adhesives.[221]

5.2. *Surfaces*

5.2.1. *Theoretical experiments* — Guillet, who published one of the first major papers on PNIPAAM,[32] also worked on the foundations of inverse gas chromatography.[18,222] Briefly, inverse gas chromatography allows one to explore polymer–solvent interactions by coating the polymer on the solid support inside the column, and observing the retention times of various solute probes injected with a carrier gas. Simply, greater retention times reflect lower (more favorable) free energies of interaction as a consequence of the solute partitioning into the solid phase for a greater fraction of its passage through the column. Initial investigations on PNIPAAM discovered that acetic acid and butyl alcohol are absorbed on the column even at low temperatures, whereas the retention time of naphthalene and hexadecane molecules was only increased above the T_g of PNIPAAM. Obviously, different mechanisms of interaction exist as PNIPAAM does not dissolve in the latter pair. However utilizing naphthalene and hexadecane molecules allows detection of the T_g in good agreement with that measured using DSC, ca. 130°C.[18] Interestingly, a positive enthalpy of interaction was calculated between PNIPAAM and butanol;[222] one would expect a negative enthalpy of mixing as was observed with acetic acid.[18] The authors attempted to explain this anomaly as a consequence of the alcohol being more self-associated under the conditions investigated. They calculate that the PNIPAAM and butanol would certainly hydrogen bond at dilute concentrations in nonpolar media.

Unfortunately, inverse gas chromatography has not been carried out for the vast number of hydrogen bonding solvents and potential cosolutes for PNIPAAM. Such studies would facilitate correlating the measured free energies of

interaction of the probes to their effects on the LCST of PNIPAAM in aqueous solution. Such investigations would clearly increase the understanding of competitive interactions in influencing solution properties. Indeed, inverse GC could clearly be used to elucidate the driving force for cononsolvency (Section 3.3.1).

5.2.2. *Applications* – A wide variety of applications in addition to theoretical studies have involved PNIPAAM at surfaces. Some of these were motivated by the desire to benefit from the PNIPAAM LCST transition while trying to maintain different bulk properties. Alternatively, the impetus for such efforts came from explorations of the surface activity of PNIPAAM; as discussed above (Sections 3.1.6 and 3.3.3), even homopolymer PNIPAAM possesses surfactant-like properties.

Two Japanese patents[223,224] have been filed in which PNIPAAM and related polymers are coated onto surfaces such as glass plates. Claimed as an agent for absorbing and subsequently releasing water vapor, these polymeric composites are thus suggested for application as humidity and dew sensors as well as for use in greenhouses.[223] Obviously, above the LCST, these plates will become turbid. Therefore in the latter application, one could thereby decrease the amount of sunlight in a greenhouse when it becomes too hot.

Coating HDPE plates with aqueous PNIPAAM solutions has been similarly suggested as a technique to hydrophilize plastic surfaces.[224] Indeed contact angles to water were observed to drop from 98 to 22 degrees on treatment. No advantage to using PNIPAAM is cited, but perhaps its amphiphilic nature might improve adhesion though it is difficult to believe that such a surface would be very durable.

In an application more directly utilizing the LCST, Okahata and coworkers[84] grafted NIPAAM polymer onto porous nylon capsules for thermoselective permeation control in drug delivery applications as has been discussed for gels (Section 4.3.2.1). Good results were obtained for large solutes such as naphthalenedisulfonate: the permeability coefficient dropped more than an order in magnitude upon heating the system above the LCST. However, for smaller permeants, the permeability increased again at higher temperatures. Apparently, the entangled polymer cork hinders diffusion upon collapsing above the LCST, but later increases in mobility of the chains at higher temperatures open pores to facilitate diffusion.

Similarly, other Japanese workers have[225] grafted NIPAAM and its copolymers onto porous poly(vinyldene fluoride) membranes. More than a ten-fold change in the water filtration rate through the membrane occurred between temperatures above and below the LCST. Thus once agin, a thermal valve was contructed; the temperature of switching is a function of the comonomers used. In both of these systems, mechanical integrity is determined by the inert support rather than the PNIPAAM itself.

In addition to these synthetic membranes, work has also been done using

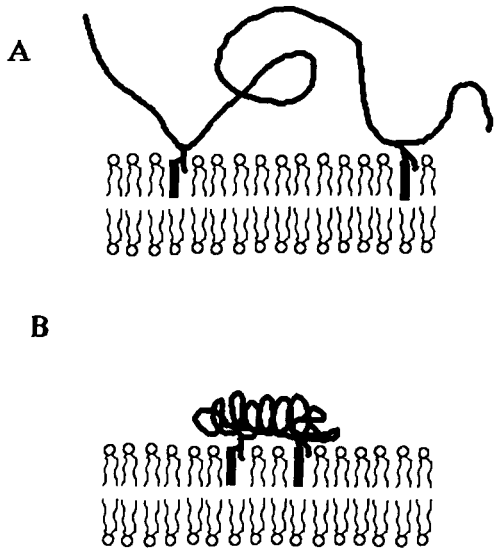


FIG. 16. "Molecular Accordion" effect for PNIPAAM in lipid bilayers.

biological membranes.[226,128] Ringsdorf *et al.*[226] incorporated the 0.5% pyrene-labelled hydrophobically modified C_{18}PNIPAAM (Fig. 7) previously discussed (Section 3.4.1) into lipid bilayers. They propose that it "anchors" into dimyristoyl phosphatidycholine (DMPC) liposomes at room temperature via the long alkyl side chain of the comonomer. This hypothesis is supported by the disappearance of excimer previously detected for the polymer in water alone, thereby suggesting that the hydrophobic chains separately anchor into the bilayer. Raising the temperature above the LCST increases the amount of excimer, which they claim is due to a "molecular accordion" effect (Fig. 16).

Such vesicles offer a greater opportunity to determine the effects of microstructural variations on interactions of amphiphiles with PNIPAAM compared to using micelles. The hydrocarbon tails of lipid molecules in a bilayer exhibit an endothermic gel-to-liquid crystal phase transition observable by microcalorimetry. This transition for DMPC liposomes is at 24°C; thus they are always in their more fluid state for the above experiment. Ringsdorf *et al.*[226] have also used the distearoyllecithin, which has a phase transition at 54°C, well above the LCST. In this case, the "accordion" could not be squeezed at the LCST as with DMPC; the increase in excimer was not detected until ca. 56°C, when the liposomes were fluid enough to permit the polymer's "anchors" to contract. Lowering the temperature again stiffens the membrane, and although the polymer chains can expand, the anchors were found to remain positioned in their high temperature state as the bilayer is again in its gel phase. The amount of excimer thus remained the same.

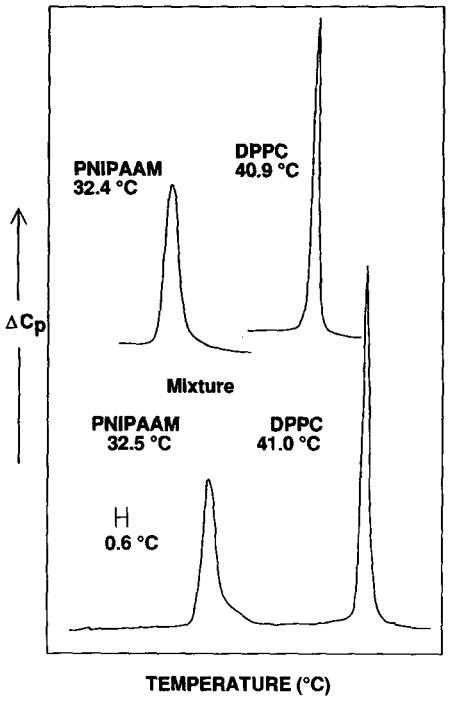


FIG. 17. DSC of PNIPAAM and DPPC solutions and their mixture. Heating rate: 15°C/hr.

The above researchers did not perform any measurements to detect whether the LCST or the liposome phase transition was affected by the mutual interactions present. Schild and Tirrell[128] have followed both these transitions simultaneously using DSC for a variety of liposomes with PNIPAAM polymers. The main set of studies focused on homopolymer PNIPAAM interacting with either dipalmitoyl L-α-phosphatidylcholine (DPPC), dioctadecyldimethylammonium bromide (DODAB), or sodium didodecylsulfosuccinate (SDDS).

Results for PNIPAAM and DPPC are illustrated in Fig. 17. No interaction appears to exist between these cosolutes since the phase transitions are additive upon mixing. Similar results were obtained with phosphatidic acid and phosphatidyl-glycerol liposomes, which have negative charges. However, investigations with cationic DODAB synthetic vesicles indicate (Fig. 18) that each species is sensitive to the other's presence. The absolute concentrations were chosen (PNIPAAM: 1.80 mg/ml; DODAB: 4.0 mg/ml (6.3 mM)) to yield endotherms of comparable size. The LCST is not elevated but the transition is broadened; the vesicle transition shows a high temperature transition (overlapping the second peak) induced by the PNIPAAM. At the concentrations and stoichiometry chosen, conversion to the higher-melting phase is incomplete.

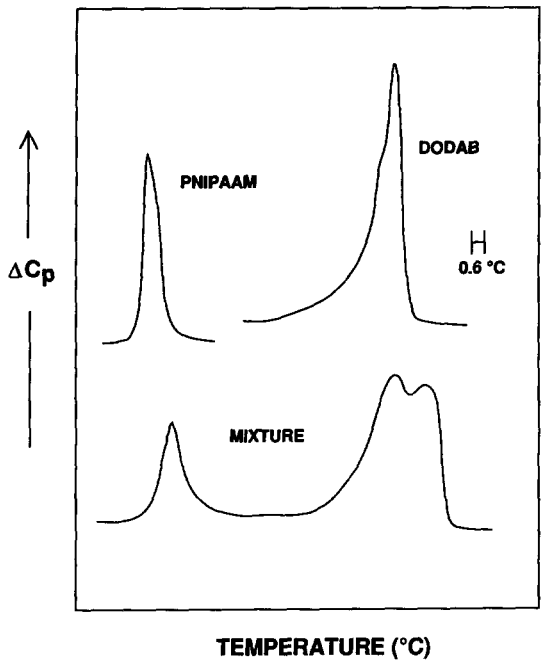


FIG. 18. DSC of PNIPAAM and DODAB solutions and their mixture. Heating rate: 15°C/hr.

Knowing that the single chain micelle-forming analog to DPPC does not interact with PNIPAAM and that the single chain analogs to DODAB such as dodecyltrimethyl-ammonium bromide (DTAB) do, Schild and Tirrell[126] concluded that the ranking of head group interactions appears independent of whether the amphiphiles are organized as micelles or vesicles. Therefore, they predicted that sodium didodecylsulfosuccinate (SDDSS) should exhibit even stronger interactions with PNIPAAM as it has a sulfur-based headgroup like the sodium *n*-alkyl sulfates that were observed to interact the most with PNIPAAM. The amphiphile was synthesized[227] and tested.

Upon adding it to solutions of PNIPAAM, they discovered that only 50 μM SDDSS was required to raise the LCST to 33°C and broaden the transition width to 1.4°C (Fig. 19). At this low concentration, the bilayer transition was unobservable. At higher concentrations where one can detect this latter endotherm, results are ambiguous. The polymer transition appears to be too broad to observe, or alternatively rapidly increases above the boiling point. The vesicle transition itself is rather irreproducible: its strong dependence on the thermal history of the sample has been reported.[228] Therefore although interactions are clearly strongest in anionic systems regardless of microstructure, for this system they were too strong to study within instrumental limitations.

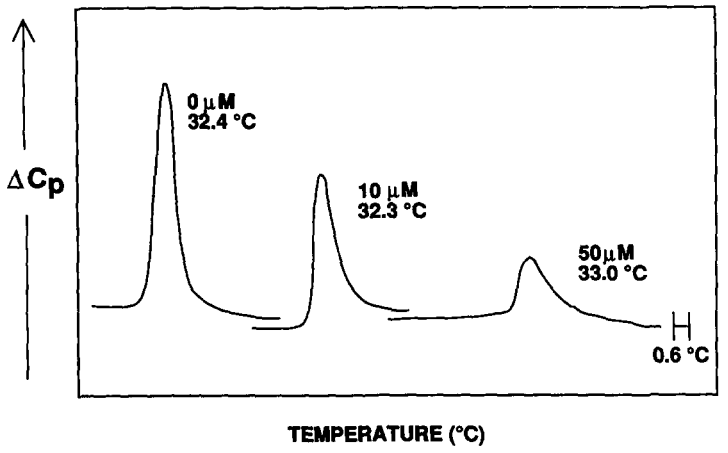


FIG. 19. DSC of the effects of SDDSS on the LCST of PNIPAAM. Heating rate: 15°C/hr.

Schild and Tirrell[229] also interacted their hydrophobically modified PNIPAAM/HDAAM copolymers[76,126] with DPPC. DSC measurements on mixed stock solutions again showed additive results analogous to Fig. 17 indicating little perturbation of the thermodynamic transitions. However, unlike with the homopolymer, it was possible to co-cast films of a chloroform solution of the copolymers and lipid onto the walls of vials, and then upon hydrating and vortexing to obtain a macroscopic film. DSC measurements on pieces of this film again showed no perturbations of the transitions. Thus one might conclude that in the "molecular accordion"[226] above, despite the polymer being anchored to the lipid bilayer, no perturbations occur in the two species' transitions. The combination of DSC and fluorescence measurements on a single system would certainly elucidate the mechanism. Theoreticians have claimed that polymer chains tied to interfaces should have perturbed critical points;[230] these experimental results would say that such is not necessarily so. It would also be of interest to study permeability through the macroscopic films as the presence of two phase transitions (the polymer and the lipid bilayer) should result in a novel temperature dependence: above the LCST permeability would drop, yet above the lipid transition it would rise. Depending on the relative temperatures of the two transitions, permeability could probably be stepped up and down accordingly.

In research closer to the area of classical colloidal science, Pelton and coworkers[66] have made PNIPAAM latexes. As the diameters of the particles decreased upon heating through the LCST, the corresponding electrophoretic mobilities increased, reflecting the increased charge density of the particles. At higher temperatures the latex coagulated. This motivated Pelton[231] to essentially

"coat" polystyrene and polystyrene–butadiene latexes with PNIPAAM in order to be able to "turn-off" colloidal stability when desired. The shifting of critical flocculation temperatures with added acrylamide comonomer and the influence of electrolytes were also investigated.

PNIPAAM has also been applied in inorganic colloidal systems as a polymeric flocculant.[232,233] Wastewater containing suspended clay and sand are flocculated rapidly by PNIPAAM and its copolymers.[232] The floc has a high content of solids. Such a separation process would be even more enhanced if there was specific binding to the polymer. A more detailed study of the adsorption of thermally reversible polymers such as PNIPAAM on microdisperse silica has been done.[233] Greater adsorption is obtained by raising either polymer concentration, molecular weight, or temperature; alternatively, the pH can be lowered, and certain kinds of ions added, to modify response.

Using surface modification for biological applications, researchers have examined the use of polystyrene culture dishes grafted with PNIPAAM[73] to provide thermo-responsive control of attachment and detachment of cultured cells. Aware that cells can adhere and grow better on hydrophobic surfaces, they successfully cultured cells on such dishes at the biologically relevant temperature of 37°C. This temperature is above the LCST; therefore, the PNIPAAM is collapsed. However, upon decreasing the temperature to 4°C, the cells were found to detach as the surface was then hydrophilic. Contact angle measurements supported this hypothesis by showing a decrease from 48 to 30° upon wetting the PNIPAAM-based dishes as opposed to a constant 54° for control PS ungrafted dishes over the temperature range of interest. Thus in a similar manner as the chill-set system previously discussed (Section 4.3.3), this application takes advantage of the expanded state rather than the collapsed state as the preferred position of the "switch".

5.3. *Films/layers*

In a very similar scheme to the sensors mentioned above (Section 5.2.2), PNIPAAM-type solutions have been laminated between glass plates to construct temperature-sensitive light-shielding materials.[234] Transmittance was found to drop from 76% to 0% for a 0.09% solution of PNIPAAM thereby sandwiched and heated above its LCST. The abstract mentions the ability to optionally include cloud point regulators. One would imagine these to be various cosolutes to shift the LCST to a desired temeprature above which one wants to darken a room. Moreover, as we have seen (Section 3.1) that different cosolutes lead to different precipitated particle sizes, one should also be able to optimize the desired degree of shade.

Photographic companies such as Polaroid and Kodak were once very interested in PNIPAAM-type polymers, although most of this research has not been published in the open literature. Polaroid's reported interest[81,235–237] was the

construction of a diffusion controlling interlayer. Normally, diffusion increases at higher temperatures, but it is desirable to have a constant diffusion rate independent of temperature. By introducing an LCST-polymer such as PNIPAAM that becomes more dehydrated as the temperature rises, it is thus possible to compensate.[235] An interesting finding was that polyacrylamide (PAM) films swelled at a slower rate that PNIPAAM ones.[236] In copolymers between the two units, the expected monotonic decrease of diffusion with increasing NIPAAM content was not observed: the 57/43 PAM/PNIPAAM copolymer swelled faster. This was explained as due to the hydrogen bonding ability being perturbed by copolymer alteration of units.[237]

Kodak has cited PNIPAAM in at least four patents. We previously discussed[63,64] their application of PNIPAAM in gel beads (Section 4.3.2), also used as a diffusion controlling interlayer as in the Polaroid work. In addition, it has cited PNIPAAM as an interlayer in an integral element for the analysis of cholesterol.[238] Its exact role there is not as clear as in a recent citation[239] where it is used as a dye-barrier and subbing layer for the dye–donor element used in dye diffusion thermal transfer D2T2 technology, a new electronic imaging technology. In this case, the polymer's hydrophilicity prevents very hydrophobic dyes from diffusing in the wrong direction during imaging. Konica[240] has also claimed a silver halide photographic material comprising PNIPAAM to improve drying speed without losing mechanical strength of layers. Again the direct application of the LCST is not that clear. However, the fact that PNIPAAM is soluble in organic solvents due to the presence of the *N*-isopropyl group whereas high molecular weight polyacrylamide is insoluble except in water may explain the interest in using PNIPAAM.

5.4. *Composites*

Finally, PNIPAAM has been incorporated into a number of composite structures, particularly fibres.[241–247] With patents appearing as early as 1959,[241] early work focused on the increased dyeability of polyolefin fibers, again facilitated by the ability of PNIPAAM to hydrogen-bond.[243] In latter work the LCST was employed: *N*-isopropylacrylamide has been grafted to cellulose fibers ($> 20\%$)[244] to create thermoreversible adsorbents. Furthermore, bicomponent self-crimping modacrylic textile fibers have been drawn from PNIPAAM, an acrylonitrile–vinylidene chloride copolymer, and an optical cellulose ester.[245] Thus by taking advantage of the differential thermal shrinkage of PNIPAAM versus the other polymers, it is possible to further retard the fiber from being straight when desirable. Orthopedic bandages having improved tackiness and workability have also been formulated.[246]

Fabrics have also been printed with resist pastes containing PNIPAAM while it is above its LCST.[247] Thermally reversible crosslinking of mouldings has been carried out, holding the samples in water while being irradiated to retard

changes in shape.[248] Again many of these applications are rather complex, but it appears that with an LCST just above room temperature, it is possible to manipulate desired fiber properties and "chill–set" as above with the polymer in bead form (Section 4.3.3) to optimize physical properties for the given application.

6. MISCELLANEOUS

6.1. *Other aqueous LCST polymers*

A number of other relatively common synthetic polymers have been reported to possess aqueous LCST's; tailoring structures by copolymerization or polymer modification to create even more systems has been discussed.[81] Although some have been briefly mentioned already (Section 3.4.2), this section will more broadly review the literature, comparing findings with those on PNIPAAM. Universality or the lack thereof will be the main issue that will be assessed. The focus will be on the more well-known synthetic polymers, but it is interesting to note that PNIPAAM and these other aqueous LCST polymers have been suggested over the years as modeling the denaturation of proteins.[81,91,92,96]

Salt effects on the LCST of poly(ethylene oxide) (PEO) have been well established in terms of the Hofmeister series.[249] The higher ranking of sulfate over bromide in terms of its greater efficiency in salting-out (greatest LCST depression at lower added salt concentration) and the weaker depression per mole of the LCST by added thiocyanate than was observed with PNIPAAM[36,128] have also been qualitatively confirmed with aqueous PEO solutions.[249] Studies of the effects of the addition of low molecular weight saccharides on the LCST of PEO certainly have aided in elucidating the driving force of the LCST.[250] Cloud point depressions were observed with all the saccharides studied but not with added cyclodextrin; 1,6-substituted saccharides had a greater effect than 1,4-species where an intramolecular hydrogen bond can be envisioned. Thus the role of competitive hydrogen bonding is certainly as important as has been stressed throughout this review.

PEO has probably been the most extensively studied nonionic polymer in regards to interactions of nonionic polymers with surfactants; most notably, Cabane has done neutron scattering investigations in which each component of the system was in turn selectively deuterated. Increasing numbers of micelles of a constant size were concluded[251] to bind above the CAC. However, one cannot measure increased polymer solubility through increases in the LCST of PEO, since the transition is already very close to the boiling point of water. This higher solubility of PEO relative to related structures such as PVME and poly(propylene glycol) (PPG) has been explained as a result of geometric conditions[252] that allow its polymer chains to have an unstrained coupling to the surrounding continuous network of water.

Better comparison with PNIPAAM is possible when the PEO exists as oligomeric comb-like side chains of polymethacrylate backbones.[253] Perturbations of the cloud points of these less soluble polymethacrylates are in accord with the trends observed for PNIPAAM solutions for salt effects and the elevation of the LCST in the presence of SDS. Thus although PEO is more soluble than PNIPAAM, and therefore has a higher LCST and a higher CAC for added SDS,[254] qualitatively, both appear to be affected by cosolutes through analogous phenomena for the experiments mentioned. PEO molecules with terminal groups of different hydrophilicity (MeO, AcO, or $PhNHCO_2$) have been seen to possess respectively lower LCSTs as well.[255] Thus by introducing greater hydrophobicity onto even one site of the polymer, the LCST is depressed.

The introduction of a methyl group into each repeat unit of PEO can be viewed as the route to creating PPG; the increased steric hindrance for fitting the polymer into the structure of water[256] depresses the LCST to such a degree that only oligomers are soluble. DSC[36] revealed an extremely broad transition width (12°C) for an oligomer (MW = 1000) with an LCST at ca. 41°C. When the molecular weight reaches 3000, the LCST is already below 20°C.[196] In this last study,[196] it was also found possible to elevate the LCST by the addition of various amide compounds such as urea. Such higher hydrophobicity as indicated by the low LCSTs of such low molecular weights has led to the claim that PPG is one of the few polymers that interacts with nonionic surfactants.[256] Although we have concluded that PNIPAAM can weakly interact with Triton® X-100,[75,128] comparisons cannot be direct since it is a different nonionic species from the *n*-octylthioglucoside Engberts and coworkers[256] employed. However, the findings are not unique as claimed, as the Winnik (using HPC)[257] and Lindman (using ethyl(hydroxyethyl)cellulose, EHEC) research groups[258] have also observed interactions of nonionic polymers with various nonionic surfactants. Thus although interactions with nonionic surfactants in general tend to be weaker than those with charged amphiphiles, there appear to be a number of different polymers that interact with them.

Ethylene oxide–propylene oxide statistical copolymers have also been synthesized. These have LCSTs intermediate between those of PEO and PPG, decreasing as expected with increasing propylene oxide content.[259] Both inorganic and organic additives were investigated; viscometry has also been done. Other researchers[260] have investigated triblock copolymers (hydroxyl or acetyl-terminated) with similar expected yet more complex results. Interestingly, studies with these sorts of polymers with added solvents (formamide and solvents in its family) have shown both simple nonsolvent and cononsolvent effects dependent on the identity of the added second solvent.[261] This appears to contrast with results obtained with PNIPAAM (Section 3.3.1).

Although mostly applied in blends with polystyrene where a polymer–polymer LCST exists, poly(vinyl methyl ether) (PVME) also possesses an LCST in

aqueous solution. In 1971, Horne and coworkers[262] reported the effects of various cosolutes on its cloud point. The ordering of the depressive effects of inorganic salts on the LCST (Hofmeister effect) was qualitatively similar to that with PNIPAAM (and PEO); an elevated LCST for added thiocyanate was also observed, an anomaly that appears to exist for a number of polymer solutions. Analogous results were also reported by Hey *et al.*[263] who hypothesize that such universality results from a simplistic effect of the salts inducing a volume change in the water structure. The Horne group[262] also reported an elevation of the LCST of PVME by added methanol; Schild and Tirrell confirmed this behavior[33] and showed it was in contrast to the cononsolvent effect seen with PNIPAAM. DSC,[33] however, did show a similar qualitative trend in the measured enthalpies within the same order of magnitude. Transition temperatures of samples of two different molecular weight investigated were identical[33] in accord with a Russian study,[264] showing the molecular weights to be high enough such that the LCST is essentially the limiting theta temperature. Nonetheless, chemical structural differences in this case do lead to an entirely different solubility response upon addition of the same cosolute.

Higashimura and coworkers[265,266] have developed a living cationic polymerization for vinyl ethers which would allow the synthesis of block[265] and end-functionalized[266] PVME macromolecules. Thus far, this scheme has been used to create amphiphiles constructed from other vinyl ether monomers as confirmed by surface tension analysis. If PVME-rich (LCST-possessing) polymers were made, this would expedite exploring the effect of microstructure on LCSTs. Narrow molecular weight samples would be an added benefit from using this synthetic technique, although the molecular weights themselves obtained by this synthetic approach tend to be relatively low.

Japanese researchers[267–271] have made PVME gels, typically through crosslinking with gamma ray irradiation.[267] These exhibit LCST behavior and have been applied in wastewater sludge dewatering, much as in the same way Cussler applies PNIPAAM (Section 4.3.1). The water-absorbing rate of the gel varied with the properties and solid concentration of the sludge, as would be expected. All the sludges tested were dewatered by repeated use of the gel. This work by Hirasa and coworkers has served as the impetus for work with macroporous PNIPAAM hydrogels as previously mentioned (Section 4.1.1).

Poly(vinyl methyl ether)-cross-polystyrene semi-interpenetrating networks have also been recently reported.[272] Despite studies of water permeability which show the obvious result of lower swelling in the presence of increased PS, only the "dry" polymer–polymer LCST was measured. The opportunity to heat these networks above their LCST (PVME–water) while in aqueous media was overlooked.

Both PEO and PVME have been interacted with viscoelastic surfactant solutions.[273] Both polymers appeared to destroy the viscoelastic structure of the solutions, indicating a transition from rodlike to spherical micelles. Depressed

CACs were sometimes observed, and the LCST of PVME was found to be perturbed in a similar manner to that observed with PNIPAAM[128] in the presence of worm-like as compared to spherical micelles.

Poly(2-ethyl oxazoline) (PEOX) was reported to form a different type of phase separated solution compared with PNIPAAM[106] above its LCST. Dow workers[274] have also confirmed this result. Polaroid workers[275] have recently published a more detailed study. A variety of measurements including static light scattering yielded the conclusion that partial organization exists even well below the LCST, and that the origin is hydrogen bonding. The collapse above the LCST was followed by dynamic light scattering, and many thermodynamic calculations were done.

The Winnik research group[104,131–133,257,276] has published a number of studies involving hydroxypropylcellulose (HPC). However, in their fluorescent studies, enough pyrene was incorporated to create excimers. Their subsequent studies[104] detected "double LCST" transitions with such highly labelled polymers. The second transition was found to result from the thermal dissociation of the excimers; therefore, solution behavior of labelled HPC is clearly perturbed much more relative to its nonlabelled control than in the case of the labelled PNIPAAM studied by Shild and Tirrell (Section 3.1.5). Nonradiative energy transfer (NRET)[276] was concluded to occur between HPC chains, in contrast to findings for PNIPAAM (Section 3.1.5). The higher degree of labelling present again in this work by Winnik can be compared to analogous experiments with PNIPAAM by Schild and Tirrell[74,128] using the same fluorene–pyrene pair where it was concluded that no NRET exists. Use of different degrees of substitution hinders conclusions, but Winnik[132] has also obtained the same result as Schild and Tirrell[74,128] with PNIPAAM with a different donor–acceptor pair and maintaining a higher level of labelling as mentioned above (Section 3.1.5). Thus HPC appears to self-associate below the LCST far more than PNIPAAM does.

Polymer–surfactant complexation of HPC with SDS and hexadecyltrimethylammonium bromide (HTAB) was similarly probed by free and polymer-bound pyrene.[131] However, in addition to also measuring "simple" CACs, a recent study determining aggregation numbers led Winnik and coworkers to propose a different mechanism than that defined by the neutron scattering work[251] of Cabane. Above the CAC, the Winnik group claim there are a constant number of cluster binding sites on HPC, and that cluster size increases with further addition of surfactant.[131] This contrasts with Cabane's findings that a greater number of micelles of identical size bind to polymer above the CAC with increasing surfactant concentration.[251] The difference is rationalized to be a consequence of HPC being more hydrophobic, stiffer, and heterogeneous in structure relative to PEO. It would be interesting, of course, to see where PNIPAAM (and PVME, etc.) fit in, given similar sets of experiments with the same technique.

The Winnik group has not yet reported the effects of surfactants on the LCST

of HPC. Schild and Tirrell[36] have measured the LCST of a number of HPC polymers by themselves in aqueous solution, including the same sample the Winnik group modifies for its studies (MW = 100,000). Broader peaks were observed relative to the transitions of PNIPAAM, yet the enthalpies were still between 1 and 2 kcal/mol. However, the observation that the solution behavior of PNIPAAM and HPC is different is further supported by the effects upon substituting D_2O for H_2O. Whereas the LCST of HPC[100] is slightly depressed by D_2O, Schild and Tirrell clearly saw an elevation of 1.0 ± 0.1°C for the LCST of aqueous PNIPAAM in 90% D_2O.[277] Further contrast with PNIPAAM is evident by the lack of observation of cononsolvency with added methanol for aqueous HPC solutions.[277]

Studies with the related polymer ethyl(hydroxyethyl)cellulose (EHEC), also suggest elevation of the LCST by added SDS together with a promotion of surfactant micellization.[278] Phase diagrams with added HTAB exhibited the same abrupt increase in the LCST[279] as measured with the PNIPAAM system.[76,128] A much more detailed experimental paper[258] shows that many of the effects on the LCST obtained with additives to PNIPAAM are qualitatively similar to those observed with EHEC. However, once again, comparisons can only be suggested since different apparatus and criteria were employed; studies[278] with added alcohols were also incomplete as they covered a much narrower range of concentration. This appears to be a consequence of viewing them as additives instead of cosolvents.[33] Nonetheless, the work is full of valuable data; it would be of interest to see if the synergistic salt effect on surfactants occurs with other polymers such as PNIPAAM. Theoretically, Karlstrom *et al.*[258] apply an adaptation of Flory–Huggins theory, attempting to create a universal theory to explain the effects of *all* cosolutes. They knowingly ignore the invalidity of such a mean-field approach where there is nonrandom mixing. Moreover, they fit LCST curves with many interaction parameters having no connection with reality. Nonetheless, some insight is obtained to apply to applications regarding the selection of surfactants for real systems.

Poly(vinyl alcohol/acetate) copolymers (PVA)[196,280] with LCSTs have also exhibited similar cosolute effects to those of PNIPAAM. A polymer of degree of polymerization 2000 and acetate content 30% was reported to have an LCST at 24°C (0.05% solution). Much higher or lower amounts of acetate groups respectively led to complete insolubility or solubility at all temperatures as expected. In this paper of 1969, Saito contrasted the effects of inorganic and organic cosolutes.[280] He purports that the latter affect the LCST by binding and the former by changing water structure. Alas, there is still not complete evidence for such a universal hypothesis; indeed, in a review of protein conformations in water, contradictory evidence is cited using polyacrylamide gel chromatography that the ions bind to amide groups.[102] Russian work has also been done on LCSTs in PVA polymers.[281]

Several of the polymers above (HPC, EHEC, PVA) were examined[282] in terms

of stabilizing latexes in a similar manner as with PNIPAAM. Increased adsorption on the various latexes was generally observed with a reduced polymer solubility (lower LCST). Work has also been published on the effect of pressure on the LCSTs of PPG and PVA-type copolymers;[283] such work on PNIPAAM would aid development of theories mentioned above (Section 4.2.1). Other papers have been published on these and other polymers but as we stated above, this section of the review is not meant to be as thorough. What it does show is that although there are many common features in the aqueous solution behavior of aqueous LCST polymers, quantitative differences do exist that depend not only on relative hydrophobicities but also on microstructural details.

6.2. *Future directions*

Although it is now clearly possible to design PNIPAAM and other aqueous LCST polymer systems for specific applications, theoretical prediction of polymeric response from basic principles is still rather elusive. The general problem of coil–globule transitions[109,284] has been theoretically treated, although the order of the transition is still debated. The presence of random scatterers in solution has been derived to result in a change in polymer dimensions;[285] nonetheless, this does little to predict whether the LCST will be depressed or elevated as this appears to depend on the identity of the cosolute rather than the fact that it takes up space on a lattice. Experimentally, the ternary systems also clearly vary in degree of organization: in aqueous PNIPAAM, salts are probably more randomly distributed in solutions as compared to surfactants which organize as micelles. A recent report[286] discusses the rounding of first order transitions with quenched disorder. It is unclear whether our aqueous solutions of PNIPAAM qualify, but we certainly see such transition broadening with a large number of cosolutes, which may be viewed as creating such an effect. In a paper overlooked while assembling the body of this report, Li and Tanaka attempted to classify the PNIPAAM gel system in the Ising universality class.[287] Other recent[288,289] papers have been published in this general field. However, one must question the ability to predict behavior in aqueous solutions since it has been difficult to create simulations even with many water molecules present, let alone macromolecular solutes. If molecular modelling is to be applied, realistic simulations are necessary!

From an experimental perspective, greater understanding of the effects of cosolutes and especially amphiphiles upon PNIPAAM can be achieved by obtaining data at high cosolute concentrations as was done with added cononsolvents. Moreover, toward the opposite corner of the phase diagram triangle from that which has been typically investigated, the existence of solid–solid transitions and perturbations of the glass transition temperature of PNIPAAM could be probed in addition to the types of ordered liquid crystalline structures that can be expected with added surfactants. In semi-dilute and concentrated

systems, rheological data can be obtained to probe whether such solutions predominate with PNIPAAM itself. Such studies have been done with PEO[290] and HPC.[291] Another relevant approach can be seen from work done on poly-(enaminonitrile) systems by Moore and coworkers.[292] These polymers exhibit an LCST in polyether solvents and the corresponding blends with PEO have also been shown to possess LCST's. Thus we might try to find polymer blends of PNIPAAM that have similar transitions and also investigate the solubility of PNIPAAM in their monomers. Compiling data on these interactions throughout the entire phase diagram will facilitate correlating experiments, theories, and applications of PNIPAAM-type polymers in order to best increase understanding and utilization of their LCST transition.

6.3. *Postscript*

Since the initial draft of this manuscript, several other papers have appeared on PNIPAAM. In order to maintain this review as state-of-the-art, they are included here. At the American Chemical Society (ACS) meeting in New York in August, 1991, Maeda presented a paper on pseudo-grafting of polyacrylamide onto DNA through use of an intercalative comonomer. By using NIPAAM instead of AM, his research group also found it possible to create a thermal DNA separation system in the same style as Hoffman and coworkers have accomplished with PNIPAAM and proteins (Section 3.5.2). As a matter of course in their experiments, Maeda observed that gel electrophoresis had to be done at low temperature (ca. 5°C) to avoid precipitation of the polymer complex. This was clearly due to a cononsolvent effect (Section 3.3.1) since glycerol was added to the system during the analysis. Most interesting, by enclothing the DNA in PNIPAAM, it was possible to change the solubility properties to that of the grafted polymer.

Fujishige and coworkers[294] have added their own version of an NMR experiment to their numerous papers on PNIPAAM. Using pulse-saturated transfer (PST)-CPMAS NMR, they observed carbonyl and methylene chemical shifts to change in a stepwise manner at the LCST. Given the diversity in experimental conditions and parameters that PNIPAAM has been investigated with using NMR (Sections 3.1.6 and 4.1.1), comparisons in greater detail need to be undertaken.

Other citations that appeared by mid-October 1991 were more detailed investigations of earlier reports. Park and Hoffman[295] found that with the *Arthrobacter simplex* cells that they had immobilized in PNIPAAM gels[211] (Section 4.3.2.2), the conversion of the steriod increased as the PNIPAAM–PAM copolymer gels became more hydrophobic. A model was proposed in an attempt to explain their observations. From a different perspective, a number of researchers including Tanaka and Irie have applied to patent photoresponsive

PNIPAAM gels,[296] the science and technology of which are described in this review (Sections 3.5.3 and 4.3.3).

Binkert and coworkers have published full-length papers[297,298] of both of their previous studies of PNIPAAM which respectively used fluorescence[80] and light scattering[105] as techniques. In both of these submissions, far more detail is presented than in the brief notes. Comparisons with the existing literature were also very enlightening.

Time-resolved measurements of fluorescence polarization anisotropy[297] were used to monitor the LCST of dansyl-labeled PNIPAAM in aqueous solution. The fluorescently labeled polymer was synthesized by reaction of dansyl chloride with a PNIPAAM copolymer that in turn was synthesized from a feed ratio of 500 : 1 NIPAAM: *p*-aminostyrene. At a polymer concentration of 1 mg/ml, the reorientational relaxation of the labels was found to be anisotropic; it would be resolved into two components. This was modeled as a consequence of rotations of the label around a free axis and of polymer-coupled reorientation. The former mode is sensitive to microviscosity; the latter reflects chain flexibility. Both of the associated relaxation times possess transitions at the LCST. Moreover, evidence was found for gradual changes in conformation below the LCST in accord with the results of Winnik (Section 3.1.5).

Binkert and coworkers' static and dynamic light scattering study[298] entails extensive studies of the interactions of aqueous PNIPAAM with sodium dodecyl sulfate (SDS). A phase diagram is presented (Fig. 20) that succinctly summarizes the system, viewing temperature and surfactant concentration as the independent variables. They emphasize that the phenomenon they define as intermolecular solubilization (that the surfactant prevents aggregation of collapsed polymer chains above the LCST) permits comparison to the theoretical globule state far more readily than other such scattering investigations (Section 3.1.3). Critical concentrations detected are mentioned as corroborating the results of Schild and Tirrell (Section 3.3.3), although Binkert and associates are cautious not to speculate on the exact structure of the complexes since their techniques cannot discern such a level of order. Furthermore, although the connection is not openly made, the fact that this light scattering study found transition broadening with increased surfactant concentration is also in accord with Schild and Tirrell's observations with microcalorimetry (Section 3.3.3).

Finally, the Griffins[299] have recently introduced yet another technique, forced Rayleigh scattering, to follow the diffusion of a dye-labelled polypeptide through PNIPAAM gels and chains. They claim a pre-transition exists in the gel, certainly a conclusion unlike those reported above (Section 4). This clearly shows that much more work remains to be done with PNIPAAM. Since submitting this review, even more papers have come out at the end of 1991 into February, 1992. All are listed in the references for the sake of timeliness.[301-309] Perhaps, the most novel of them[309] involves modifying GPC columns with PNIPAAM to obtain thermo-controllable chromatography.

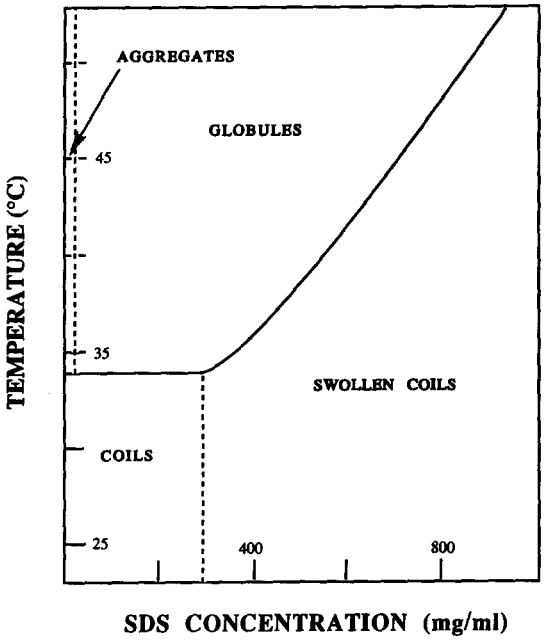


FIG. 20. Phase diagram of PNIPAAM and solution dodecyl sulfate (SDS) in water.

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