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Phase-Selective Solubility of Poly(*N*-alkylacrylamide)s

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Abstract: The extent of the phase-selective solubility of poly(*N*-alkylacrylamide)s was studied by UV−vis and fluorescence spectroscopy using poly(*N*-isopropylacrylamide) and poly(*N*-octadecylacrylamide) as representative polar and nonpolar poly(*N*-alkylacrylamide)s in a mixture of polar and nonpolar thermomorphic solvents. Phase-selective solubilities of greater than 10000:1 were seen with each labeled polymer in polar and nonpolar solvents such as heptane and DMF or heptane and 90% EtOH−H_2O. Using a poly(*N*-acryloxysuccinimide) as a common precursor, a pool-split synthesis was devised to prepare a library of poly(*N*-alkylacrylamide)s whose members varied only in the size of their *N*-alkyl substituent. The solubilities of these library members were measured in both the polar and nonpolar phases of a thermomorphic heptane/90% EtOH−H_2O mixture at 25 °C. Such solvent mixtures are miscible hot (70 °C) and biphasic cold (25 °C). The results show that poly(*N*-pentylacrylamide) is selectively soluble (>99.5%) in the polar EtOH-rich phase at rest. Poly(*N*-alkylacrylamide)s with larger *N*-alkyl groups are predominantly (C_6, 85%; C_7, 95%) or exclusively (>C_8, >99.5%) in the heptane-rich phase at rest.

Polymer solubility is important in many applications of macromolecular materials. Polymer solubility is particularly important in work where soluble polymers serve as supports for catalysts, reagents, sequestrants, or substrates.[1] The most common problem in designing a suitable soluble polymer support is the need to achieve a high enough solubility so that useful concentrations of catalysts, substrates, or reagents are present. However, it is equally important to ensure that the polymers used as supports have selective solubility because a soluble polymer support is only useful if it is completely separable from the solution under some other condition. It is most common to achieve this result by a change of solvents or conditions so that a soluble polymer support becomes completely insoluble. Such a solubility change can be achieved by solvent precipitation,[2] pH change,[3] cooling,[1b,4] or heating.[5] Alternatives to separations that do not involve precipitation and filtration are of interest too. For example, membrane filtration can separate a solution of a large polymeric species and a smaller lower molecular weight product.[6] Membrane filtration is especially useful with dendridic polymers whose shape facilitates this sort of separation.[7] More recently, work from our group and others has shown that a polymer's selective solubility in one phase of a biphasic mixture can be as useful as either precipitation or membrane filtration.[8,9] Here we describe our studies of the effects of polymer structure on the phase-selective solubility of polymers in thermomorphic liquid/liquid biphasic mixtures—studies that show minor changes in polymer structure have a profound effect on phase-selective solubility.

The work described here focuses on poly(*N*-alkylacrylamide)s using a variety of solvent mixtures. These polymers were chosen for study because we have already used these supports in biphasic liquid/liquid separations. These polymers are accessible by a synthetic route that we developed for the synthesis of a

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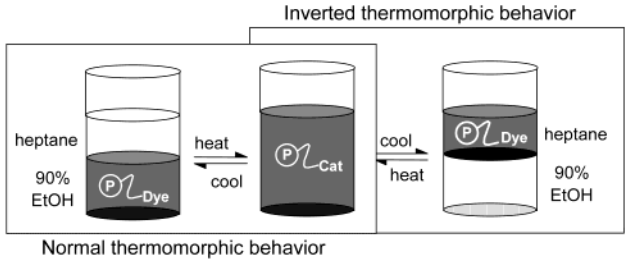
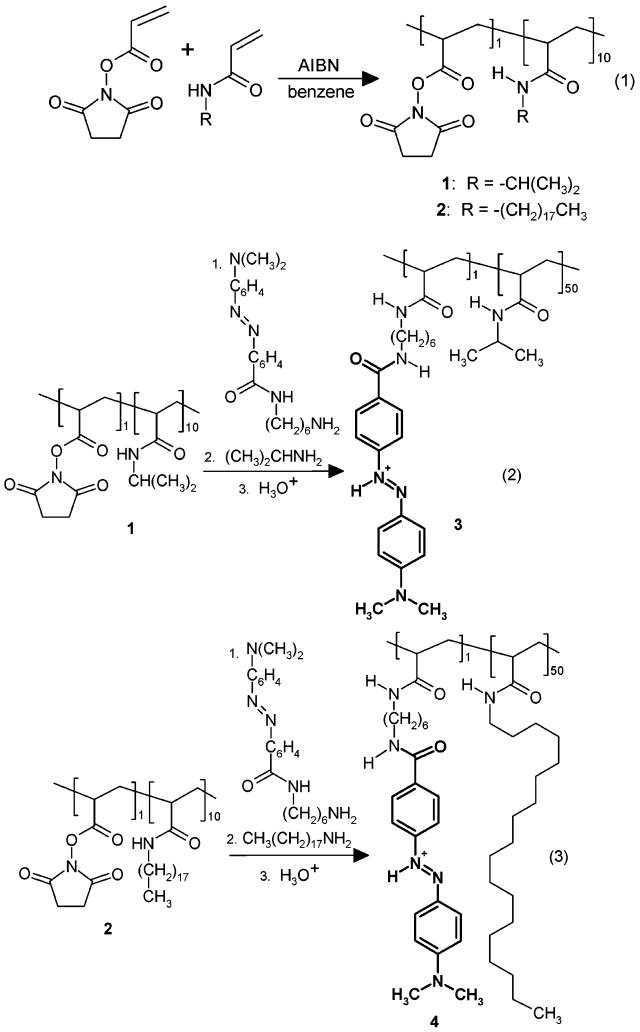


Figure 1. Normal and inverse thermomorphic separations of a poly(*N*-alkylacrylamide)-bound azo dye (a surrogate for a catalyst, reagent, or substrate) in a thermomorphic heptane/90% EtOH−H_2O mixture.

library of poly(*N*-alkylacrylamide)s. This synthesis provides a route to poly(*N*-alkylacrylamide)s that vary only in the size of their *N*-alkyl groups. It avoids the problem of variation in molecular weight distribution that might complicate comparisons of poly(*N*-alkylacrylamide)s prepared from *N*-alkylacrylamide monomers.[10] Polar/nonpolar solvent mixtures commonly used in thermomorphic systems or latent biphasic systems already shown to be useful in catalysis and synthesis were studied in the most detail. The phase-selective solubility of poly(*N*-isopropylacrylamide) in polar/polar mixtures too was briefly examined. Finally, fluorescence labels were used as more sensitive probes of the extent of polymer phase-selective solubility. Using a dansyl probe, we were able to show that the phase-selective solubility for polymers in nonpolar/polar solvent mixtures can exceed 10^5:1.

Results and Discussion

Our past work showed that poly(*N*-isopropylacrylamide) **3** and poly(*N*-octadecylacrylamide) **4** labeled with *p*-Methyl Red have very different solubilities.[8a,c] As shown in Figure 1, samples of these two polymers labeled with the protonated form of *p*-Methyl Red exhibited opposite phase-selective solubilities when placed in a mixture of a nonpolar solvent (heptane) and a polar solvent (90% ethanol−water). These polymers were prepared by a conventional radical polymerization of the respective *N*-isopropylacrylamide or *N*-octadecylacrylamide monomer with a reactive ester comonomer (*N*-acryloxysuccinimide) (eq 1). The product copolymer's (**1** or **2**) active ester group was then allowed to react first with a primary amine derivative of *p*-Methyl Red and then with isopropylamine or octadecylamine (to consume any unreacted *N*-hydroxysuccinimide ester) to form the dye-labeled poly(*N*-isopropylacrylamide) (PNIPAM) **3** (eq 2) or poly(*N*-octadecylacrylamide) (PNODAM) **4** (eq 3). The product polymers were labeled with a 1−2 mol % loading of Methyl Red as the azo dye label and were red in acidic solution or yellow in neutral solution. The unprotonated form of the azo dye-labeled **3** had a λ_{max} at 437 nm in EtOH. The same neutral dye supported on **4** dissolved in heptane had a λ_{max} at 419 nm. The protonated form of the azo dye-labeled **3** had a λ_{max} at 513 nm in a 90% EtOH−H_2O solution. The same protonated dye supported on **4** dissolved in heptane had a λ_{max} at 515 nm. A typical molecular weight (M_v) of the PNIPAM polymer **3** (THF, 30 °C)[11] was 6×10^5. Both



polymers **3** and **4** were readily soluble in a 70 °C miscible mixture consisting of equal volumes of heptane and 90:10 (v/v) ethanol/water, but **3** and **4** had significantly different solubilities at room temperature. Cooling a hot heptane/EtOH−H_2O homogeneous solution of either **3** or **4** produced a biphasic mixture with a less dense nonpolar phase containing mostly heptane (ca. 3% ethanol was in the heptane phase after cooling-mediated phase separation) and a more dense polar phase consisting mostly of ethanol and water (ca. 7% heptane is in the polar phase after cooling-mediated phase separation). In the case of the polar polymer **3**, >99.9% of the polymer was in the polar phase. This estimate is based on the absorbance difference of the nonpolar and polar phases (the absorbance was <0.002 for the nonpolar phase and >2.00 for the polar phase). These estimates assumed that **3** and **4** would have similar extinction coefficients in the polar or nonpolar phase. The extent of phase separation was also readily assayed visually for either the protonated or nonprotonated dye-labeled polymers (photographs of these phase-separated solutions of the protonated and nonprotonated forms of **3** and **4** are provided in the Supporting Information). In contrast, cooling a hot heptane/EtOH−H_2O solution containing **4** produced a biphasic mixture where >99.9% of the nonpolar PNODAM-bound dye was in the nonpolar phase. This differential phase-selective solubility of a polar and nonpolar polymer-bound dye mirrors the phase-selective solubility behavior of similar polymer-bound catalysts

(10) The variation in molecular weight distribution is a recognized problem that affects the utility of *N*-alkylacrylamides in a variety of problems including, for example, drug delivery applications and is one reason more well-defined but more expensive polymers such as dendrimers are of increasing interest; cf. Gillies, E. R.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2002**, *124*, 14137−14146.

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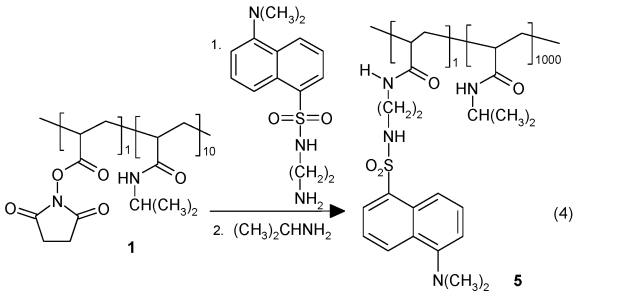
Table 1. Spectroscopic Estimates of Solubility for *p*-Methyl Red- and Dansyl-Labeled PNIPAMs and PNODAMs and *p*-Methyl Red-Labeled Poly(ethylene glycol) in Various Thermomorphic or Biphasic Solvent Mixtures

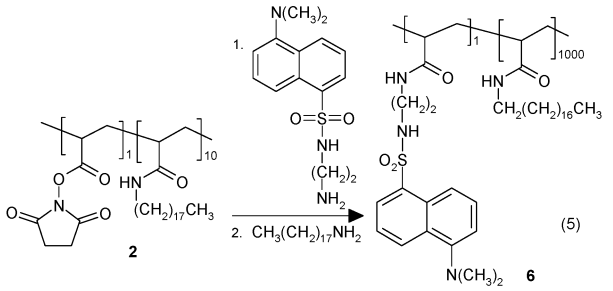
polymer probe	solvent mixture	nonpolar phase solubility[a] (%)
Methyl Red−PNIPAM	heptane−EtOH(aq)[b]	<0.1
Methyl Red−PNIPAM	heptane−DMF[c]	<0.1
dansyl−PNIPAM	heptane−EtOH(aq)[b]	<0.01
Methyl Red−PNODAM	heptane−EtOH(aq)[b]	>99.9
Methyl Red−PEG_{5000}	heptane−EtOH(aq)[b]	<0.1
Methyl Red−PNODAM	heptane−DMF[c]	>99.9
dansyl−PNODAM	heptane−EtOH(aq)[b]	>99.99
dansyl−PNIPAM	heptane−DMF[c]	<0.001
dansyl−PNODAM	heptane−DMF[c]	>99.99
Methyl Red−PNIPAM	Et_3N−water[d]	>99.9 (Et_3N phase)
dansyl−PNIPAM	Et_3N−water[d]	>99.9 (Et_3N phase)

[a] The relative amounts of polymer-bound dye or fluorophore were measured in each phase after a miscible hot homogeneous mixture of solvents and polymer was cooled to room temperature to form a biphasic mixture. Relative solubilities (e.g., >99.9% or <0.001%) were estimates based on the minimum detectable amount of probe after a series of serial dilutions. [b] This solvent mixture consisted of a 1:1 (vol/vol) mixture of heptane and EtOH−H_2O (90% EtOH by volume). [c] This solvent mixture consisted of a 1:1 (vol/vol) mixture of heptane and dimethylformamide. [d] This solvent mixture consisted of a 1:1 (vol/vol) mixture of triethylamine and H_2O and differed from the other solvent mixtures in that it was miscible cold (0 °C) and biphasic hot (25 °C).

and led us to explore in greater detail both the extent of phase-selective solubility of such polymers and the effect of polymer structure on such phase-selective solubility.

To further test the extent of phase-selective solubility, we prepared analogues of **3** and **4** that contain dansyl groups using the reactions shown in eqs 4 and 5. The resultant polymers **5**





and **6** behaved exactly the same as the Methyl Red-labeled polymers **3** and **4**. However, assays of the concentration of these fluorophore-labeled polymers were more sensitive. This allowed us to both use a lower loading of probe on the polymer and estimate that phase-selective solubilities of **5** and **6** are as high as $>10^5$:1 in polar solvents or $>10^4$:1 in nonpolar solvents.

Table 1 lists the phase-selective solubility of the both dye- and fluorophore-labeled polymers in several solvent mixtures. The solvent mixtures in this list are all thermomorphic (they are biphasic at one temperature and completely monophasic at another temperature). Immiscible mixtures of polar and nonpolar solvents (e.g., water and heptane) or other solvents with varying temperature-dependent miscibility (e.g., toluene and 85% EtOH−H_2O) are not listed here. Generally, such solvents have comparable (>99.9%) phase-selective solubilities for the polar and nonpolar polymer-bound dyes **3** and **4** in the polar and nonpolar phases of these biphasic mixtures. The phase-selective solubilities of polymers in solvents such as those listed in Table 1 were studied in more detail in this work because similar polymer-supported species and similar solvent mixtures are useful in homogeneous catalytic reactions and catalyst recovery. High selective solubility of a dye-labeled polymer can be presumed to be predictive of high levels of separation of a similar ligand- or catalyst-containing polymer in synthetic chemistry since the dye or fluorophore in these polymers (**3**−**6**) is a surrogate for a catalyst, reagent, or substrate.

The high phase-selective solubility of these polymers has important consequences for catalysis. Whitesides previously noted[12] that biphasic systems using enzymes as macromolecular catalysts in aqueous biphasic reactors often cannot be readily recovered without resort to countercurrent operation with multiple partitions of the product mixture because enzyme phase selectivities (distribution coefficients) are typically between 0.1 and 10 in ternary aqueous biphasic systems. However, the phase-selective solubility of up to >100000:1 seen for these linear poly(*N*-alkylacrylamide) supports and the use of roughly equal volumes of the polar and nonpolar phases means that a separation can easily effect >99.99% polymer (and presumably catalyst) recovery.

Most of the examples in Table 1 above are for the two polymers we have used in catalysis and synthesis—PNIPAM and PNODAM.[8] PEG derivatives too have been widely used as supports in polymer-supported chemistry and in thermomorphic systems.[2a,8a] We briefly examined the phase-selective solubility of one example—commercially available PEG_{5000}. This polar polymer has phase-selective solubility like that of the polar PNIPAM derivative. However, unlike the poly(*N*-alkylacrylamide)s, it would not be as simple to tinker with the polymer microstructure to design a heptane-soluble support. Moreover, our work showed that high phase-selective solubility was only obtained for this polymer after continuously extracting an aqueous solution of this polymer with heptane either before Methyl Red labeling or as a Methyl Red-labeled derivative. We believe this extraction removes lower molecular weight PEG derivatives that are not as phase selectively soluble.

A caveat for Table 1 is that the poly(*N*-alkylacrylamide)s listed here only contain *N*-isopropyl and *N*-octadecyl substituents. These substitutents of these poly(*N*-alkylacrylamide)s are significantly different. We also wished to ascertain how sensitive phase-selective solubility is to the size (hydrophobicity) of the pendant *N*-alkyl groups of these poly(*N*-alkylacrylamide)s. We already knew from others' work that the *N*-alkyl substituent's hydrophobicity affects the poly(*N*-alkylacrylamide)s' temperature-dependent solubility.[13] Such effects are useful in synthesis, and varying the nature of an *N*-alkyl substituent can produce quite subtle changes.[5,14]

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We expected that the phase-selective solubility of polymers too would be affected by the hydrophobicity of the *N*-alkyl substituent. However, it was not clear if small changes in polymer substituent structure would lead to dramatic changes in polymer solubility. The difference between PNIPAM and PNODAM shows that there is a spectrum of phase-selective solubility that is dependent on the size of the *N*-alkyl substituents. However, these *N*-alkyl substituents are so different that they are likely to be at the extremes of the polar-phase-soluble or nonpolar-phase-soluble regions of this phase-selective solubility behavior spectrum. Predicting the effects intermediate-sized *N*-alkyl groups have on solubility is less certain. A comparison of solubility parameters calculated using substituent effects for two poly(*N*-alkylacrylamide)s that differ by only one or two methylene groups in their *N*-alkyl substituents suggests that changing the alkyl group size by a few carbons would lead to a less than 1% change in the solubility parameter δ.[15] However, the solubility of poly(*N*-alkylacrylamide)s such as PNIPAM and PNODAM is affected by polar effects and hydrogen bonding, so the relative solubility of poly(*N*-alkylacrylamide)s with similar alkyl substituents is best tested experimentally.

There are some experimental problems associated with directly comparing the phase-selective solubility of a series of poly(*N*-alkylacrylamide)s prepared by polymerization reactions such as eq 1. Specifically, a comparison between different poly(*N*-alkylacrylamide)s is complicated because conventional radical polymerization leads to polymers that do not necessarily have the same polydispersity and degree of polymerization. Indeed, it is difficult to prepare samples of the same polymer in batch to batch reactions such that the degree of polymerization and polydispersity are identical. While it is possible that the degree of polymerization and the polydispersity are not important factors in phase-selective solubility, we preferred to avoid this ambiguity. We therefore used the synthesis of polymeric active esters developed originally by Ringsdorf[16] as a route to a library of poly(*N*-alkylacrylamide) polymers that can be compared without the ambiguities of variable polydispersity and degree of polymerization. Whitesides had previously used a similar approach with sequential amidation of the polymeric active ester groups by various amines as a synthetic route to polymeric inhibitors useful in biology.[17]

We used a pool-split synthesis route to prepare libraries of poly(*N*-alkylacrylamide)s. This chemistry employs a common polymer precursor and no fractionation steps. Thus, this chemistry leads to a library of polymer samples, all of which have the same degree of polymerization and polydispersity but which vary in the structure of their pendant *N*-alkyl groups. By combining this synthesis with a labeling procedure using the azo dye described above, we have been able to study the effect of *N*-alkyl group structure on the spectrum of phase-selective solubility for poly(*N*-alkylacrylamide)s. The results allow us to directly assay and compare the effects of polymer structure on polymer phase-selective solubility.

Before using this chemistry to make a library to test phase-selective solubility, we carried out several control experiments. First, to verify that the procedure in Scheme 1 produces polymer products that behave the same as the products prepared using eqs 1−3, we separately prepared dye-labeled PNIPAM and PNODAM polymers **8** and **15** via the reactive polyacrylate **7** and compared these polymers to **3** and **4**. In this synthesis, a homopolymer of NASI was prepared using AIBN initiation. The product active ester homopolymer was then allowed to react with a 50% molar excess of a 100:1 (mol/mol) mixture containing either isopropylamine or octadecylamine and an amine-containing derivative of Methyl Red. In this first synthesis, the product PNIPAM and PNODAM polymers **8** and **15** were separated from excess amines and isolated by solvent precipitation. The phase-selective solubility of these Methyl Red-labeled PNIPAM and PNODAM polymers was identical to that seen for **3** and **4** prepared via the more conventional route (eqs 2 and 3).

Next we developed a purification procedure for removal of the excess amines in the syntheses of Scheme 1. Excess amine is required in Scheme 1 to ensure no reactive ester remains in the product polymer. We had previously shown that unreacted NASI esters could hydrolyze readily to form acrylic acid groups[5c]—an event that would produce a terpolymer whose phase-selective solubility might be quite different from that of the desired poly(*N*-alkylacrylamide). However, while excess amine avoids this problem, the resulting presence of unreacted low molecular weight dye complicates the analysis of the phase-selective solubility of the products. Thus, we required a purification step that would remove low molecular weight amines without any fractionation of the product poly(*N*-alkylacrylamide)s. Such a separation can be accomplished by solvent precipitation (vide supra). However, solvent precipitation is a potential fractionation step, and we wanted to maintain in our library synthesis the same polydispersity and degree of polymerization for all samples. Therefore, we instead removed excess low molecular weight amines from our product poly(*N*-alkylacrylamide) library members using a sulfonated ion-exchange resin that we had previously shown to be a useful amine sequestration agent in parallel synthesis of amines from carbamates.[18] In a control experiment, we showed that polymers such as **8** and **15** do not react with this sequestration agent—a sulfonated ion-exchange resin (Amberlyst 15). This was expected since our earlier work had shown that this resin readily reacts chemioselectively with simple amines and/or BOC-protected amines but that it does not react with amides. The lack of reactivity of poly(*N*-alkylacrylamides) with the sulfonated cross-linked polystyrene was confirmed by our observation (UV−vis analysis) of no change in the solution concentration of the chromophore due to **8** on treatment of a THF solution of **8** with this polymeric sulfonic acid.

Once procedures were in hand to remove the excess amine and dye used in the synthesis of poly(*N*-alkylacrylamide)s prepared via the polymeric active ester **7**, we were able to directly prepare a small library of poly(*N*-alkylacrylamide)s **8**−**15** containing *N*-isopropyl, *N*-*n*-butyl, *N*-*n*-pentyl, *N*-*n*-hexyl, *N*-*n*-heptyl, *N*-*n*-octyl, *N*-*n*-dodecyl, and *N*-*n*-octadecyl groups. A common precursor polymer (**7**) was prepared, and portions of this polymer were added to DMF solutions containing a 1.5-fold excess of a 100:1 mixture of a primary amine and a primary

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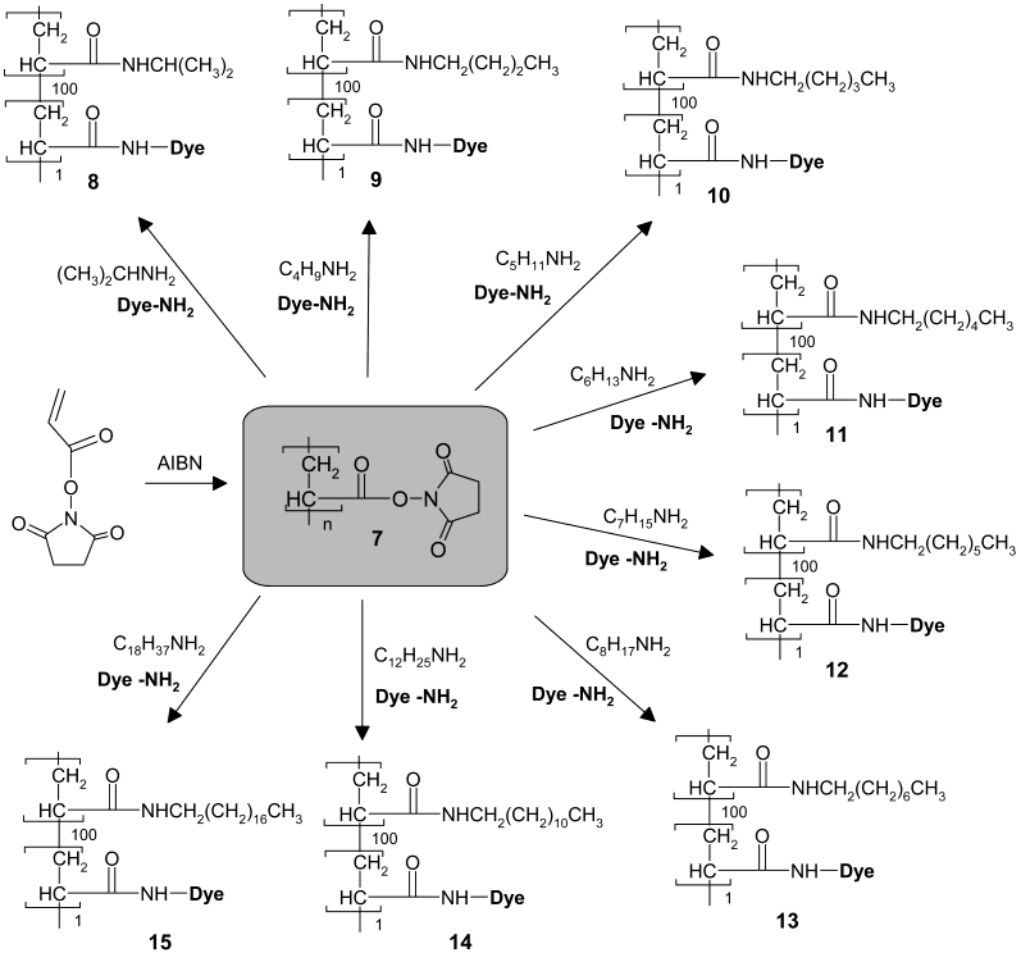
(17) Mammen, M.; Dahmann, G.; Whitesides, G. M. *J. Med. Chem.* **1995**, *38*, 4179−4190.
(18) Liu, Y.-S.; Zhao, C.; Bergbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998**, *63*, 3471−3473.

Scheme 1. Pool-Split Synthesis of a Library of Poly(*N*-alkylacrylamide)s That Vary Only in the Size of Their *N*-Alkyl Substituent



amine derivative of Methyl Red. The reaction mixtures were heated to 50 °C to ensure solubility of all the reaction components. After 24 h, the reaction mixture was cooled, and a sulfonic acid containing ion-exchange resin (Amberlyst 15) was added. Shaking the resulting mixture for 24 h removed any excess low molecular weight amine or unbound dye. At this point, a qualitative measure of the similarity of the samples of polymers **8**−**15** was the visual similarity of color for the eight different solutions, all of which had the same concentration of chromophore. The remaining solvent was then removed at reduced pressure to yield samples of **8**−**15** that were used directly in phase-selective solubility studies.

Once a collection of Methyl Red-labeled poly(*N*-alkylacrylamide)s **8**−**15** with differently sized *N*-alkyl side chains was in hand, the phase-selective solubility of these polymers was tested using visible spectroscopy. In each test, an individual poly(*N*-alkylacrylamide) was added to a mixture of a 1:1 (vol/vol) mixture of heptane and 90% aqueous ethanol (EtOH:H_2O = 90:10 (v/v)). Heating to 70 °C produced a single miscible solution from this solvent mixture and also dissolved the polymer. At this point, the mixtures were cooled to room temperature, at which time two phases, a nonpolar heptane phase and a polar aqueous ethanol phase, formed. In general, phase separation occurred readily. If phase separation were slow, centrifugation would be used to facilitate complete phase separation. Each phase was then sampled and analyzed by UV−vis spectroscopy.

The results of these studies were that Methyl Red-labeled poly(*N*-alkylacrylamide) polymers with eight, twelve, and eighteen carbon chains had phase-selective solubility in heptane. No (<0.5%) Methyl Red-labeled polymer could be detected in the polar phase in these three cases. Poly(*N*-alkylacrylamide)s with three, four, or five carbon chains had phase-selective solubility in the polar ethanol phase. No (<0.5%) Methyl Red-labeled polymer could be detected in the nonpolar heptane phase in these two cases. Intermediate phase-selective solubility was seen for poly(*N*-alkylacrylamide)s containing six or seven carbons in the pendant *N*-alkyl amido groups. Poly(*N*-hexylacrylamide) was 85% soluble in the heptane phase (average of two experiments). Poly(*N*-heptylacrylamide) had 91% phase-selective solubility in the heptane phase (average of two experiments). These results are summarized graphically in Figure 2. These experiments all involved analysis of the Methyl Red-containing polymers under conditions where the Methyl Red is not protonated.

While the solubility differences seen for polymers **8**−**15** mirrored those seen for polymers made via eqs 2 and 3, the degree of polymerization of the reactive polyester **7** used in Scheme 1 is not as large as is the case for polymer prepared by eq 2 or 3. The lower degree of polymerization of **7** was measured indirectly by analyzing the M_n and M_w of the PNIPAM derivative of **7** by GPC using 0.01 M LiBr in DMF as the eluent on a TOSOH BIOSEP column. This analysis showed that this PNIPAM derivative has a M_n and M_w of 1.8×10^5 and $3.4 \times$

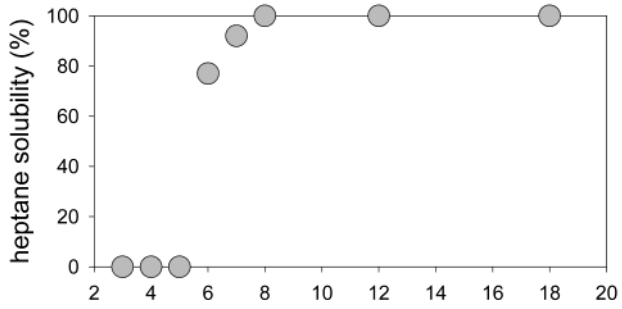


Figure 2. Heptane solubility versus the number of carbons in the *N*-alkyl group of *p*-Methyl Red-labeled poly(*N*-alkylacrylamides) prepared according to the method shown in Scheme 1 as measured by UV−vis spectroscopy of the polar and nonpolar phases of a mixture of heptane/90% ethanol−water (1:1 vol/vol) at 25 °C. In all cases, the phase-selective solubility was measured after the mixture had been heated to 70 °C (miscibility) and then allowed to cool to a resting biphasic state.

10^5, respectively. This suggests that phase-selective solubility can be seen for PNIPAM and PNODAM polymers with varying degrees of polymerization.

Phase-selective solubility of polymers can also be achieved in thermomorphic systems that employ two polar solvents. An example of such a system would be triethylamine and water. This system differs from other thermomorphic mixtures we have studied in that this thermomorphic solvent mixture has an LCST for its miscibility; an equal volume of these two solvents is miscible at 0 °C and immiscible at 25 °C. In this case, a PNIPAM-bound Methyl Red dye or dansyl probe was found to reside exclusively in the Et_3N phase after a homogeneous 0 °C 1:1 (vol/vol) mixture of Et_3N and H_2O was warmed to room temperature and phase separated. In this experiment, the PNIPAM was present at 2 wt %. This separation was completely reversible.

Conclusions

Phase-selective solubility can readily be engineered into a polymer. Small changes in the size of the *N*-alkyl group of a poly(*N*-alkylacrylamide) lead to significant changes in phase-selective solubility in situations where a polymer can dissolve in either a polar or a nonpolar phase of a thermomorphic mixture of heptane/90% EtOH−H_2O. The homopolymer of *N*-acryloxysuccinimide is a useful precursor to these poly(*N*-alkylacrylamide)s, and the product polymers can be separated from excess amines either by conventional precipitations or through the use of a polymeric reagent. Future work will examine poly(*N*-alkylacrylamide)s containing mixtures of *N*-alkyl groups, less polydisperse samples, and other polymers.

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Supporting Information Available: Full experimental details and photographs of PNIPAM and PNODAM resting biphasic mixtures illustrating the clean and complete separation of phases containing either protonated or nonprotonated *p*-Methyl Red dye labels. This material is available free of charge via the Internet at http://pubs.acs.org.

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