MOLECULARLY ENGINEERING HOMOGENOUS CATALYSTS

A Senior Honors Thesis

by

REAGAN REBEKAH HUGHES

Submitted to the Office of Honors Programs
& Academic Scholarships
Texas A&M University
in partial fulfillment of the requirements of the

UNIVERSITY UNDERGRADUATE
RESEARCH FELLOWS

April 2001

Group: PHYSICAL SCIENCE

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Approved as to style and content by:

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Edward A. Funkhouser

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ABSTRACT

Molecularly Engineering Homogeneous Catalysts
(April 2001)

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A critical issue in the design of new 'Green' recoverable reusable catalyst is the separation strategies used for catalyst recovery. Using materials and solvents that are miscible at elevated temperature but phase separate at low temperature we have developed new strategies for homogeneous catalyst recovery. Poly (N-isopropylacrylamide) and poly (N-octadecylacrylamide) supports, for example, yield recoverable catalysts that are selectively soluble in the lower (polar) phase and the upper (non-polar) phase, respectively. To explore the phase distribution continuum for other polymers, we have prepared poly (N-acryloxysuccinimide) (PNASI) and used this reactive polymer to prepare dye-labeled C3-C18-poly (N-alkylacrylamide) supports. UV analysis of these dye-modified polyacrylamides' phase solubility at ambient and elevated temperature will be described. Such experiments probe the phase behavior of these polymer supports as a function of side chain length and can be accomplished in a combinatorial fashion using PNASI as the common starting material. The potential for such supports in catalysis will be described.

To my mom

Acknowledgments

Dr. David Bergbreiter

Philip Osburn

The Bergbreiter Group

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INTRODUCTION

Abstract

This paper reviews the recent progress in developing new schemes to recover and reuse homogeneous catalysts. The goals of this work are to maintain or also increase the already high levels of selectivity and reactivity for these catalysts while imbuing them with greater environmental friendliness. The specific focus of my work is one of the main issues associated with homogeneous catalysts recovery: development of a solvent system that allows high reactivity for a catalysts but which incorporates by design a facile separation method by which catalyst and products can be separated. Here I describe new, recoverable, reusable polymer supports with phase selective solubility and show how this phase selective solubility is based on a polymer's pendant side chain hydrophobicity or hydrophilicity.

Catalysis can arguably be considered the most important area in chemistry; due to its wide application in every field of science. With its wide variety of uses, the further improvement in catalysts and the development of new methods for catalysis benefits the scientific community as a whole. Catalysts open up new worlds of reactions and enable breakthroughs in medicine, chemistry, and other areas by providing economic access to new chemicals and materials. Such chemistry not only has the potential to increase the standard of living; it can also increase academic knowledge.

One area of relatively new research in catalysis deals with the broad area of homogeneous catalysis. Homogeneous catalysis is catalysis where the reactants and catalysts are in the same phase. Such a situation optimizes the catalytic effectiveness of a homogeneous transition metal catalyst vis-à-vis a heterogeneous (insoluble) transition metal catalyst in that every metal in the homogeneous catalyst can be active. In the case of a heterogeneous catalyst, only metals at the surface of the metal are involved in

catalysis – the majority (the rest) of the metal atoms are inaccessible to substrates. These homogeneous catalysts are widely used in pharmaceutical chemistry and other fine chemical synthesis because such catalysts often have high selectivity and reactivity as a result of the exquisite control of the electronic and steric environment around a metal afforded by ligands.[1] However, these systems present problems in the separation of the catalyst from the solvent and products. Recovery and reusability of the catalyst is desired because of the high cost of the transition metals and ligands commonly used to make the catalyst, because of environmental concerns about disposal of such metals and ligands, and because of concern about the toxicity of such metals or ligands in a final product.

The focus of the work below is on the design and use of polymer supports for recovery/reuse of homogeneous catalysts. The idea of using polymers as supports for reagents or catalysts is a relatively new area of chemistry. It is chemistry that really began with Merrifield's Nobel-prize winning work on solid phase synthesis of peptides in the 1960s.[2] In this work, an insoluble polymer was modified to bind an aminoacid substrate. This substrate was then used in synthesis and recovered and separated from excess reagents or byproducts by simple filtration – filtration that was facilitated by the fact that the support was insoluble due the presence of crosslinking in the polymer supports.

Subsequent studies by other groups involved the use of similar insoluble polymer supports for homogeneous catalysts. The goal of adding polymer-supported ligands was to make homogenous catalysts separable without changing the reactivity of the catalyst.

In such chemistry, an insoluble polymer-bound catalyst would be suspended in a solvent, the reaction would occur, and the polymer would be separated from the product by filtration after the reaction was complete. Although this appears to be simple and easy, this procedure has not been widely adopted because it has some problems. The catalysts in this method are insoluble. As solids, their reactivity with the reactants in the liquid phase is affected by diffusion and different solvation within a crosslinked polymer environment. This leads to by-product formation and less effective catalysis. Secondly, the insoluble cross-linked polymers are more difficult to characterize. NMR spectroscopy cannot readily analyze such materials. Instead, techniques like IR spectroscopy or elemental analysis - techniques that date back to the 1950s have to be used.[3] This problem has been alleviated by the use of gel-phase NMR techniques.

Biphasic liquid/liquid catalysis is an alternative to solid/liquid catalysis. Three known useful examples of such biphasic systems include phase transfer catalysis, the Shell Higher Olefin Process (SHOP) for the production of α-olefins from ethylene, and the Rhone-Poulenc process for the hydroformylation of propylene.[4] Fluorous biphasic chemistry and thermomorphic chemistry are similar newer strategies for biphasic catalysis. All of this chemistry is of interest because catalysts in such situations have high reactivity and the procedures by design allow facile product isolation, facile catalyst separation from the products, and facile catalyst reuse.

Fluorous biphasic catalysis uses fluorocarbon-hydrocarbon mixtures as a mixed solvent system. These two phases can form one phase with mild heating to 36.5 °C with a suitable solvent pair. Cooling to room temperature results in phase separation.[5] The

fluorocarbon phase is analogous to the aqueous phase in aqueous biphasic catalysis. However with fluorous biphasic catalysis special sorts of ligands with "Teflon ponytails" are necessary for the catalyst to dissolve in the fluorocarbon solvent. [6,7,8] Also using a fluorous layer is not desirable because fluorocarbon solvents are costly and cannot be easily quantitatively recovered. This spurred research on to investigate solvent systems that would react as the fluorous biphasic method would but which would be 'Greener' and cheaper. Such alternative systems could thus be more practical on a large industrial scale than a fluorous biphasic system.

Aqueous biphasic catalysis has achieved success in using soluble low molecular weight catalysts attached to water-soluble ligands. The main problem with biphasic catalysis is that the catalyst has decreased reactivity because it is in a different phase than the water-insoluble organic reactants. Some reactivity is achieved by vigorous stirring; however, this reactivity is still significantly lower than what could be achieved under monophasic conditions.

While biphasic catalysis as exemplified by fluorous biphasic catalysis and aqueous biphasic catalysis has demonstrated utility, there is an alternative to such schemes. In this alternative scheme, two separate phases are heated to miscibility prior to catalysis. In such systems, cooling after the catalytic reaction separates the phases. This concept of combining and separating phases by temperature changes and using soluble polymers as supports for catalysts to insure phase selective solubility of the catalyst vis-à-vis the reactants and the products has been described as thermomorphic catalysis. Going from two phases to one phase and back again is very desirable due to

increased reactivity that is achieved in a miscible system and the simplicity of a liquid/liquid separation at the end of a reaction.

The use of thermomorphic conditions for catalysis could be an important advance in the area of homogenous catalysis. As previously mentioned the precedence for this scheme is found in the fluorous biphasic catalysis. Thermomorphic catalysis combines the ease of biphasic separation with the greater efficiency of monophasic catalysis. The basic concept of this system is to use a soluble polymer-supported catalyst and a solvent system that starts as a biphasic solution but becomes monophasic upon heating. This allows the reaction to occur in a single miscible phase. Then upon cooling, the solution separates back into two phases with the catalyst and product in separate phases. If the polymer has a strong phase preference, there is a quantitative isolation of the polymer-bound catalyst.

An example of the use of thermomorphic conditions for catalysis is Bergbreiter's use of a poly (*N*-isopropylacrylamide) (PNIPAM) support and a 90% aqueous ethanol/heptane solvent system. When [PNIPAM-NH $(CH_2)_3PPh_2]_3RhCl$ (**1**) was dissolved with 1-dodecence in a biphasic 1:1 (v:v) mixture of 90% aqueous ethanol and heptane at 22°C, no 1-dodecene hydrogenation occurred. However, when the mixture was heated to 70°C the biphasic mixture became a single phase and hydrogenation occurred. Then upon cooling again to 22°C, the heptane phase separated. GC analysis demonstrated that dodecane formed. The absence of residual homogeneous hydrogenation activity in the separated heptane phase demonstrated that the PNIPAM-supported catalyst could be fully recovered. This scheme for using homogeneous

catalysis also provides for good catalyst recyclability. Four cycles were run without a loss of catalytic activity.

A problem with this method for catalysis is the modest yield of products in early cycles. This reflects the partitioning of some product into the other phase under the biphasic separation conditions. No loss of yield occurs since reactant conversion is quantitative. The yield is just distributed between the two phases. As the catalyst is recycled by removing the heptane phase, the catalyst phase becomes saturated with product and the yield improves, eventually becoming quantitative. Since it is desirable to recycle the catalyst and use it in multiple cycles, the low yield of product in the initial cycles eventually becomes inconsequential.[9]

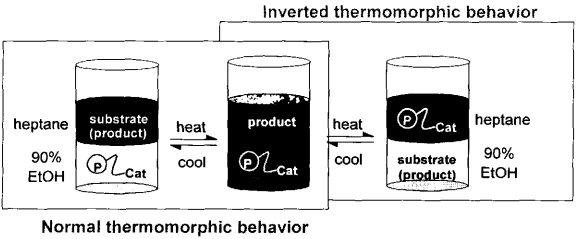


Figure 1. Normal and inverted thermomorphic behavior in a solvent mixture that is monophasic when heated and biphasic when cooled where a polymer stays in polar or nonpolar phase, respectively

A variety of other systems can also be used in preparing recoverable/reusable catalysts, catalysts that are "Green" catalysts in that they by design involve a separation technique or a scheme to simplify design of a homogeneous process using a

homogeneous catalyst. An example of this would be catalysts attached to polymers whose solubility is temperature dependent. Such catalysts include both ordinary catalysts and the so-called "smart" catalysts developed by the Bergbreiter group.[10] This sort of catalysis does not involve a biphasic mixture that becomes monophasic. Instead, the catalyst itself goes in and out of solution, due to temperature dependent solubility of a polymer support. Catalysts in these systems are easily separable by filtration and have a wide variety of possibility for applications in industry.

Polyethylene was one of the first polymers with temperature-dependent solubility used in this area because of the previous knowledge of its temperature dependence. Polyethylene bound catalysts have normal temperature dependent solubility.[11] Normal temperature dependence means that when polyethylene is heated it dissolves.

PNIPAM is another example of a polymer whose temperature-dependent solubility can be useful. However, unlike polyethylene, PNIPAM has inverse temperature dependence. This means that as PNIPAM is heated in a water solution, a precipitate forms. With inverse temperature dependence, redissolution of the polymer occurs on cooling. Many polymers like PNIPAM precipitate when heated above their lower critical solution temperature (LCST). Proteins act similarly to PNIPAM in that they precipitate when heated. However, PNIPAM differs from proteins in that it goes back into the solution upon cooling. Copolymerization of PNIPAM with other monomers of varying hydrophyilicity leads to copolymers that precipitate at varying temperatures. PNIPAM is also useful because its solubility aids characterization and makes the substituents reactivity identical to that of an electronically equivalent low

molecular weight analogue.[12] Such catalysts are useful because of their ease of separation through solid/liquid filtration and their ability to be in the same phase as the reactants after a temperature change as seen in Figure 2.

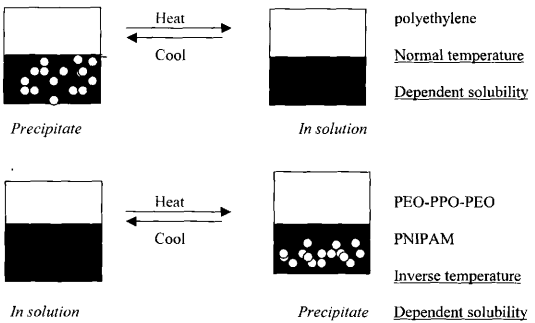


Figure 2: Polymer-bound catalysts with temperature dependent solubility

As previously stated, homogeneous catalysis has been moving away from fluorous biphasic catalysis in an attempt to become more environmentally friendly. Thus there are other alternatives to the systems described above. The previously mentioned aqueous biphasic catalysts were appealing because water is a "green" solvent. However, there has been growing concern over the contact of organics with process water, which lead to the creation of dilute aqueous organic waste streams. Because these streams are difficult to manage and treat, there has been renewed interest in alternative solvents. For example, there is considerable interest in supercritical carbon dioxide as a

solvent system.[13] When carbon dioxide is compressed and heated beyond its critical point (73 atm and 31°C), it forms a highly compressed supercritical fluid (SCF) with properties between those of liquids and gases. One advantage of SCFs is the miscibility of gases in the media compared to the very limited solubility of gases in liquid solvent. This is very useful if the reaction is first order in the concentration of the gaseous reagent.[14]

SCF also provides a solution to one of the main difficulties in homogeneous catalysis - recovering the expensive transition metal catalyst. One method of recovery unique to SCF uses controlled pressure reduction to selectively precipitate the catalyst precursor and active catalyst. However, this process assumes that these species have a lower solubility than the products in SCF at lower densities. SCF's other advantages involve their ability to control phase behavior, dissolution of reactants, and precipitation of products or catalysts with only modest changes in temperature or pressure.

Even with these advantages, the use of SCF in homogeneous reactions has only gained attention since the 1990s and even though $scCO_2$ appears to be the ideal medium, it has only attracted serious study more recently. This is because of the poor solubilizing power of $scCO_2$, which limits choice of catalysts, reagents, and substrates to nonpolar, nonionic, and low molecular weight compounds. However, the choices have been broadened with the development of surfactants, cosolvents, and other reagents that increase the solubility of polar and charged species in $scCO_2$. Another disadvantage of $scCO_2$ involves the need for high pressure and narrow temperature range. Because higher pressures are more expensive, it is not recommended for the average researcher

but has been useful with the Habor-Bosch process and the polymerization of ethene on large scales. Another quirk of SCF is that it is not always an inert reaction media, which can result in either useful processes or hazardous uncontrollable reactions. For example, three hazardous reactants are C_2H_2 or C_2F_4, which are prone to explosive deflagration and SiH_4, which spontaneously ignites if it leaks from the pressurized vessel. An example of a more beneficial reaction is the polymerization of scC_2H_4, an important industrial process. Even $scCO_2$ reacts easily, inserting itself into M-H, M-R, M-OR, and M-NR_2 bonds in transition metals complexes and reacts with primary or secondary amines.

The use of supercritical CO_2 as a solvent system has some requirements for catalysts. For example, as mentioned previously, there is a need to increase solubility for most metal complexes used with SCFs. One method to accomplish this is ligand modification, switching to ligands containing aryl substituents with ligands containing alkyl groups or perfluorinated alkyl groups. Such groups produce dramatic changes in solubility.

A second method to increase catalyst solubility in SCFs is the addition of cosolvents; an approach already used to increase solubility of aromatic reagents. For example, Lin found that 5 % methanol quadrupled the solubility of bis (diethyldithiocarbamato) mercury (II) in $scCO_2$.

Environmental concerns have not only spurred an interest in nontraditional solvent systems but also have prompted the search for processes that avoid the handling and generation of toxic materials. This has included the exploration of alternative means

of heterogeneizing homogeneous catalysts. This is another area in which homogeneous catalysts have risen to fill the void. Specifically, heterogenized homogeneous catalysts obtained from organometallic complexes have been immobilized both on insoluble polymers and on other sorts of materials that maintain a homogeneous catalyst's in high yields, and selectivity.[15] For example, Margalef-Catalia and coworkers developed a synthetic path that converts a primary amine to a secondary amine by imine intermediate formation. This process is catalyzed by preformed rhodium or iridium complexes on a clay, montmorillonite. This process features a single step transformation and milder, solvent free conditions. Also, this reaction may be possible on an industrial scale because of the easy recoverability and reusability of the clay-bound catalyst. The reaction involves the condensation reaction of ketones with primary amines. This involves an addition in which the basic nitrogen of the amine adds to the carbonyl carbon of the ketone. The intermediate loses a water molecule to make the imine in the second step. In the final step, this imine intermediate undergoes catalytic hydrogenation to yield a secondary amine. The use of removable and reusable iridium complexes on montmorillonite clay has been reported to be a highly efficient system. This system also minimizes the barriers associated with the unremovable homogeneous solution catalysts. The overall result of this research was the development of a solid-supported transition metal complex that has high catalytic activity in a free solvent media, providing an environmentally friendly and resource saving reaction.

A final problem that arises with transitional metal catalysis is the steady deactivation of the catalyst over several cycles. This is especially acute with phosphine-ligated

transition metal complexes because they deactivate more quickly.[16] To attempt to overcome this problem, Bergbreiter's group began work on synthesis of palladacycles in an attempt to find a more robust catalyst. The group was spurred to do this by the success of Denmark using chiral bis (oxazoline) palladium (II) catalysts that proved to be active. Denmark's use of oxazoline ligands avoided the problem of phosphine oxidation. They were also inspired by Milstein and coworkers description of a phosphorus-carbon-phosphorus (PCP)-type tridentate ligand useful in a Heck-type vinylation of aryl halides. As Bergbreiter and coworkers discovered, new tridentate SCS-type palladium (II) complexes are effective catalysts for Heck reactions between aryl iodides and alkene acceptors. The catalyst was synthesized using straightforward chemistry from readily available starting materials. The new SCS type Pd (II) catalyst is an example of a more robust homogeneous catalyst because of it high durability and easy recyclability. It is also attractive because of its simple, efficient synthesis and modification.[17]

Stability to an oxygen-containing environment is also desired. This would eliminate the time consuming deoxygenation processes and enhancing the recyclability are goals in this area.[18] In a recent journal report by Bergbreiter and coworkers, they discussed the advantage of using the SCS-Pd catalyst because of its air stability.[19] Research was spurred in this area because of the air sensitivity of a polymer-bound Pd(0) catalyst caused a steady deactivation of the catalyst. As in the preceding paragraph, this limitation could be overcome by using the more stable tridentate sulfur-carbon-sulfur (SCS) Pd (II) catalyst. The use of the air stable Pd (II) catalyst simplifies the reaction

protocol. Catalyst stability is demonstrated with no observation of degradation or a decrease in rate over the three cycles for Heck reactions. Adding a fresh heptane solution of the reactants and reheating the system for the required time easily recycles the catalyst. Another advantage of the increased air stability is the simplicity of the reaction setup. Since all manipulations can be done in an air environment, the setup takes only minutes. When the reaction was performed with an air-sensitive catalyst and using Schlenk techniques, the reaction setup took a significant amount of time. Morever using a polymer-supported catalyst such as PEG or PNIPAM that is a selectively soluble polymer support allows for facile product isolation and catalyst recycling using thermomorphic conditions. Both, the Heck and Suzuki reactions occurred with quantitative catalyst recycling. These findings were significant because they increased the diversity of useful reactions that use thermomorphic conditions.

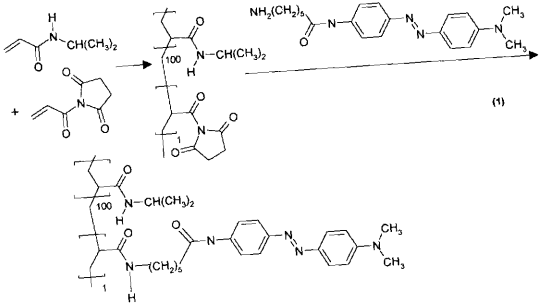
In conclusion, homogenous catalysis is a rapidly growing area of catalysis. Future developments will include the development of new solvent systems. Right now, there are only a limited number of solvents, especially aprotic solvents that can be used in an environmentally friendly way. Also there are a limited number of polymers that can be used in catalysis. This may be a problem if polymers are to be used to recover and recycle homogeneous catalysts. Finally, catalyst stability can pose a problem. Although tridentate SCS-type Pd (II) complexes are a significant advance in this area, there is a need for more catalysts that are similarly air stable. Success in developing new solvent systems, new ways to recover/reuse catalysts and more stable catalysts will in the future make homogeneous catalysts even more useful than they already are.

My work described below focuses on one of these issues - designing new, recoverable, reusable polymer supports with phase selective solubility based on a polymer's pendant side chain hydrophobicity or hydrophilicity. More specifically, my work below shows how the phase solubility selectivity of a polymer change as the polymer side chain is modified. This work shows how polymer solubility shifts from aqueous 90 % ethanol solubility with a three carbon pendent chain to heptane solubility with an eighteen carbon pendent chain as the length of the carbon chain is varied.

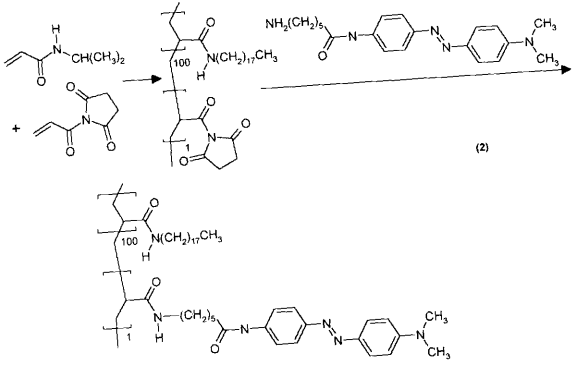
RESULTS AND DISCUSSION

The goal of my research project was to determine the how the size of a pendant alkyl groups of an *N*-alkyl acrylamide effects the phase selectivity solubility of the polyacrylamide in a thermomorphic biphasic mixture at room temperature. This project was based on prior experiments that showed a poly(N-alkyl acrylamide) polymer was soluble in a polar phase using a three carbon pendent chain but soluble in a nonpolar phase if an eighteen carbon pendent chain were present in a thermomorphic heptane/90% aqueous ethanol mixture.

My plan in this project was to test the phase selectivity solubility of the polyacrylamides with different sized pendent carbon chains by attaching a visible methyl red derivative dye. Quantitative analysis of both the polar and nonpolar phase with visible spectroscopy would then allow me to determine the effects of the size of the *N*-alkyl group on polyacrylamide phase selective solubility.Synthesis of the desired polymers could be achieved in several ways. In prior work, these polymers were prepared using the chemistry shown in equations 1 and 2.

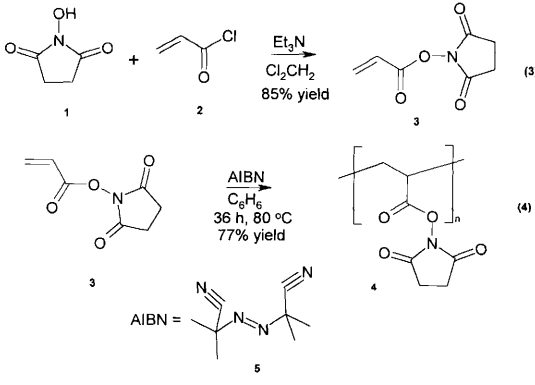


(1)



(2)

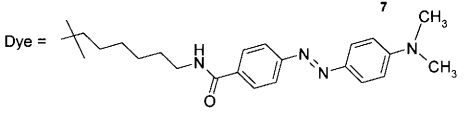
These synthesese however are independent polymer syntheses and likely produce polyacrylamides with different degrees of polymerization and dispersity (M_w/M_n). As discussed below, my goal was to prepare a set of *N*-alkyl acrylamide polymers all of whom had the same degree of polymerization and dispersity. To accomplish this, the pendent *N*-alkyl carbon chains and visible dye were both attached to a polymer backbone of poly (*N*-acryloxysuccinimide) (PNASI) (**4**). The synthesis of PNASI is shown below in equation 4. PNASI was prepared from radical polymerization of *N*-acryloxysuccinimide (NASI) (**3**) initiated by α,α'-azobis(isobutyronitrile) (AIBN). The reactive ester of acrylic acid, NASI, was in turn synthesized by the reaction of *N*-hydroxysuccinimide (**1**) and acrylchloride (**2**). NASI was chosen as a monomer for formation of the polyacrylamide precursor because it had a reactive double bond for polymerization and because it contains a reactive ester group which can react with amines to synthesize *N*-alkyl amides.

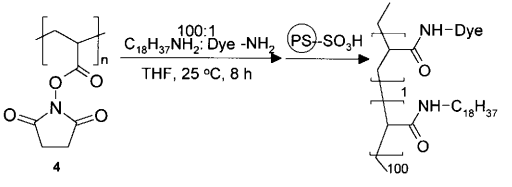


Although PNASI monomers had been copolymerized with *N*-alkyl acrylamides and then used in previous research by Bergbreiter's group to make phase selective three and eighteen carbon pendent polymers (cf. eqs 1 and 2 above), the synthetic procedure used here involves an initial synthesis of a poly(acrylic acid) ester. Since this polymerization is different, the first task in this project was to test the phase solubility of the three and eighteen *N*-alkyl acrylamides prepared in equations 5 and 6 to see if these methyl red containing copolymers had phase selective solubility like that reported previously for the polymer prepared in eqs 1 and 2 . If these polymers with C3 and C18pendent alkyl chains had the previously demonstrated phase selective solubility, I could then go on to prepare poly(*N*-alkyl acrylamides) with pendant alkyl groups having

an intermediate number of carbons.[20] In these syntheses, a single batch of PNASI was used for the synthesis of all the poly(*N*-alkyl acrylamide) polymers to eliminate effects of different dispersity and different degree of polymerization between the two polymers.

In my initial synthesis, the methyl red-labeled poly(*N*-isopropylacrylamide) (PNIPAM) (**7**) was made from PNASI (**4**), isopropylamine, and a methyl red derivative (**6**) in DMF as a solvent. Methyl red-labeled poly(*N*-octadecylacrylamide) (PNODAM) (**8**) was synthesized in the same way except with octadecylamine substituted for isopropylamine. Also, in this case the octadecylamine was not soluble in DMF so an alternative solvent, THF, had to be used The alkyamine and the methyl red derivative were reacted in a 100:1 ratio to cause an 100:1 repeating unit ratio. This ratio of *N*-alkyl groups to methyl red was large enough to insure that there was enough spectroscopic label in the product polymer for analysis. It also insured that the product polymer's solubility would be essentially identical to that of a homopolymer of the poly(*N*-alkyl acrylamide). An excess of the mixture of the *N*-alkyl amine and the amine-containing methyl red derivative was used in proportion to NASI to ensure that all the reactive ester groups have been reacted and but the ratio of the *N*-alkyl amine for the pendent chain to methyl red was maintained at 100:1. The product polymers were isolated by





The results of my synthesis of methyl red labeled poly(*N*-isopropyl acrylamide) and poly(*N*-octadecyl acryLamide) successfully mirrored the previous research results. The methyl red derivative of poly(*N*-isopropylacrylamide) was completely soluble in the polar 90% ethanol phase and the methyl red derivative of poly(*N*-octadecylacrylamide) was completely soluble in the nonpolar heptane phase as illustrated in Figure 3. These results were also seen using *N,N*-dimethyl acetamide (DMA) as the polar phase and heptane as the nonpolar phase, showing the phase selective solubility of these polymers

in a polar and non-polar phase respectively is not a unique characteristic of the aqueous 90% ethanol and heptane thermomorphic system.

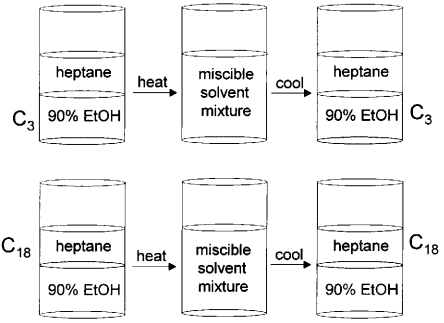


Figure 3: Phase selective solubility of poly(*N*-isopropyl acrylamide) and poly (*N*-octadecyl acrylamide)

Since my results with methyl red derivatives of both PNIPAM and PNODAM mirrored previous results, additional syntheses of poly(*N*-alkyl acrylamides) with intermediate-sized carbon length chain pendant chains were carried out. To do this, amines with three, four, five, six, seven, eight, twelve, and eighteen carbons were mixed at a 100:1 ratio with the amine-derivative of methyl red and were reacted with the aliquout of the same batch of PNASI as seen by Figure 4.

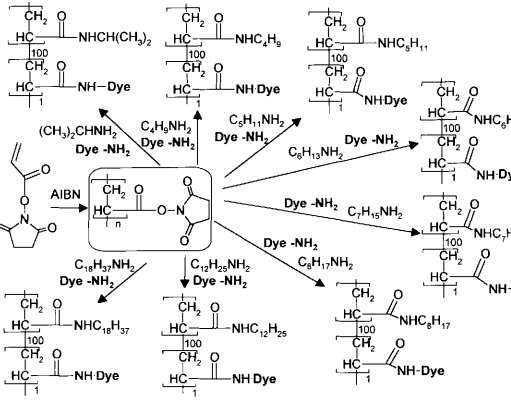


Figure 4. Synthesis of methyl red-labeled poly (*N*-alkyl acrylamide)s from a common polymer precursor

This approach is analogous to the pool-split syntheses used in combinatorial chemistry. The use of the same batch of PNASI to synthesize all the N-alkyl acrylamide polymers eliminates the possibility of different dispersities and degrees of polymerization in the product polymers. This pool-split synthesis thus insures that any variations in the phase selective solubility of the product poly(*N*-alkyl acrylamides) reflects only the effects of the size of the *N*-alkyl pendent groups. This common procedure different in a minor way from the initial work in that THF was used as the solvent for all the reactions, since all the alkylamines are soluble in heated THF. The

isolation procedure was also changed because the solvent precipitation could lead to fractionation.

The new isolation procedure involved removing the excess amine with Amberyst-15, then removing the solvent under reduced pressure. To confirm that all the exess amine and low molecular weight polymer was removed by the Amberylst-15, the PNIPAM was tested with visible spectroscopy after 6 hours of shaking. The solution was shaken for another hour and tested again with visible spectroscopy. The absorbance did not change, demonstrating that all the excess amine had been absorbed. This can be seen in Figure 5 below.

The experiment shown in Figure 5 also suggests that the poly(*N*-alkyl acrylamide) polymers do not absorb into the sulfonic acid resin. This result means that the Amberlyst treatment does not remove polymer but that it only removes the low molecular weight amine-containing reactants.

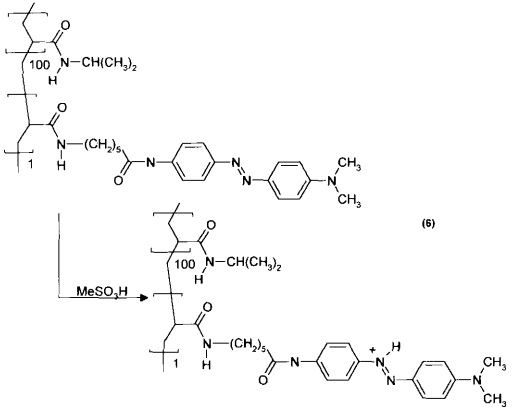
Once a collection of methyl red labaeled poly(N-alkyl acrylamides) with different sized N-alkyl side chains were in hand, the phase selective solubility of these polymers was tested using visible spectroscopy. In each test, an individual polyacrylamide was placed in the mixture of polar and nonpolar solvents. Heating was used to dissolve the polymer. A heptane/90% aqueous ethanol (EtOH:H20 = 90:10 (v/v)) was used in all cases. Once the polymer had dissolved, the solvent mixture was heated until a single phase was present. Then the solution was cooled back to room temperature at which time two phases, a polar aqueous ethanol phase and a non-polar heptane phase formed. In general, phase separation occurred readily. If phase

separation were slow, centrifugation was used to facilitate complete phase separation. Each phase was then sampled and analyzed by UV-visible spectroscopy. This was done so that partial phase selective solubility by some of the polymers could be detected.

The results of these studies were that methyl red labeled poly(*N*-alkyl acrylamide) polymers with eight (Figure 11), twelve (Figure 12), and eighteen (Figure 13) 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*-alkyl acrylamides) with three (Figure 6) and five (Figure 8) carbon chains had phase selective solubility in the polar ethanol phase. No (<0.5%) methyl red labeled polymer could be detected in the non-polar heptane phase in these two cases. A poly(*N*-alkyl acrylamide) containing a four carbon chain however (Figure 7) was slightly soluble in the heptane phase. Given the aforementioned solubility of the pentylamine derivative, that is not expected. It is possible that this result reflects some contamination. Intermediate phase selective solubility was seen for poly(*N*-alkyl acrylamides) containing six (Figure 9) or seven (Figure 10) carbons in the pendant *N*-alkylamine chains. In the case of the poly(*N*-alkyl acrylamides) containing a six carbon chain, the polyacrylamide was 90% soluble in the heptane phase. In the case of the poly(*N*-alkyl acrylamides) containing a seven carbon chain, 92% phase selective solubility in the heptane phase was seem. These results are summarized graphically in Figure 14.

The above experiments all involved analysis of the methyl red containing polymers under conditions where the methyl red is not protonated. It is also possible to analyze methyl red containing polymers under acidic conditions – a procedure that could

be useful in future studies. Such an analysis would allow us to obtain two separate estimates of the amount of polymer in each phase and might avoid problems we noted with potential contaminants if the contaminant's UV-visible spectrum was not sensitive to acid. To test this, methane sulfonic acid was added to the three carbon length chain methyl red copolymer dissolved in THF. This is expected to result in protonation of the azo dye as shown in equation 6. Such protonation increases conjugation in the dye and



a bathochromic shift. This can be seen below in Figure 15 where the methyl red absorbance peak shifts from 425.0 nm to 529.0 nm.

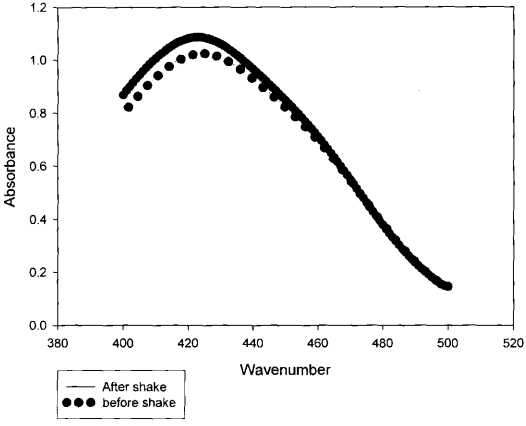


Figure 5: Visible spectra of a methyl red-labeled poly(*N*-dodecyl acrylamide) (C_{12}) before and after additional shaking with Amberlyst-15 resin

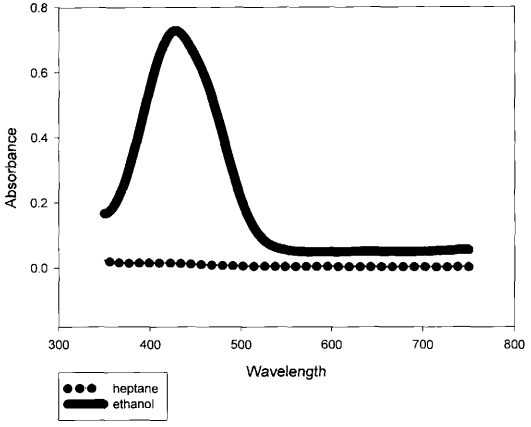


Figure 6: Visible spectra of a methyl red-labeled poly (*N*-isopropyl acrylamide) (C_3) showing phase selective solubility of this polymer in the polar ethanol phase at a biphasic 90% ethanol-water/heptane mixture

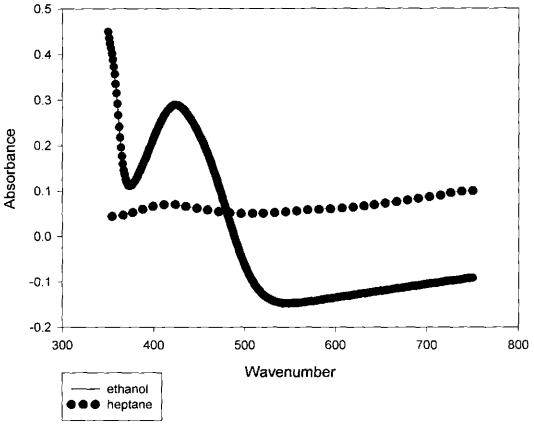


Figure 7: Visible spectra of a methyl red poly (*N*-butyl acrylamide) (C_4) showing phase selective solubility of this polymer in the polar ethanol phase at a biphasic 90% ethanol-water/heptane mixture

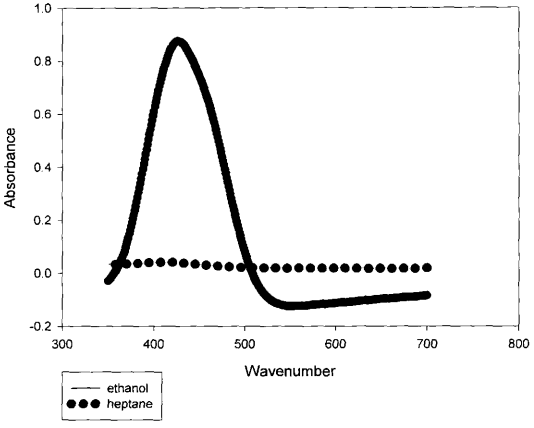


Figure 8: Visible spectra of a methyl red poly (*N*-pentyl acrylamide) (C_5) showing phase selective solubility of this polymer in the polar ethanol phase at a biphasic 90% ethanol-water/heptane mixture

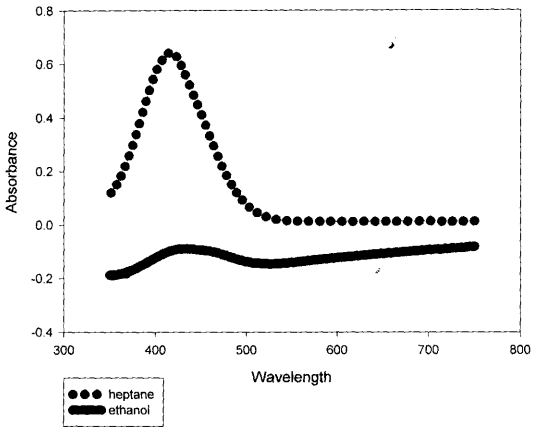


Figure 9: Visible spectra of a methyl red poly (*N*-hexyl acrylamide) (C_6) showing phase selective solubility of this polymer in the polar ethanol phase at a biphasic 90% ethanol-water/heptane mixture

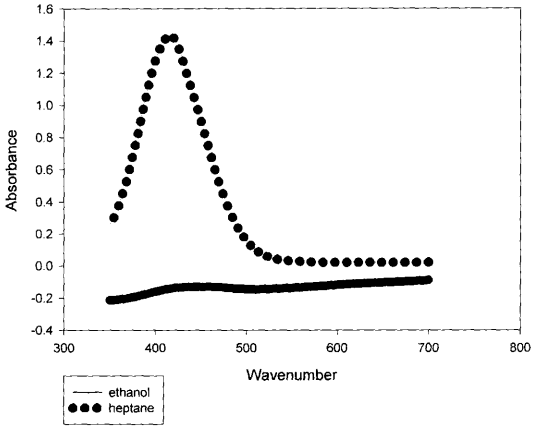


Figure 10: Visible spectra of a methyl red poly (*N*-heptyl acrylamide) (C_7) showing phase selective solubility of this polymer in the polar ethanol phase at a biphasic 90% ethanol-water/heptane mixture

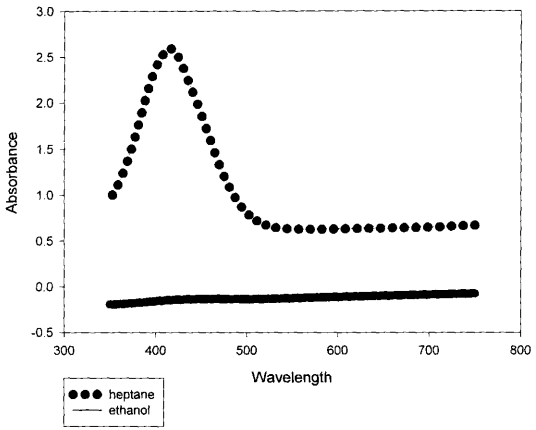


Figure 11: Visible spectra of a methyl red poly (*N*-octyl acrylamide) (C_8) showing phase selective solubility of this polymer in the polar ethanol phase at a biphasic 90% ethanol-water/heptane mixture

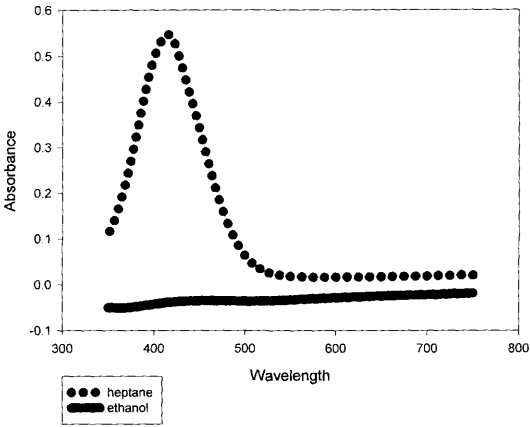


Figure 12: Visible spectra of a methyl red poly (*N*-dodecyl acrylamide) (C_{12}) showing phase selective solubility of this polymer in the polar ethanol phase at a biphasic 90% ethanol-water/heptane mixture

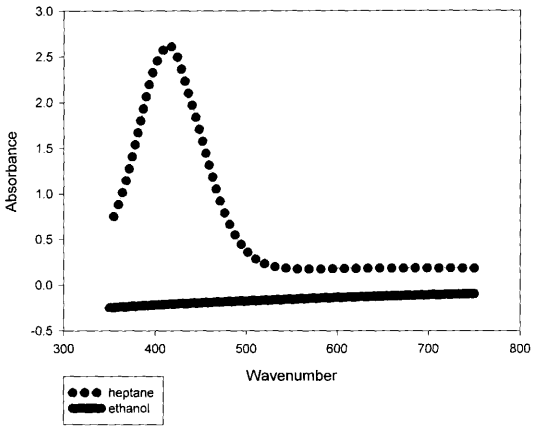


Figure 13: Visible spectra of a methyl red poly (*N*-octadecyl acrylamide) (C_{18}) showing phase selective solubility of this polymer in the polar ethanol phase at a biphasic 90% ethanol-water/heptane mixture

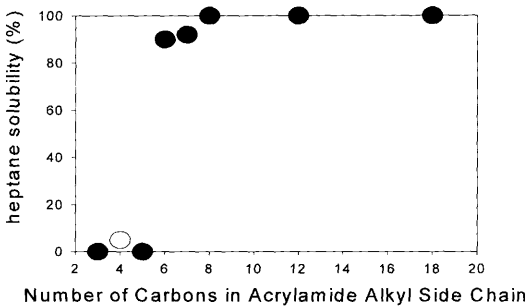


Figure 14: Graph of poly(*N*-alkyl acrylamide) carbon chain length phase selective solubility as a function of the number of carbons in the *N*-alkyl group of the poly (*N*-alkyl acrylamide)

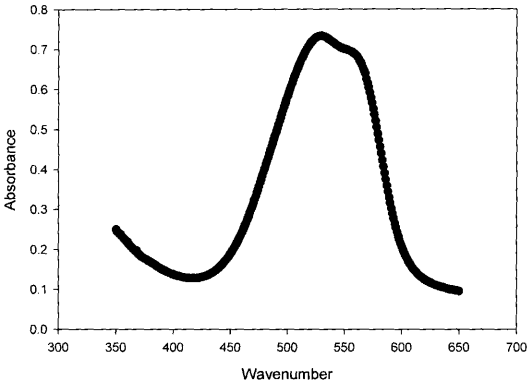


Figure 15: A bathochromic shift in the visible spectrum caused by $MeSO_3H$ treatment of methyl red labeled poly (*N*-isopropyl acrylamide)

EXPERIMENTAL

General Methods

^{1}H NMR spectra were recorded on a 300 MHz Unity nuclear magnetic resonance spectrometer with TMS as the internal reference. In cases where anhydrous solvents were required, anhydrous THF was used. Anhydrous THF was obtained by distillation from sodium-benzophenone ketyl under nitrogen. Spectroscopic grade heptane and ethanol were used as solvents in cases where UV-Visible spectra were studied. All other reagents and solvents were reagent grade. The visible spectroscopy was carried out using a Cary 100 UV-Visible spectrophotometer in a cell thermostatted at 25°C.

N-Acryloxysuccinimide

A solution of *N*-hydroxysuccinimide (10.0 g, 86.9 mmol, Aldrich) and triethylamine (8.79 g, 12.1 mL, 0.726 g/mL, 86.9 mmol, Aldrich) was prepared in approximately 150 mL of ice-cold dichloromethane. This solution was maintained at 0°C using an ice bath and acrylchloride (7.9 g, 7.1 mL, 1.114 g/mL, 86.9 mmol, Aldrich) was added dropwise over the span of twenty minutes. During this addition, a white precipitate presumed to be triethylamine hydrochloride formed. After all the acrylchloride was added, the solution was stirred an additional hour at 0°C. The solution was allowed to warm to room temperature and a white precipitate formed. The white precipitate was removed by filtration and the organic phase was then washed 5 times with approximately 20 mL ice-cold water and 5 times with approximately 20 mL of brine. This organic phase was then dried with magnesium sulfate. The magnesium

sulfate was removed by filtration and the organic phase was concentrated under reduced pressure using a rotary evaporator to a volume of ca. 8 mL. This more concentrated methylene chloride solution of the crude active ester product was then poured into 200 mL of hexane with stirring. A white precipitate of *N*-acryloxysuccinimide was formed. The product precipitate was isolated by filtration and dried under reduced pressure to yield 8.46g of NASI (85% yield). The product active ester was characterized spectroscopically: ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 4H), 6.20 (d, 1H), 6.40 (d, 1H), 6.75 (d, 1H). It was stored under nitrogen prior to use or used immediately in polymerizations because of the possibility of hydrolysis of this reactive ester by water.

Poly(*N*-acryloxysuccinimide)

N-Acryloxysuccinimide (6.0 g, 34.5 mmol) was dissolved in approximately 150 mL of benzene and stirred for 30 minutes under nitrogen at room temperature. To this solution, a solution of α,α'-azobis(isobutyronitrile) (AIBN) (50 mg, 0.304 mmol, Aldrich) dissolved in benzene was added under nitrogen. The resulting solution was stirred at 80°C for approximately 45 hours. The solution was then cooled to room temperature. A white precipitate of the desired product, poly (*N*-acryloxysuccinimide) was formed on cooling. The product polymer precipitate was isolated by filtration and washed with dry tetrahydrofuran (3 x 15 mL) and dried in vacuo to yield 3.6 g of PNASI (60 % yield). The product was characterized spectroscopically: ^{1}H NMR (DMSO-d_6) δ 2.0 (s, 2H), 2.8 (s, 4H), 3.05 (s, 1H). A trace of the monomer (ca. 2%) remained in the product based on ^{1}H NMR spectroscopy.

NMR Spectrum of Poly(*N*-Acryloxysuccinimide) showing a trace of monomer (peaks in the δ 5.0 – δ 6.0 region)

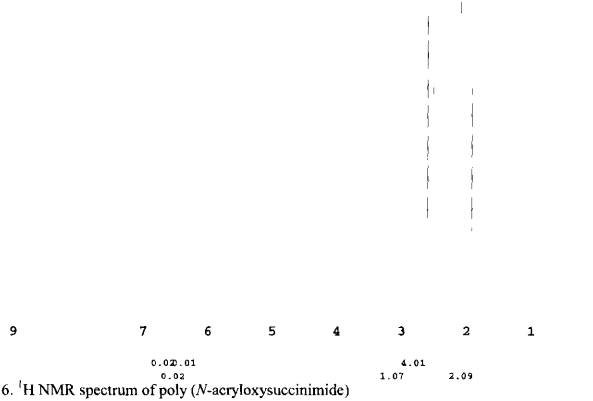


Figure 16. ^{1}H NMR spectrum of poly (*N*-acryloxysuccinimide)

Failed Polymerizations of Poly(*N*-Acryloxysuccinimide)

The polymerization failed initial when different conditions were used. First, if the *N*-acryloxysuccinimide was added at the same time as the AIBN, a solid polymer product was not obtained. Second if, the *N*-acryloxysuccinimide and AIBN in the benzene solution were only heated to 60°C, the polymerization did not work. Finally, the polymerization also failed when the reaction was open to air and not under nitrogen. In all these cases, a failed polymerization was presumed to have occurred if no precipitate formatted after cooling the *N*-acryloxysuccinimide and AIBN in benzene down to room temperature after 45 hours of attempted polymerization.

Preparation of *N,N*-Dimethyl-*p*-aminophenylazobenzoic Acid[21]

This was prepared by a collaboration graduate student Mr. Jonathan Frels according to the following procedure. Sodium carbonate (3.2 g, 30.2 mmol) and *p*-aminobenzoic acid (8.0 g, 58.3 mmol) were added to 100 mL of water. This mixture was heated until the solids were dissolved. The solution was then cooled to 0°C and sodium nitrite (4.2 g, 60.9 mmol) was added. This solution was slowly added to 10 mL of concentrated HCl and 50 mL of water maintained at 0°C. After stirring for 30 minutes, 6 mL of *N, N*-dimethylaniline and 4 ml of glacial acetic acid were added dropwise with vigorous stirring. The solution was allowed to warm to room temperature over one hour and a deep red suspension formed. The suspension was filtered to yield the crude *N,N*-dimethyl-*p*-aminophenylazobenzoic acid (*p*-Methyl Red). The crude *p*-Methyl Red was recrystallized from DMF. The crystals were collected by filtration,

rinsed twice with distilled water, and dried under vacuum. The purified product was obtained as deep red crystals in a yield of 8.7 g (68.7 %). The melting point of the recrystallized product was 254-256 °C (lit. 263 °C). The product was characterized spectroscopically: IR (KBr pellet) 2900, 1680, 1600, 1520, 1420, 1360, 1300, 1140, 950, 870, 820 cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.20 (s), 6.90 (d), 7.95 (d), 8.10 (d).

Primary Amine-terminated *p*-Methyl Red[22]

This was prepared by a collaborating graduate student, Mr. Jonathan Frels, according to the following procedure. *N,N*-Dimethyl-*p*-aminophenylazobenzoic acid (3.87 g, 14.36 mmol), prepared as described above, and 100 mL of dichloromethane were added to an oven-dried flask and the apparatus was flushed with nitrogen. Then carbonyl diimidazole (2.404 g, 14.38 mmol) in 40 mL of dichloromethane was added via syringe and the mixture stirred vigorously under nitrogen. After stirring for seven hours, the solution was transferred by forced siphon into nitrogen-flushed flask containing 1,6-hexanediamine (8.48 g, 71.5 mmol) in 85 mL of dichloromethane. The mixture was stirred slowly overnight. The dark red solution was washed with water (3x150 mL), dried over magnesium sulfate and filtered. The solvent was then removed under reduced pressure and the residue was dried in vacuo to yield 3.77g (71 % yield) of a red solid: mp 175.5-176.4 °C; ^1H NMR ($CDCl_3$) δ 1.36 (m, 6H), 1.65 (m, 4H), 2.62 (t, 2H), 3.12 (s, 6H), 3.52 (q, 2H), 6.20 (t, 1H), 6.76 (d, 2H), 7.90 (s, 4H), 7.95 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.07, 154.95, 152.76, 143.58, 134.78, 127.69, 125.36, 122.20, 111.43, 42.04, 40.28, 40.03, 33.56, 29.64, 26.79, 26.51; HRMS (*m/e*) Calcd for $C_{21}H_{29}N_5H$: 367.2372. Found: 367.2368. This amine-derivative of *p*-methyl red was analyzed by

UV-visible spectroscopy. A spectrum of the basic and acidic forms of this dye are shown in figures Y and Z, respectively. The basic form of the dye has a broad intense absorption maximum (λ_{max}) at 425.0 nm. The acidic form of the dye has a broad intense absorption maximum (λ_{max}) at 529.0 nm. The red-shift on acidification is due to increased conjugation due to protonation of a basic diazo nitrogen.

Visible Spectrum for Primary Amine-terminated *p*-Methyl Red under Basic Conditions

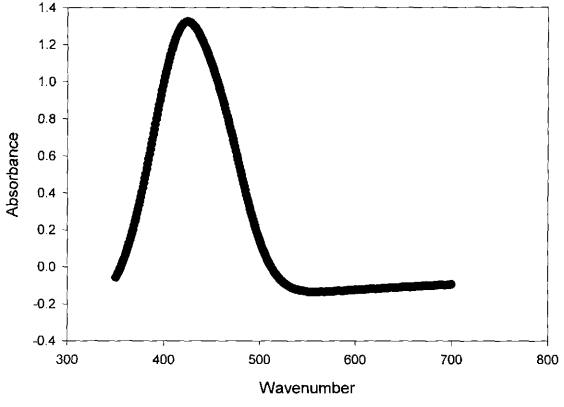


Figure 17. Visible spectrum of non-polymeric *p*-methyl red under basic conditions

Methyl red-labeled Poly(*N*-isopropylacrylamide)

Poly(*N*-acryloxysuccinimide) (0.10 g, 0.59 mmol) was dissolved in 50 mL of ether. To this solution, the amine-containing methyl red derivative prepared as described above (0.002g, .05917 mmol) and isopropylamine (0.035 g, .05 mL 5.9 mmol) were added. The resulting solution was stirred for several hours at room temperature. At this point, the solution was presumed to contain a mixture of the desired methyl red-labeled poly(*N*-isopropylacrylamide), excess isopropylamine, and excess of the amine-containing methyl red derivative. Amberlyst-15 is an insoluble macromolecular sulfonic acid containing polystyrene ion exchange resin that has been shown in prior work to bind quantitatively with low molecular weight amines. To remove the excess low molecular weight, this amine mixture of polymer product and starting materials was shook with 10 g Amberlyst-15 for 6 hours at room temperature using a wrist action shaker. The solvent was removed from the Amberlyst-15 crystals under reduced pressure. The resulting solvent was concentrated under reduced pressure to ca. 5 mL. This more concentrated solution was poured into 20 mL hexanes, resulting in an orange powder. The precipitate was isolated by filtration and was dried in vacuo. The polymer was characterized spectroscopically: ^{1}H NMR ($CDCl_3$) 1.05 (s, 600H), 1.65 (d, 200H), 2.05 (s, 100H), 3.05 (s, 6H), 3.25 (s, 100H), 4.0 (s, 100H), 6.6 (d, 2H), 7.8 (d, 4H), 7.9 (s, 1H).

Methyl-Red labeled Poly(octadecylacrylamide)

Poly(*N*-acryloxysuccinimide) (0.10g, 0.59 mmol), amine-containing methyl red derivative (0.002, .059 mmol), and octadecylamine (1.59 g, 5.9 mmol) were dissolved in 50 mL tetrahydrofuran (THF). The solution was heated to 50 °C and stirred for several hours. The solution was then shaken with 10 g Amberlyst-15 for 6 hours at room temperature using a wrist action shaker. The product solution was separated from the Amberylst-15 by filtration. The solution was then concentrated under reduced pressure to ca. 5 mL. This more concentrated solution was poured into 20 mL of methanol and an orange precipitate formed. The precipitate was isolated by filtration and dried in vacuo.

Visible spectroscopy with Methyl red-labeled Poly(*N*-isopropylacrylamide) and Methyl-Red labeled Poly(octadecylacrylamide)

The Methyl red-labeled Poly(*N*-isopropylacrylamide)and Methyl-Red labeled Poly(*N*-octadecylacrylamide) (MP-PNODAM) (30 mg) were dissolved in 10 mL of 90% EtOH or 10 mL of heptane, respectively. One mL of each solution was removed and diluted to 10 mL in the perspective solvent. To make a biphasic system, to the 10 mL solution of 90% EtOH, 10 mL of heptane was added and to the 10 mL solution of heptane, 10 mL of 90% EtOH was added. This solution was stirred vigorously and heated at 70-80°C until the two phases were miscible with each other. The solutions were then cooled until phase separation had been completed, as indicated by each phase becoming clear and a well defined phase separation. Each phase was tested using visible spectroscopy. The MR-NIPAM had 0% solubility in the heptane phase, while the MR-NODAM had 100 %

solubility in the heptane phase based on the absence of any significant absorbance (above background noise) in the 350.0 nm – 700.0 nm region.

A similar experiment using 10 mL of DMA and 10 mL of heptane with both the MR-PNIPAM and MR-PNODAM led to similar results. In this case, the MR-PNIPAM remained in the polar DMA phase after miscibilization (heating) and phase separation (cooling) while the MR-PNODAM remained in the nonpolar heptane phase after miscibilization (heating) and phase separation (cooling).

Cleaning of Amberylst-15[23]

To purify the Amberylst-15 (Aldrich), it was soaked in methanol for 24 hours. It was washed with methanol and neutralized with 4 M ammonia in methanol. The neutral resin was acidified with 3 M hydrochloric acid in 50 % methanol and rinsed with methanol, THF, and dichloromethane, successively. The acidic capacity of the resin was determined to be 3.5 mequiv/g by titration.

Pool–Split Synthesis of Methyl Red Labeled Copolymer

In order to prepare solutions of methyl red-labeled acrylamide copolymers with different alkylamine substituents but with identical degrees of polymerization and dispersity (M_w/M_n), a pool-split synthetic scheme was used. This scheme, illustrated in Figure B, used a common sample of poly(*N*-acryloxysuccinimide) prepared as described above. A sample of this polymer was then dissolved in THF and allowed to react with a mixture of the amine-derivative of methyl red and an alkylamine. Each mixture of methyl red amine and alkylamine used 0.003 g (0.00887 mmol) of the methyl red derivative and 0.887 mmol of the alkylamine. The amounts of alkylamines used in each

mixture varied based on the molecular weight of the alkylamine and were as follows: isopropylamine (0.08 mL, 0.694 g/mL), butylamine (0.09 mL, 0.740 g/mL), amylamine (0.10 mL, 0.752 g/mL), hexylamine (0.12 mL, 0.133 g/mL), heptylamine (0.13 mL, 0.777 g/mL), octylamine (0.15 mL, 0.782 g/mL), and dodecylamine (0.165 g). Each reaction used a total volume of 20 mL of THF. Each amidation reaction was carried out under identical conditions. The mixture of active ester polymer and amines was heated to 50 °C for 24 hours. At this point, each of the reddish solutions contained the desired methyl red labeled acrylamide copolymer, excess unreacted primary amine-terminated methyl red and excess alkylamine. While the product polymers at this point could have been isolated by a solvent precipitation as described above, such a precipitation process could fractionate the polymer, separating the polymer into fractions with differing degrees of polymerization and differing dispersities. To avoid this, a slightly different work-up was used. As was described above, the excess amine was removed from these solutions using Amberlyst 15. This treatment involved shaking each solution with 0.35 g of Amberlyst 15 for 24 hours at room temperature using a wrist action shaker. The red suspensions were then filtered to remove the Amberlyst resin. The eight different polymers were then isolated from each experiment by removing the solvent under reduced pressure. Drying in vacuo led to a mixture of polymer samples that were then tested for phase selective solubility as described below.

To test whether the Amberlyst-15 had removed all of the low molecular weight amines in each of the above experiments, one of the samples (the isopropylamine-containing derivative) was analyzed by UV-visible spectroscopy. The absorbance at

424.0 nm was noted. Then this sample shook an additional hour room temperature. At this point, the suspension was allowed to settle and the supernatant was again analyzed by UV-visible spectroscopy. At this point, the absorbance of the supernatant was 1.0867 at 423.0 nm. Since there was no change in intensity of the absorbance peak for the methyl red dye, this indicated that all the excess methyl red had been removed by the Amberlyst-15. This same experiment also validated the earlier assumption that Amberlyst-15 does not absorb the methyl red-labeled polyacrylamide polymers since the polymer most likely to have been absorbed by the sulfonic acid-containing resin was the smallest, most polar polymer, the methyl red derivative of poly(*N*-isopropylacrylamide).

Visible Spectroscopy with the Split Pool Polymers

A solution was prepared using 3 mg of each polymer made in the previous procedure using a mixture of 10 mL 90% EtOH and 10 mL heptane. The solution was heated with a heat gun to dissolve the polymer in the biphasic solution. This solution was then stirred vigorously and heated to between 70-80°C until the two phases were miscible. The two phases were cooled to room temperature until phase separation was complete, as indicated by the clarity of the two phases. For the four, five, six, and seven carbon length chain alkylamine acrylamides, the solution was allowed to sit overnight to insure complete phase separation. The other acrylamides containing other sized carbon chains took between 5 and 15 minutes to separate cleanly. The three carbon chain again had 0% solubility in the heptane phase, while the seven, eight, twelve, and eighteen have 100% solubility in the heptane phase. The four, five, and six are intermediate in phase selective solubility with some polymer in both phases in varying amounts.

CONCLUSION

Poly (*N*-alkyl acrylamides) could be successfully prepared by reacting poly (*N*-acryloxysuccinimide) with an alkyl amine and trace amounts of an azo dye called methyl red. The poly (*N*-acryloxysuccinimide) was prepared from *N*-hydroxysuccinimide. This method for synthesis of poly (*N*-acryloxysuccinimide) is an alternative to the copolymerization of *N*- acryloxysuccinimide and *N*-alkyl acrylamide. The copolymerization of *N*- acryloxysuccinimide and *N*-alkyl acrylamide could not be used as a synthetic route because in this project control of dispersity and degree of polymerization was desired. By using a single batch of poly (*N*-acryloxysuccinimide), these variables were constant to eliminate effects of dispersity and degree of polymerization on polymer solubility. To purify the poly (*N*-alkyl acrylamide), solvent precipitation could have been used. However, since solvent precipitation could cause fractionation, an insoluble sequestering agent, Amberlyst-15, was used to remove low molecular weight amines. This sulfonic acid-containing sequestering agent was shown by visible spectroscopy to have removed all the low molecular weight amine but to not absorb a methyl red labeled poly (*N*-alkyl acrylamide).

The visible spectroscopy for phase selective solubility at poly (*N*-alkyl acrylamide) results are similar to the results found previously for the copolymerization of *N*- acryloxysuccinimide and *N*-alkyl acrylamide synthetic route. Poly (*N*-alkyl acrylamide) pendent chains of three, four, and five carbons had exclusively or nearly exclusively phase selective solubility in the aqueous 90% ethanol phase. Poly (*N*-alkyl acrylamide) pendant chains of six and seven carbons had 90-95% phase selective

solubility in the heptane phase. Poly (*N*-alkyl acrylamide) pendent chains of eight, twelve and eighteen carbons had exclusively phase selective solubility in the heptane phase.

These results could find use in that control of phase selective solubility of polymers could enable others to prepare phase separable polymeric reagents that have exclusive phase selective solubility. Such polymers could also find applications in the design of soluble polymeric catalysts that can be recovered by liquid/liquid phase separation. By using the results described above to tailor the phase selective solubility of a polymer it should be possible to insure that the polymer and its catalysts have a strong phase preference that is opposite.

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