# A Combinatorial Approach to Studying the Effects of *N*-Alkyl Groups on Poly(*N*-alkyl and *N*,*N*-dialkylacrylamide) Solubility

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Soluble polymers including poly(*N*-alkylacrylamide)s with low mole percent loadings of pendant groups are of interest in applications in catalysis, synthesis, sequestration, and soluble affinity chromatography where their thermal and phase-dependent solubility facilitates purification and separation. This work describes a library synthesis and study of the effects of polymer composition on the phase-selective solubility of dye-labeled poly(*N*-*n*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers. To study the relative importance of *n*-octadecyl versus *n*-butyl groups, copolymers with different ratios of *n*-octadecylacrylamide and *n*-butylacrylamide but with similar degrees of polymerization and polydispersity were prepared by a split-pool synthesis using a highly soluble poly(*N*-acryloxy-2-dodecylsuccinimide) as the precursor. Polymer sequestrants were used to remove excess amines and the byproduct *N*-hydroxyl-2-dodecylsuccinimide without fractionation of the polyacrylamides. Other studies of dye-labeled poly(*N*,*N*-dialkylacrylamide)s prepared by the polymerization of *N*,*N*-dialkylacrylamides with methyl, ethyl, propyl, butyl, pentyl, and hexyl *N*-alkyl groups in a variety of thermomorphic or latent biphasic polar/nonpolar solvent mixtures showed that poly(*N*,*N*-dialkylacrylamide)s like poly(*N*-alkylacrylamide)s have phase-selective solubility that is highly dependent on the size of the *N*-alkyl group.

## Introduction

Polymer solubility is an important property of polymers and has been the subject of extensive experimental and theoretical study. Solubility can facilitate both analysis and use of polymers and both basic theory and qualitative discussions of polymer solubility are routinely addressed in polymer textbooks.[1] Extensive tabulations describe the solubility of various homopolymers in a range of solvents.[2] However, there are many aspects of polymer solubility that are not understood. For example, our recent work has addressed the origins of the Hofmeister effect, where aqueous solution components affect the poly(*N*-isopropylacrylamide) lower critical solution temperatures (LCSTs), providing new insight into the basis of these thermally induced phase changes.[3] We have also shown how library syntheses of isomeric polymers with mixtures of *N*-propyl and *N*-isopropyl groups or of poly(*N*-isopropylacrylamide)s with defined end groups can be used to probe effects of polymer structure on LCSTs.[4,5] Earlier we had introduced the concept of using split-pool synthesis to prepare libraries of polymers with similar degrees of polymerization to probe the effect of *N*-alkyl group structure on the phase-selective solubility of poly(*N*-alkylacrylamide) homopolymers,[6] polymers whose utility as catalyst supports has been established in other work.[7] That work showed that the polymer phase-selective solubility of poly(*N*-alkylacrylamide)s is surprisingly dependent on the structure of the *N*-alkyl group of the poly(*N*-alkylacrylamide)s with a distinct >1000-fold difference between the polar and nonpolar phase solubility occurring for poly(*N*-alkylacrylamide)s having an *N*-pentyl versus an *N*-hexyl alkyl group. This report describes similar dramatic changes in the phase-selective solubility of copolymers of *N*-butyl- and *N*-octadecylacrylamide and as the mole percent of the more hydrophobic groups in the polymer was varied in the copolymer. In addition, synthesis of a series of poly(*N*,*N*-dialkylacrylamide)s and a study of their phase selective solubility show that the relatively sharp changes in phase selective solubility seen for secondary polyacrylamides with different sized *N*-alkyl groups are also seen for tertiary poly(*N*,*N*-dialkylacrylamide)s in a range of different thermomorphic polar/nonpolar solvent mixtures.

The phase-selective solubility of polymers is important in applications where soluble polymers are used as phase anchors to recover and reuse catalysts, separate products, or as sequestrants.[7−12] Such chemistry generally requires that a soluble polymer support be soluble in the miscible solvent mixture containing substrate during a reaction but selectively soluble in a separate phase from product in a biphasic solvent mixture during workup and separation. Such phase-selective solubility can be designed into polymers and can be used in either latent and thermomorphic liquid/liquid biphasic systems with homopolymers as supports.[13,14]

A variety of solvents can be used in liquid/liquid biphasic systems.[8] Our group has mainly used heptane/ethanol/water or heptane/DMF solvent mixtures for latent or thermomorphic systems. Heptane/ethanol is an example of a latent biphasic system. This solvent mixture is monophasic at rest but a small perturbation (e.g., the addition of <5 vol % of water or the addition of some tetrabutylammonium iodide

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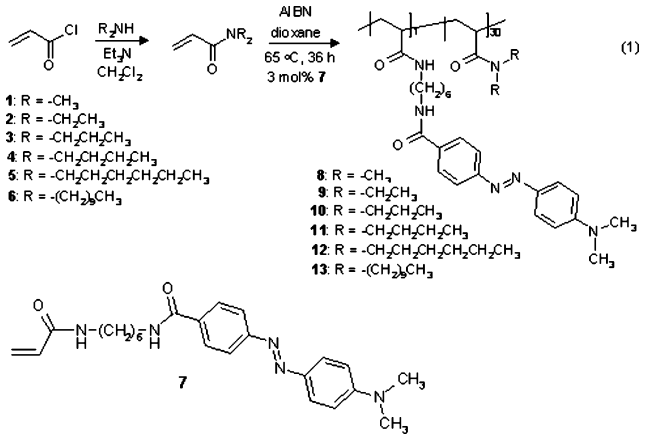
salt) is sufficient to produce a biphasic mixture. A thermomorphic system is a biphasic liquid/liquid solvent mixture that is biphasic at room temperature and that has significant miscibility at higher temperature.[14] For example, an equivolume mixture of heptane/DMF or heptane/90% aqueous ethanol is biphasic at room temperature but miscible at 70 °C. Recooling either of these miscible solvent mixtures reforms the original biphasic mixture. Such phase changes are seen in many solvent mixtures including, for example, fluorous/organic solvent systems.[15−17]

Applications of these and other phase-separating systems have emphasized the use of homopolymers or of copolymers that usually contain >95 mol % of a single type of repeating unit. For example, soluble polymers like poly(ethylene glycol) whose end groups are modified to support catalysts,[18] poly(*N*-isopropylacrylamide) with 1−5 mol % of the pendant amides modified to serve as catalyst ligands,[19,7] or poly(acrylic acid)-supported catalysts[20] can be ≥99.9% selectively soluble to the polar phase of a heptane/DMF or heptane/ethanol/water system. Nonpolar more hydrophobic polymers like terminally poly(isobutylene),[21,22] poly(*tert*-butylstyrene),[23] poly(octadecylacrylate)s,[9] poly(*N*-vinyloxazoline)s,[24] poly(*N*-octadecylacrylamide),[25] or polydimethylsiloxanes[26] can be equally phase-selectively soluble in the nonpolar phase of these same solvent mixtures so long as the mole percent loading of pendant groups or of terminal groups used as ligands or catalysts is <5 mol %. Similar effects are seen with fluorous polymer-bound catalysts in fluorous/organic thermomorphic systems.[16,17] However, while these polymers exhibit useful phase-selective solubility, greater versatility and higher loadings of reagents or catalysts might be possible using soluble polymer supports if copolymers can be designed where one of the copolymer substituents can define the phase-selective solubility of the polymer-supported species. The studies below address this issue. These studies also show that the dependence of phase-selective solubility on alkyl group size seen for earlier poly(*N*-alkylacrylamide)s is also seen with poly(*N*,*N*-dialkylacrylamide)s.

## Results and Discussion

Poly(*N*-alkylacrylamide) homopolymers that have pentyl versus hexyl *N*-alkyl groups exhibit a surprisingly high phase-selective solubility difference in a thermomorphic heptane/90% EtOH/$H_2O$ biphasic system.[6] To determine if this selective solubility is unique to secondary poly(*N*-alkylacrylamide)s, we have explored the phase selective solubility of a similar class of polymers, poly(*N*,*N*-dialkylacrylamide)s. Our earlier studies of both poly(*N*-alkylacrylamide)s and of LCSTs for poly(*N*-propylacrylamide) or poly(*N*-isopropylacrylamide) employed a library synthesis using aminolysis of the activated polyester poly(*N*-acryloxysuccinimide) (PNASI). However, our initial work using this same procedure to prepare tertiary poly(*N*,*N*-dialkylacrylamide)s showed that aminolysis of these activated esters using secondary amines was significantly slower. Incomplete aminolysis would leave reactive esters that could readily hydrolyze to form $-CO_2H$ groups that would likely affect our analysis of phase selective solubility. Accordingly we prepared poly(*N*,*N*-dialkylacrylamide)s using the synthetic sequence shown in eq 1.




The polymers prepared had a 3 mol % loading of the spectroscopic label **7** to facilitate phase selective solubility studies. The polymer products so prepared are not as identical in polydispersity and degree of polymerization as the library members studied in our earlier work nor are they as comparable as the library members of copolymers discussed below. However, the $M_w$ values are roughly comparable, as shown in Table 1.

To study the phase selective solubility of the polymers **8**−**13**, each sample of polymer was dissolved in a solvent to form a solution whose methyl red concentration was ∼$10^{-4}$ N. Then an equal volume of a second polar or nonpolar solvent was added to produce a biphasic mixture. The mixture was then heated to ∼70 °C. After a few minutes, a clear yellow homogeneous solution was obtained. This solution was then allowed to cool to room temperature, at which point the initial biphasic mixture reformed. Phase separation upon cooling is relatively fast (a video is provided in Supporting Information) with complete phase separation occurring in just a few minutes. After the phases had separated, samples of each phase were collected and analyzed by UV−vis spectroscopy. A number of different thermomorphic solvent mixtures were studied for most polymers. These included heptane/DMF, heptane/90% ethanol water, heptane/ethylene glycol diacetate, and pentadecane/dimethyl carbonate. The overall phase changes that occurred are illustrated by the drawings in Figure 1, and the phase selectivities that were seen are listed in Table 2 and shown graphically in Figure 2.

In the heptane/DMF mixture, poly(*N*,*N*-dimethyl-, poly(*N*,*N*-diethyl-, and poly-(*N*,*N*-dipropylacryl-amide) were selectively soluble in the DMF phase, whereas poly(*N*,*N*-dialkylacrylamide)s with four or more carbons in their alkyl groups were selectively soluble in the heptane phase. Similar results are seen for the heptane/90%EtOH·$H_2O$ and heptane/ethylene glycol diacetate mixtures. The same trends were seen in the pentadecane/dimethyl carbonate mixture. There was much ambiguity about the phase-selective solubility in only a few cases. At least in one example, the polymer had only modest phase-selective solubility. In that example, that is, the case of **11** in pentadecane/dimethyl carbonate, poly(*N*,*N*-dibutylacrylamide) was not very soluble in either solvent.

These results show that the dramatic differences seen in earlier phase-selective solubility for secondary poly(*N*-

**Table 1.** Weight Average Molecular Weights, Polydispersity Indexes, and Degrees of Polymerization for Poly(*N*,*N*-dialkylacrylamide)s[a]

| polymer | $M_w$ (Da) | PDI | DP |
|---|---|---|---|
| **8** | 60 430 | 1.13 | 528 |
| **9** | 48 420 | 1.43 | 261 |
| **10** | 32 070 | 1.60 | 127 |
| **11** | 72 880 | 1.34 | 292 |
| **12** | 84 640 | 1.67 | 210 |
| **13** | 56 330 | 1.62 | 98 |

[a] Polymerization reactions were carried out in dioxane at 65 °C, and the product polymers were characterized by GPC using a Viscotek GPC instrument with a Viscotek I-MBMMW-3078 mixed-bed column, a triple-detector system, including a Model VE3580 RI detector, and OmniSEC software.

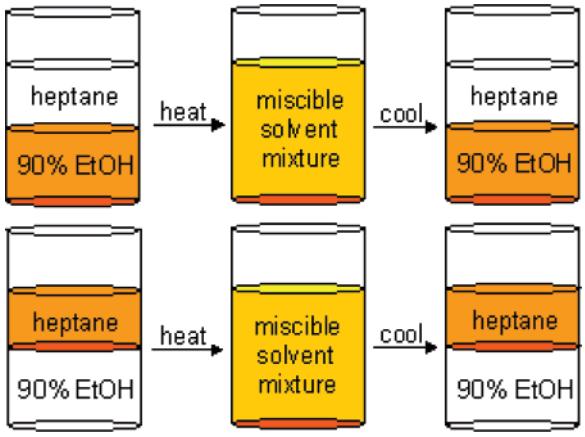



**Figure 1.** Phase changes for polymers **8**−**13** upon heating and cooling in thermomorphic polar/nonpolar solvent mixtures. The dye-labeled polymer was variously in either the less-dense nonpolar phase, the more-dense polar phase, or in a few cases, present to a significant extent in both phases.

alkylacrylamide)s with different-sized *N*-alkyl substituents are also seen for tertiary poly(*N*,*N*-dialkylacrylamide)s with different-sized *N*-alkyl substituents. The results of these studies, listed in Table 2, show that the origin of this phase-selective solubility behavior is not simply the result of the size of the *N*-alkyl substituent. While our earlier studies showed changes in phase-selective solubility when the *N*-alkyl substituent size changed from five to six carbons, the results here show that changing from propyl to butyl groups in poly(*N*,*N*-dialkylacrylamide)s is similarly effective in changing solubility. The effect of changing the total number of carbons in the substituents for a polar-phase soluble polymer (six for polymer **10**) to a larger number of carbons (e.g., eight for polymer **11**) appears to be more important than substituent chain length. The phase-selective solubility and the effect of alkyl group size on the phase-selective solubility are general for a range of polar/nonpolar solvent mixtures.

To study the effect of polymer structure on poly(*N*-alkylacrylamide) copolymer phase-selective solubility ,we used a version of a library synthesis of these polymers that we described earlier.[6] An earlier study showed that it was possible to prepare a library of poly(*N*-alkylacrylamide) homopolymers with different *N*-alkyl groups which have the same degree of polymerization and polydispersity using a split-pool synthesis approach. This earlier approach used PNASI as the starting material. PNASI is an activated polyester that can be easily cleaved when treated with primary amines. This methodology works well for the preparation of different poly(*N*-alkylacrylamide) homopolymers. However, it was deficient when applied to the synthesis of the copolymers. Since PNASI is only soluble in few polar solvents (e.g., DMF, DMA, DMSO), this methodology was unsuccessful because more hydrophobic copolymers containing octadecyl groups are insoluble in these solvents. This limitation led us to produce a more soluble version of PNASI by the addition of an alkyl group to the PNASI to obtain an activated ester polymer that had better solubility. We chose

**Table 2.** Phase-Selective Solubility of Poly(*N*,*N*-dialkylacrylamide)s in Various Thermomorphic Systems[a]

| polymer | solvent mixture (50:50, vol/vol) | solubility ratio (nonpolar/polar) | phase-selective solubility (%) |
|---|---|---|---|
| **8** | heptane/DMF | 1:>678 | 0.15 |
| **9** | heptane/DMF | 1:>1000 | 0.1 |
| **10** | heptane/DMF | 1:>1000 | 0.07 |
| **11**[b] | heptane/DMF | >50:1 | 98.0 |
| **12** | heptane/DMF | >420:1 | 99.8 |
| **13**[b] | heptane/DMF | >784:1 | 99.9 |
| **8** | heptane/ 90% EtOH/$H_2O$ | 1:>1000 | 0.1 |
| **9** | heptane/ 90% EtOH/$H_2O$ | 1:>1000 | 0.1 |
| **10** | heptane/ 90% EtOH/$H_2O$ | 1:>1000 | 0.05 |
| **11** | heptane/ 90% EtOH/$H_2O$ | >1000:1 | 99.9 |
| **12** | heptane/ 90% EtOH/$H_2O$ | >525:1 | 99.8 |
| **13** | heptane/ 90% EtOH/$H_2O$ | >190:1 | 99.5 |
| **8** | heptane/ $AcOCH_2CH_2OAc$ | 1:>2000 | 0.05 |
| **9** | heptane/ $AcOCH_2CH_2OAc$ | 1:>2000 | 0.05 |
| **10** | heptane/ $AcOCH_2CH_2OAc$ | 1:2.7 | 27.0 |
| **11** | heptane/ $AcOCH_2CH_2OAc$ | >1000:1 | 99.9 |
| **12** | heptane/ $AcOCH_2CH_2OAc$ | >500:1 | 99.8 |
| **13** | heptane/ $AcOCH_2CH_2OAc$ | >500:1 | 99.8 |
| **8** | pentadecane/ $CH_3OCOOCH_3$ | 1:>2000 | 0.05 |
| **9** | pentadecane/ $CH_3OCOOCH_3$ | 1:>2000 | 0.05 |
| **10** | pentadecane/ $CH_3OCOOCH_3$ | 1:>2000 | 0.05 |
| **11** | pentadecane/ $CH_3OCOOCH_3$ | 1:3 | 25 |
| **12** | pentadecane/ $CH_3OCOOCH_3$ | > 513:1 | 99.8 |
| **13** | pentadecane/ $CH_3OCOOCH_3$ | > 140:1 | 99.3 |

[a] Phase-selective solubilities were measured by analyzing the polar and nonpolar phase for the presence of the azo dye at ~430 nm. These analyses assumed the azo dye had the same extinction coefficient in both solvents. [b] In this example, the polymer had low solubility in either solvent.

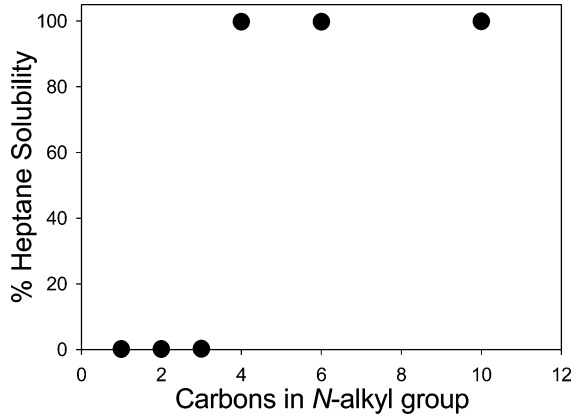
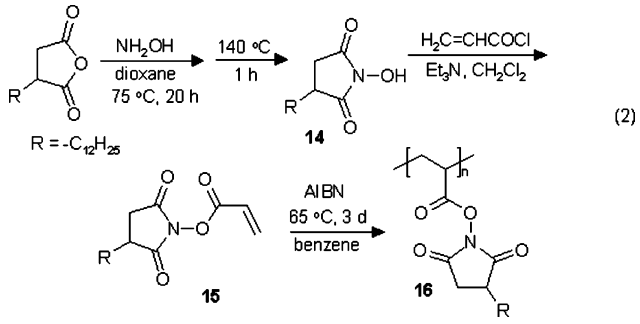



**Figure 2.** Nonpolar phase selectivity versus the number of carbons in the alkyl groups of *p*-methyl red-labeled poly(*N*,*N*-dialkylacrylamide)s as measured by UV−vis spectroscopic analysis of the polar and nonpolar phases of the thermomorphic mixtures (cf. Table 2). The data plotted are for a heptane/90% ethanol/water thermomorphic mixture.

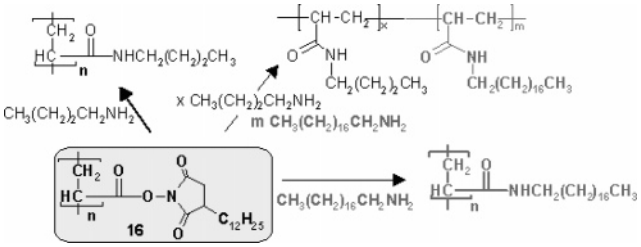
to synthesize poly(*N*-acryloxy-2-dodecylsuccinimide) or PNADSI using the chemistry in eq 2.




PNADSI proved to be more generally soluble than PNASI and had excellent solubility in $CH_2Cl_2$ ensuring that the starting materials and the products stayed in solution during the synthesis of the copolymers. PNADSI is also soluble in ethyl ether, chloroform, benzene, dioxane, and THF at a 0.3 M concentration.

Our past work had previously shown that *p*-methyl red-labeled homopolymers poly(*N*-*n*-butylacrylamide) and poly(*N*-*n*-octadecylacrylamide) show opposite phase-selective solubility in a heptane/90% ethanol·$H_2O$ thermomorphic mixture.[6] Poly(*N*-*n*-butylacrylamide) is ≥99.9% selectively soluble in the polar phase, and poly(*N*-*n*-octadecylacrylamide) was found to be ≥99.9% selectively soluble in the nonpolar heptane phase. The results in these systems showed that polymers with an *n*-butylacrylamide repeating unit are more soluble in polar solvents than polymers whose repeating units had larger more-lipophilic *N*-alkyl substituents. Increasing the size of an *N*-alkyl substituent by one carbon in these earlier studies led to a >1000-fold change in polar/nonpolar phase solubility. It is unclear what would happen if you have a polar and a nonpolar component in the same polymer. Thus, we created libraries of *p*-methyl red-labeled poly(*N*-*n*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers with different ratios *N*-*n*-octadecylacrylamide and *N*-*n*-butylacrylamide to test the relative importance of "polar phase-soluble" and "nonpolar phase-soluble" monomer groups in determining a copolymer's phase-selective solubility.

**Scheme 1.** Split-Pool Synthesis of Homopolymers of Poly(*n*-*N*-butylacrylamide) and Poly(*n*-*N*-octadecylacrylamide) and of Copolymers with Mixtures of *n*-Butyl and *n*-Octadecyl Groups Using Poly(*N*-acyloxy-2-dodecylsuccinimide) as a Common Starting Material




The library synthesis of copolymers used PNADSI as the parent polymer to prepare poly(*N*-alkylacrylamide) copolymers that would be as identical as possible in terms of polydispersity, degree of polymerization, and stereochemistry (Scheme 1). To confirm that the aminolysis of PNADSI produces materials like those we prepared earlier,[6] we first prepared poly(*N*-*n*-butylacrylamide) and poly(*N*-*n*-octadecylacrylamide) by allowing PNADSI to react with either *n*-butylamine or *n*-octadecylamine and studied the phase-selective solubility of the product homopolymers. These homopolymers showed the same phase-selective solubility as poly(*N*-*n*-butylacrylamide) and poly(*N*-*n*-octadecylacrylamide) homopolymers prepared earlier. Then a series of PNNODAM/PNNBuAM copolymers were prepared by treating PNADSI with different ratios of *n*-octadecylamine, *n*-butylamine, and *p*-methyl red in $CH_2Cl_2$. The ratio of the amine component (*n*-butylamine and *n*-octadecylamine) to the *p*-methyl red label was 100:1. Since unreacted PNADSI could hydrolyze, forming acrylic acid groups that could affect the measured phase-selective solubility of poly(*N*-*n*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers, a 3.5-fold excess of amines was used. This led to a product mixture that contained some amine, some unreacted methyl red label, and the byproduct *N*-hydroxy-2-dodecylsuccinimide from the amidation reaction. While these products can be removed by precipitation of the polymers in appropriate solvents, we sought to purify the products without significant fractionation. This was accomplished by using solid-phase resin sequestrants,Amberlyst 15 and Amberlite IRA 400 ($^-$OH form) resins, to sequester the excess amines and the *N*-hydroxysuccinimide byproduct, respectively.

We previously showed that Amberlyst 15 is a very selective agent for amine sequestration in the presence of a poly(*N*-alkylacrylamide). This result was reconfirmed in experiments using methyl red-labeled poly(*N*-isopropylacrylamide) and poly(*N*-octadecylacrylamide) homopolymer solutions containing unreacted amines. These experiments showed that amines were effectively removed from the polymer with this sulfonated ion-exchange resin (Amberlyst 15) without any change in polymer concentration based on the absence of any change in the absorption resulting from the dye-labeled polymer as measured by UV−vis spectroscopy.

*N*-Hydroxy-2-dodecylsuccinimide was removed from the products of our library synthesis in a similar way using

**Table 3.** Molecular Weight, Degree of Polymerization, and Polydispersity of Copolymers Prepared by Aminolysis of Poly(*N*-hydroxydodecylsuccinimide) with *n*-octadecyl- and *n*-Butylamine[a]

| octadecylacrylamide (mol %) | $M_w$ | DP | PDI |
|---|---|---|---|
| 100 | 143 820 | 143 | 3.12 |
| 58 | 94 120 | 228 | 2.11 |
| 48 | 79 300 | 213 | 2.08 |
| 0 | 57 410 | 180 | 2.5 |

[a] Phase-selective solubilities were measured by analysis of the polar and nonpolar phases for the presence of the azo dye at ~ 430 nm. These analyses assumed that the azo dye had the same extinction coefficient in both phases.

Amberlite IRA 400 (an ammonium hydroxide containing ion-exchange resin). Amberlite IRA 400 is known to be useful as a sequestering agent for the removal of *N*-hydroxysuccinimide.[27] Experiments showed that 2 equiv of Amberlite IRA 400 added to solutions containing 1 equiv of *N*-hydroxydodecylsuccinimide completely removed the succinimide from solution. Separate studies using methyl red-labeled PNNODAM/PNNBuAM copolymers were then used to show that this basic resin does not adsorb the copolymer. UV−vis absorption spectroscopy that showed the concentration of the dye-labeled copolymers was the same before and after treatment with the Amberlite IRA resin confirmed that no polymer absorption by the Amberlite resin occurred.

The product copolymers prepared in this chemistry were characterized by $^1$H NMR spectroscopy and by GPC analysis. $^1$H NMR spectroscopy was used to determine the ratio of octadecylacrylamide and *n*-butylacrylamide in the PNNODAM/PNNBuAM copolymer. The determination of the ratios of acrylamides in the copolymer was based in the integration of the $CH_3$ peaks of each amide. The triplet of the $CH_3$ group of the *n*-octadecyl group of the polyacrylamide copolymer appears at $\delta$ 0.88 while the triplet of the methyl group of *n*-butylacryl, the polyacrylamide copolymer, is at $\delta$ 0.92. $^1$H NMR spectra shown in the experimental section show how the changes in methyl group peak of octadecylacrylamide increased when higher amounts of octadecylamine were used during the amidation of PNADSI. These $^1$H NMR spectroscopy studies showed that *n*-octadecylamine and *n*-butylamine react at approximately the same rate with PNADSI. When a 1:5 molar ration of *n*-octadecylamine/*n*-butylamine was used to prepare a copolymer, the product copolymer had a 1:4 ratio of *n*-octadecylamide/*n*-butylamide groups based on the integration of the methyl groups assigned to each group. Similar results were seen in the synthesis of other PNNODAM/PNNBuAM copolymers.

The molecular weight and molecular weight distribution of the PNNODAM/PNNBuAM copolymers were analyzed by gel permeation chromatography (GPC) using a Viscotek multidetector system. The GPC instrument uses a highly fluorinated mixed-bed column to minimize problems of sorption of these polyacrylamides seen with other columns. The results obtained from the GPC studies show that PNNODAM-PNNBuAM copolymers have a degree of polymerization of ~200 ± 20 and a PDI of ~2.1 (Table 3). The data for the homopolymer poly(*N*-*n*-octadecylacrylamide) suggest that this polymer has significantly different polydispersity and a lower degree of polymerization than

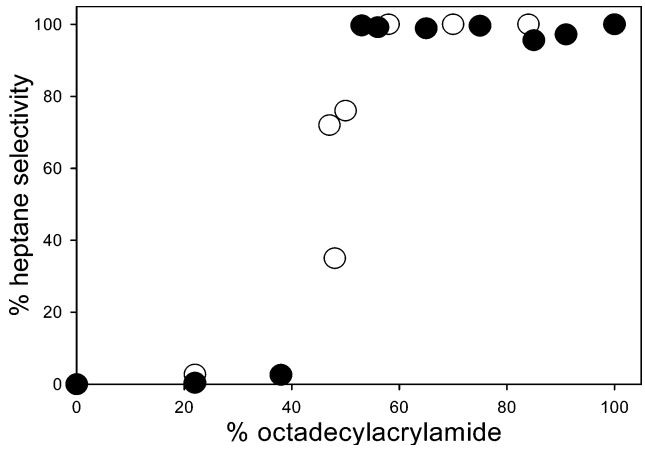



**Figure 3.** Phase selective solubility of *N*-*n*-butyl *N*-*n*-octadecyl polyacrylamide copolymers in heptane versus DMF. The results of multiple experiments are shown by the open and closed symbols.

the other polymers in this table. We could not determine if this reflected a real difference or if column−substrate interactions of this polymer affected the GPC analysis. Our experience with other analyses of other poly(*N*-alkylacrylamide)s on other supports has shown that such interactions can occur: indeed, the proprietary support used was chosen because it did not have such problems for poly(*N*-isopropylacrylamide). What we can say is that the PDI of the other polymers is consistent with what would be expected for a conventional radical polymerization and that this suggests that the data in Table 3 for the poly(*n*-octadecylacrylamide) homopolymer may be less reliable.

Earlier studies of poly(*N*-alkylacylamide) homopolymers demonstrated that poly(*N*-alkylacrylamide)s with six or more carbons in their *N*-alkyl group are phase-selectively soluble in the heptane phase of a heptane/aqueous ethanol or heptane/DMF thermomorphic solvent mixture. The opposite was observed for poly(*N*-alkylacrylamide)s with five or fewer carbons in their *N*-alkyl group. Such polymers are selectively soluble in the polar DMF or 90% EtOH/$H_2O$ phase. In the study of PNNODAM/PNNBuAM copolymers, we expected to see that the octadecylacrylamide monomer had a dominant influence in the polymer's solubility. However, the results shown in Figure 3 and listed in Table 4 showed that on the basis of the mole percentage, the hydrophilic and the hydrophobic butyl and octadecyl substituted repeating units are of comparable importance in the determination of the phase-selective solubility. On a weight percent basis, the polar phase soluble *N*-butyl-substituted repeating unit has more influence. In retrospect that is perhaps understandable because polar−polar interactions are generally stronger interactions than hydrophobic interactions. These results do, however, differ from results of earlier studies of structural effects on LCSTs where studies of poly(*N*-*n*-propylacrylamide-*co*-*N*-*i*-propylacrylamide) copolymers showed a linear dependence of the LCST temperature with the mole percent of *n*-propyl groups.[3] In the example here, the phase-selective solubility of the nonpolar phase changed dramatically with the composition of *n*-butyl- and *n*-octadecyl-substituted repeating units in the copolymer.

**Table 4.**
Poly(*N*-*n*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) Copolymer Phase-Selective Solubility in a Heptane/DMF Thermomorphic System[a]

| octadecyl content of copolymer (mol %) | solubility ratio (nonpolar/polar) | phase-selective solubility in heptane (%) |
|---|---|---|
| 100 | >2000:1 | 99.99 |
| 84 | >1000:1 | 99.7 |
| 70 | >1000:1 | 99.9 |
| 58 | >1000:1 | 99.4 |
| 50 | 3.4:1 | 76 |
| 48 | 1:2 | 35 |
| 22 | 1:725 | 2.7 |
| 0 | 1:>1000 | 0.2 |

[a] Phase-selective solubilities were measured by analysis of the polar and nonpolar phases for the presence of the azo dye at ~ 430 nm. These analyses assumed that the azo dye had the same extinction coefficient in both phases.

## Conclusion

Poly(*N*,*N*-dialkylacrylamide)s exhibit phase-selective solubility in thermomorphic polar/nonpolar solvent mixtures that depends on the size of the *N*-alkyl substituent. As is true with poly(*N*-alkylacrylamide)s, a significant difference between polar versus nonpolar phase solubility is seen when the size of the alkyl substituent changes (in this case from three to four carbons). Poly(*N*-acryloxy-2-dodecylsuccinimide) has been shown to be a more versatile precursor for synthesis of libraries of poly(*N*-alkylacrylamide)s that can be easily purified using polymeric resins as sequestrants for excess reagents or byproducts. Studies of libraries of poly(*N*-alkylacrylamide) copolymers prepared by aminolysis of PNADSI showed that long-chain *N*-alkyl groups do not dominate the phase-selective solubility of these copolymers because *n*-butyl and *n*-octadecyl groups were roughly comparable in determining phase-selective solubility in the poly(*N*-*n*-octadecylacrylamide-*co*-*N*-*n*-butylacrylamide) copolymers.

## Experimental Section

**Materials.** Dodecylsuccinic anhydride was obtained from TCI America. All other reagents were purchased from Aldrich Chemical Co. These and other commercial reagents were used without further purification.

**Instrumentation.** $^1$H NMR spectra were obtained using a Varian Mercury 300, Inova 500, or Inova 300 spectrometer at 300 or 500 MHz. $^{13}$C NMR spectra were obtained using a Mercury 300, Inova 500, or Inova 300 spectrometer at 75 or 125 MHz. The phase-selective solubility studies were performed using a Cary 100 scanning UV−vis spectrophotometer using azo dye (*p*-methyl red) labeled polymers. The poly(*N*-alkylacrylamide)s were analyzed by gel permeation chromatography using a Viscotek GPC instrument. The experiments were carried out using a Viscotek I-MBMMW-3078 mixed-bed column, a triple-detector system including a Model VE3580 RI detector, and OmniSEC software.

**Synthesis of *N*-Hydroxy-2-dodecylsuccinimide (14).** Hydroxylamine hydrochloride (4.9 g, 69.3 mmol) was suspended in 25 mL of dioxane. The suspension was added to a 100 mL round-bottomed flask containing 18.6 g (69.3 mmol) of 2-dodecylsuccinic anhydride, and the mixture was stirred at 75 °C for 20 h. After the dioxane was removed at reduced pressure, the residue was dried at 140 °C for 1 h under vacuo. The hot product was precipitated in 50 mL of hexanes with stirring. Complete precipitation occurred when the mixture cooled down to room temperature. The precipitate was filtered and recrystallized from diethyl ether. The reaction yielded 9.83 g (67%) of the desired product. mp: 74−77 °C (ref 28, mp 76 °C). IR (KBr pellet, cm$^{-1}$): $\nu$ 3123, 1774, 1716, 1678. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.881 (3H, t, $J$ = 7 Hz), 1.29 (bs, 20H), 1.55 (1H, m), 1.90(1H, m), 2.40 (1H, dd, $J$ = 3, 14 Hz), 2.84 (2H, m), 8.14 (bs, 1H).

**Synthesis of *N*-Acryloxy-2-dodecylsuccinimide (15).** *N*-Hydroxy-2-dodecylsuccinimide (7.17 g, 25.3 mmol) was added to a 250 mL round-bottomed flask containing triethylamine (3.5 mL, 25.3 mmol) and 170 mL of $CH_2Cl_2$. Then, the solution was cooled with an ice−water bath to 0 °C, and acryloyl chloride (3 mL, 35 mmol) in 15 mL of $CH_2Cl_2$ was added dropwise over a period of 30 min using an addition funnel. After 1 h at 0 °C, the solution was allowed to warm to room temperature and was washed four times with 150 mL of $NH_4Cl$, once with 150 mL of $H_2O$, and once with 150 mL of brine. The solution was dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was dried in vacuo and yielded 7.84 g (92%) of product having a mp of 41−45 °C. IR (KBr pellet, cm$^{-1}$): $\nu$ 2910, 2840, 1775, 1740, 1624, 1453, 1418. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.882 (3H, t, $J$ = 7 Hz), 1.231−1.345 (21H, bm), 1.41 (1H, m), 1.64 (1H, m), 1.95 (1H, m), 2.52 (1H, m), 2.95 (2H, m), 6.16 (1H, dd, $J$ = 1, 10.5 Hz), 6.32 (1H, dd, $J$ = 10.5, 17 Hz), 6.69 (1H, dd, $J$ = 1, 17 Hz). HRMS: ($C_{19}H_{31}O_4NH^+$ (M + H$^+$)) 338.2331.

**Synthesis of Poly(*N*-acryloxy-2-dodecylsuccinimide) (16, PNADSI).** *N*-Acryloxy-2-dodecylsucc-inimide (14.42 g, 42.8 mmol) and AIBN (0.012 g, 0.07 mmol) were dissolved in 250 mL of benzene in a dry 500 mL round-bottomed flask equipped with a condenser and a magnetic stir bar. While toluene could be used in place of benzene (as a less hazardous solvent), there is less chain transfer with benzene. The solution was degassed three times using the freeze−pump−thaw procedure. The solution was heated to 65 °C and stirred for 3 d to form the polymeric active ester poly(*N*-acryloxy-2-dodecylsuccinimide) which was isolated by removal of the benzene under reduced pressure. The crude polymeric material was then dissolved in 50 mL of THF, and the solution was added slowly to 500 mL of dry acetonitrile. A gum formed quickly. After centrifugation, the solvent was decanted from this gum, and the gum was dried under vacuum to yield an amorphous polymer. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.882 (3H, t, $J$ = 7 Hz), 1.29−1.37 (21H, bs), 1.54 (1H, bs), 1.90 (1H, bs), 2.18(bs, 1H), 2.43 (1H, bs), 2.87 (2H, bs), 3.3 (1H, bs).

**Synthesis of Poly(*N*-alkylacrylamide) Copolymers (PNNODAM/PNNBuAM).** Samples of the same batch of PNADSI (0.3 g, 0.89 mequiv) were dissolved in 5 mL aliquots of $CH_2Cl_2$. In separate 10 mL round-bottomed flasks, different mixtures of *n*-octadecylamine, *n*-butylamine, and

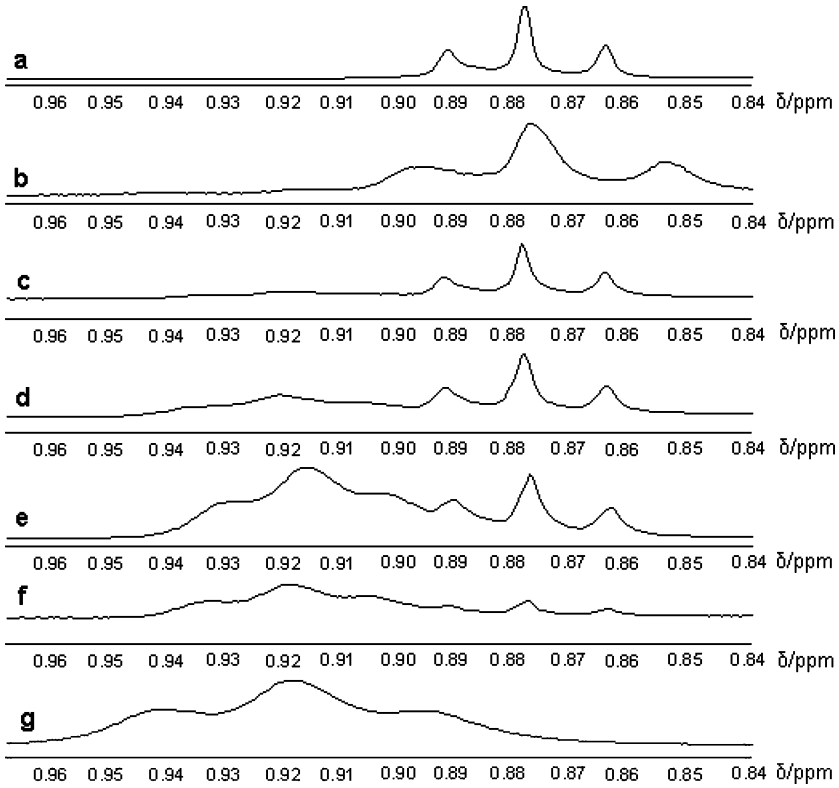



**Figure 4.** $^1$H NMR (500 MHz, $CDCl_3$) spectroscopic analysis of the ratio of *n*-butyl/*n*-octadecyl groups in poly(*N*-*n*-octadecylacrylamide)-*c*-poly(*N*-*n*-butylacrylamide) copolymers using the integration of methyl groups to determine the mole percent of *n*-octadecyl groups in the copolymers: (a) 100 mol % octadecyl; (b) 86% mol % octadecyl; (c) 73 mol % octadecyl; (d) 57%; (e) 35 mol % octadecyl; (f) 25 mol %; (g) 0 mol % octadecyl.

a primary amine-labeled derivative of *p*-methyl red were dissolved in 5 mL of $CH_2Cl_2$. The amine solutions were transferred to these PNADSI solutions. Each mixture used the same total amount of amines: 3 mmol of *n*-octadecylamine/*n*-butylamine and 0.03 mmol of the amine-terminated *p*-methyl red. The reaction mixtures were stirred at room temperature for 24 h, and 2 g of Amberlyst 15 was added to remove the excess of amines. After the suspension was shaken for 24 h, the solution was filtered, and the filtrate was treated with 2 g of Amberlite IRA 400 (OH form) for another 24 h to remove the byproduct *N*-hydroxy-2-dodecylsuccinimide. The resulting red suspensions were filtered to remove the resin, and the solvent was removed under reduced pressure. Each product polymer was then dried under vacuum and analyzed by $^1$H NMR spectroscopy. These $^1$H NMR analyses were used to determine the relative amount of octadecyl and butyl groups in the product copolymers using the NMR spectra shown in Figure 4.

**Synthesis of *N*,*N*-Dialkylacrylamides.** The synthesis of *N*,*N*-diethylacrylamide (**2**) is representative of the procedure used for all *N*,*N*-dialkylacrylamides. Diethylamine (4.1 mL, 39.3 mmol) and triethylamine (5.5 mL, 39.5 mmol) were dissolved in 263 mL of dichloromethane in a 500 mL round-bottomed flask. The solution was cooled to 0 °C, while being stirred, and acryloyl chloride (3.32 mL, 39.2 mmol) in 50 mL of $CH_2Cl_2$ was added dropwise over a period of 1 h at 0 °C using an addition funnel. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h. The solution was then washed twice with 50 mL of $NH_4Cl$ (sat) and twice with 50 mL of $Na_2CO_3$ (sat). It was then dried over $Na_2SO_4$, filtered, and concentrated at reduced pressure. The product was dissolved in 30 mL of ethyl acetate and was washed with $Na_2CO_3$ (sat) (2 × 50 mL) and twice with 50 mL of brine. Drying over $Na_2SO_4$, followed by filtration and concentration at reduced pressure, yielded an oil that was distilled to yield 2.25 g (45%) of *N*,*N*-diethylacrylamide (bp = ∼58−59 °C at 0.6 Torr). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.16 (m, 6H), 3.36 (m, 2H), 3.42 (m, 2H), 5.64 (dd, 1H, cis $\beta$-$CH_2$, $J$ = 10.3 and 2.0 Hz), 6.32 (dd, 1H, trans $\beta$-$CH_2$, $J$ = 16.7 and 2.0 Hz), 6.53 (dd, 1H, $\alpha$-$CH_2$, $J$ = 16.7 and 10.3 Hz). In some cases, acrylic acid was present in the distillate. If this were the case, the product was then dissolved in 50 mL $CH_2Cl_2$ and washed three times with 50 mL of 3 M KOH. The $CH_2Cl_2$ solution was then dried over $Na_2SO_4$, filtered, and dried at reduced pressure. The residue was dried in vacuo to yield the product as a colorless liquid product.

**Synthesis of Poly(*N*,*N*-dialkylacrylamide)s.** The synthesis of poly(*N*,*N*-dipropylacrylamide) (**10**) is representative of the procedure used to prepare all the poly(*N*,*N*-dialkylacrylamide)s. In a 500 mL round-bottomed flask equipped with a condenser and a magnetic stir bar, *N*,*N*-dipropylacrylamide (2.00 g, 12.9 mmol), acrylamide−methyl red (0.1813 g, 0.43 mmol), and AIBN (0.0074 g, 0.045 mmol) were dissolved in 86 mL of dioxane. The solution was degassed twice using the freeze−pump−thaw procedure. The solution was then stirred and heated for 36 h at 40 °C. The dioxane was removed under reduced pressure. The reaction product was purified by silica gel column chromatography using a 9:1 mixture of acetone/methanol. After the solvents

were under reduced pressure, 1.28 g of product was obtained (68% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.6−1.0 (br m, 6H), 1.0−2.0 (br m, 6H), 2−2.7 (br m, 1H), 2.8−3.8 (br m, 4H), 7.86 (m, 0.3H). GPC analysis was carried out in THF using polystyrene standards: $M_n$ = 20054, $M_w$ = 32071, PDI = 1.60.

**Synthesis of Amine-Terminated Methyl Red.** {2-[4-(Dimethylamino)phenylazo]benzoic acid} (3.90 g) and 100 mL of $CH_2Cl_2$ were added to an oven-dried flask, which was flushed with $N_2$. CDI (2.40 g) in 36.5 mL of $CH_2Cl_2$ was added by forced siphon with a cannula, and the mixture was stirred vigorously under $N_2$. After it was stirred for 7 h, the solution was transferred by forced siphon with a cannula into an $N_2$-flushed flask containing 8.47 g of 1,6-hexanediamine in 85 mL of $CH_2Cl_2$. The methyl red solution was added dropwise for 1 h using an addition funnel. The mixture was stirred under $N_2$ flow overnight. The resulting orange mixture was filtered, and a dark red solution was obtained. The solution was washed with $H_2O$ (3 × 150 mL), dried over $Na_2SO_4$, filtered, and dried under reduced pressure. The residue was dried in vacuo and yielded 2.56 g (48%) of an orange solid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.4 (m, 6H), 1.7 (m, 4H), 2.6 (t, 2H), 3.0 and 3.1 (2s, 6H), 3.5 (q, 2H), 6.8 (d, 2H), 7.5 (m, 2H), 7.7−7.8 (m, 3H), 8.4 (m, 1H), 9.1 (br, 1H).

**Synthesis of Acrylamide-Methyl Red (7).** Amine-terminated methyl red (2.56 g, 6.98 mmol) and triethylamine (0.97 mL, 6.98 mmol) were dissolved in 46.5 mL of dichloromethane in a 100 mL round-bottomed flask. The solution was cooled to 0 °C, while being stirred, and acryloyl chloride (0.89 mL, 10.5 mmol) in 50 mL of $CH_2Cl_2$ was added dropwise over a period of 1 h at 0 °C using an addition funnel. The reaction mixture was stirred at 0 °C for 1 and at room temperature for 1 h. The solution was washed with $NH_4Cl$ (sat) (1 × 50 mL). This precipitated the product, and the solution was washed with 3 M KOH (1 × 50 mL). The aqueous phase was extracted with $CH_2Cl_2$ (5 × 100 mL). The organic phase was extracted with 3 M KOH (3 × 100 mL) and $dH_2O$ (3 × 100 mL). The solution was dried over $Na_2SO_4$, filtered, and concentrated at reduced pressure. The residue was dried in vacuo and yielded 1.49 g (79%) of an orange solid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.30−1.7 (m, 8H), 3.11 (s, 6H), 3.34 (q, 2H, $J$ = 6.6 Hz), 3.46 (q, 2H, $J$ = 6.6 Hz), 5.61 (dd, 1H, cis $\beta$-$CH_2$, $J$ = 10.2 and 2.1 Hz), 5.8 (br t, 1H), 6.28 (dd, 1H, trans $\beta$-$CH_2$, $J$ = 17 and 2.1 Hz), 6.10 (dd, 1H, $\alpha$-$CH_2$, $J$ = 17 and 10.2 Hz), 6.39 (br t, 1H), 6.76 (d, 2H, $J$ = 9 Hz), 7.88 (m, 6H).

**UV−vis Analysis of the Methyl Red-Labeled Copolymers.** The *p*-methyl red-labeled PNNODAM/PNNBuAM copolymers formed above were then dissolved in either nonpolar (e.g., heptane) or polar (e.g., DMF) solvents to form a solution whose methyl red concentration was approximately $10^{-4}$ M. Then, an equal amount of the other solvent was added (e.g., the nonpolar solvent heptane was added to the polar DMF solution or the polar solvent DMF was added to the nonpolar heptane solution), and the biphasic system was heated to 70 °C. This heating produced a clear, monophasic reddish solution. Then, the solution was allowed to cool to room temperature, and the solution phase separated. Centrifugation of the product biphasic system using Jouan CT422 was used to ensure complete phase separation. The phases were then separated, and each was analyzed using a UV−vis spectrometer. The extinction coefficients were considered to be the same on each solvent.

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**Supporting Information Available.** A video illustrating the phase separation of a dye-labeled poly(*N*,*N*-dialkylacrylamide) (which is typical of separations of the poly(*N*-alkylacrylamide) copolymers) and experimental details for the syntheses of specific poly(*N*,*N*-dialkylacrylamide)s. This material is available free of charge via the Internet at http://pubs.acs.org.

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