DEVELOPMENT AND REALIZATION OF STIMULI-RESPONSIVE REGIOREGULAR COPOLYMERS WITH TUNABLE ONSET OF RESPONSE

A Dissertation in
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by
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Abstract

A series of temperature-responsive polymers with tunable onset of water dissolution was synthesized and their aqueous phase behavior was explored. The applicability of temperature-sensitive polymers relies on their ability to phase separate from water abruptly at a specific temperature. A series of polyamides and polyesters was developed, where the lower critical solution temperature (LCST) in water is controlled by the balance of hydrophobic and hydrophilic segments in the polymer. Cloud point measurements were used to study the phase transition of the aqueous polymer solutions. It was shown that by changing the size of either the hydrophobic or hydrophilic component, the LCST in water can be shifted to higher or lower temperatures by design. In order to maintain a sharp LCST phase transition, the hydrophilic and hydrophobic segments were connected in an alternating manner. This avoids “blockyness” within the backbone, which would result in broader phase transitions due to micelle formation. PEO was chosen as the hydrophilic component in all of the copolymers because of its LCST behavior in water and its proven utility in many biological applications. The hydrophobic components consisted of either aliphatic hydrocarbons or aromatic groups. Aliphatic hydrocarbons are an ideal choice for tuning the LCST because they are readily available in many lengths. By selecting sequences of different lengths, the aqueous solution LCST was tuned. Additionally, altering the copolymer molecular weight as well as the hydrophilic or hydrophobic nature of the terminal sequences was used for fine tuning the LCST.
The influence of the nature of the hydrophobic group was investigated by preparing copolymers with aromatic hydrophobic segments, including an aromatic group with a pendant carboxylic acid. The latter hydrophobic segment imparted more hydrophobicity to the copolymers than aliphatic units of similar molecular weight, and the addition of carboxylic acid groups to the copolymer resulted in a dual temperature- and pH-responsive macromolecule.

Finally, by using the “grafting from” approach in conjunction with polycondensation synthesis, a method to end-tether temperature-sensitive polyamides to a silicon wafer was devised, rendering the substrates temperature-responsive. The surface was characterized with contact angle and atomic force microscopy (AFM).
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Chapter 1

Introduction to Temperature-Sensitive Polymers

1.1 Introduction to Water-Soluble Stimuli-Responsive Polymeric Systems

Polymers are unique in that they are able to form a variety of configurational arrangements at different length scales (molecular, nano, micro and higher). Many polymeric properties make them attractive for a wide variety of applications; however, the application of polymers that change properties in response to an environmental trigger has only been recently realized. These “smart” synthetic materials are inspired by biological systems that demonstrate environmentally-responsive behavior.

“Intelligent” aqueous polymer systems are an emergent field that is of great interest due to its current and potential applications in many disciplines, particularly biotechnology [9-13]. Intelligent polymers are defined as those in which small chemical or physical stimuli cause large and reversible solubility changes. Recent interest in these polymers lies with aqueous solution properties, due to their applicability in biological technologies. These systems are regularly referred to by several names (all of which have the same meaning), for instance stimul-
responsive/sensitive, intelligent, smart, or environmentally-responsive/sensitive. This class of polymers can exist as free chains in solution, cross linked gels, or grafted or physisorbed surface coatings.

Figure 1.1. Stimuli-responsive polymers exist in several forms: (a) free in solution, (b) cross-linked, and (c) grafted to a surfaces, for example, end-tethering.

The stimuli for solubility change fall into two categories: chemical and physical. Examples of chemical stimuli are pH [1], ions, and chemical agents whereas examples of physical stimuli include temperature [2] and light [3]. Examples of properties that can be altered by these stimuli are solubility, molecular or macroscopic shape, and surface energies. For maximum utility these changes should be abrupt, large, reversible, and fast.
The applicability of stimuli-responsive polymers is highly dependent on the stimulus onset at which the property changes occur. To date, poly(N-isopropylacrylamide) [2] is the most prominent water-soluble temperature-sensitive polymer. It is thermosensitive, as such it phase separates from water upon heating at 32 °C. It has been studied intensively, both as a model temperature-responsive polymer as well as incorporated into a variety of applications. While tremendous progress has been made developing applications for PNIPAM, a number of obstacles have arisen; most applications for temperature-sensitive polymers involve biological systems. To begin with, PNIPAM has proven to be cytotoxic [4], which presents a large barrier to commercialization. Furthermore, the “trigger temperature” of PNIPAM in water is 32°C and attempts to shift it to higher or lower temperatures have had limited success [5,6]. Applications require particular temperature ranges that typically do not include 32°C, which limits the broad applicability of PNIPAM. Finally, PNIPAM is not biodegradable [2], which for some applications may be ideal, but for many biomedical uses, the biodegradation of polymeric components is key to their utility. These limitations can be overcome by employing molecular design to develop polymers with properties in water are superior to those of PNIPAM.

The phase transition temperature of thermally-responsive water-soluble polymers can be controlled by a delicate hydrophobic/hydrophilic balance in their intermolecular interaction with water. For PNIPAM, the structure of which is shown in figure 1.2, the hydrocarbon backbone and the isopropyl pendent groups provide hydrophobicity, while the amide group in each monomer offers hydrophilicity [2].
This balance within each monomer defines 32°C as the LCST of PNIPAM in water, and provides temperature sensitivity. This concept can be extended to copolymers. Polymers with tunable temperature sensitivity in water can be realized by copolymerizing monomers or oligomeric sequences with varying degrees of hydrophobicity and hydrophilicity. While this concept was theoretically proposed over 30 years ago [7], multiple efforts towards this goal were of very limited success, and only recently has its efficacy been realized [8].

1.2 Applications

Despite the limitations of currently available stimuli-responsive water-soluble polymers, a number of applications have been realized. Stimuli-responsive polymers are particularly attractive in biotechnology because they are often biocompatible and their properties are easily manipulated by external stimuli. A few examples of such applications are briefly mentioned here:
1.2.1  Protein Separations

The overall production cost of proteins is heavily dependent on the cost of bioseparations of proteins. Affinity precipitation utilizes smart polymers by coupling a ligand to the polymer and then mixes them with proteins. The ligand couples with the protein of interest and a temperature change triggers the phase separation of the protein-ligand-smart polymer. When the complex is isolated, the protein is dissociated and the ligand-smart polymer is then available to repeat the process. Unlike other separation techniques, this procedure does not necessitate the use of expensive equipment.

1.2.2  Drug Delivery

A number of thermo- and pH-sensitive systems have been developed to deliver drugs in the body. Insulin delivery devices have been conceived that deliver insulin when glucose reaches a critical level. Both pH-sensitive nano particles as well as hydrogels [9] that deliver insulin have been developed. Additionally, polymers that undergo a thermally induced sol-gel transition have been used to deliver pharmaceuticals. Other drug delivery systems that utilize light, magnetic fields, and chemical triggers also have been conceived [9].
1.2.3 Gene Therapy

For gene therapy to be successful, genetic material must be delivered to target cells without being altered or destroyed by the body. Responsive polymers can be used to protect and deliver such material into cells. The genetic material can be protected from the environment when the polymers are in their collapsed state. Upon entry to the target cell, the genetic material can be safely released when an external stimulus is applied [10].

1.2.4 Tissue Engineering

Tissue engineering is used to replace (or more frequently repair) tissues. Synthetic polymers provide a scaffold on which cells grow. In order to successfully reconstruct tissue, extra cellular space is needed to provide adequate nutrients and oxygen to the cells, while cells are supported on a matrix. Temperature-responsive materials are ideally suited for this application. Once cells grow and tissue is formed an environmental trigger can be used to cause changes in the scaffold so as to separate the tissue from the scaffold and the scaffold will eventually degrade [11]. A thermoresponsive hydrogel made of PNIPAM grafted to gelatin has been used effectively towards this end, and was employed to grow human umbilical vein endothelial cells [12].
1.2.5 Molecular Switches/Gates

Certain chemical reactions in the body are controlled by enzymes (proteins). When particular molecules bind to the enzyme, the enzyme is activated. When a smart polymer is attached to the enzyme near a binding site, the conformation of the polymer can be used to control access to the site. Therefore, the functionality of the protein is controlled by controlling access to the binding site [13].

1.2.6 Microfluidics

Lab-on-a-chip technology often utilizes micro channels that need actuators to control the flow of small volumes of fluids. Smart polymers are an ideal candidate for such uses due to their dramatic volume changes in response to an external stimulus [14]. For example, PNIPAM was synthesized and crosslinked within a microfluidic channel to produce “plugs” for flow control. The volume change that is triggered by temperature changes allowed the plug to function as a nonmechanical valve by opening and closing the channel [15].

1.3 Temperature Sensitivity

All water-soluble polymers demonstrate some kind of temperature dependent solubility. Many of such polymers are water-soluble at room temperature, but phase separate when cooled for example (poly(acrylic acid)) or heated (poly(ethylene...
oxide)). When phase separation upon cooling occurs, its behavior is characterized by the existence of an upper critical solution temperature (UCST) [16]. While a lower critical solution temperature (LCST) describes phase separation upon heating. The LCST is the minimum temperature required to trigger phase separation. Most water-soluble polymers with temperature dependent solubility are subject to LCST behavior, albeit often at temperatures that are not easily accessible by experimentation.

The most popular thermally responsive water-soluble polymer is poly(N- isopropylacrylamide) (PNIPAM). Linear PNIPAM has an LCST of 32°C. At this temperature PNIPAM aqueous solutions undergo a phase transition. At temperatures below 32°C PNIPAM is hydrophilic and fully miscible with water, while above 32°C it is hydrophobic and phase separates from water [2], as depicted in figure 1.3.

![Figure 1.3](image_url)

Figure 1.3. Temperature triggered phase separation occurs when solvated polymer chains collapse and expel water molecules; for PNIPAM occurs upon heating above the LCST (32°C).
1.4 pH Sensitivity

The aqueous phase behavior of polymers with pendant ionizable groups can change in response to environmental pH changes, similarly to UCST or LCST behavior, as shown in figure 1.4.

Figure 1.4. The presence of ionizable groups in polymer chains can render the chains pH-responsive. By changing the pH, electrostatic repulsions can be “switched” on and off.

Polymers that exhibit pH sensitivity in aqueous solution contain groups that are able to accept or donate protons when the environmental pH changes [1]. pH-sensitive polymers have aqueous solutions that phase separate over a range of pH. The pH that corresponds to the midpoint of that range is referred to as the critical pH. The range of pH over which this phase transition takes place can be governed by two factors: the pKa of the ionizable pendant groups and hydrophobic segments within the polymer backbone. The pKa corresponds to the pH at which half of the ionizable groups are ionized. While the pKa does not correspond exactly to the critical pH, its influence on
the critical pH is strong. The critical pH is controlled by a balance of hydrophobic interactions and electrostatic repulsions.

The ionization change of pendant groups influences the solubility of the polymer in water. Osmotic pressure changes that are a result of counter ions neutralizing charges on the chain can render a charged polymer soluble in water. Weak polyacids and weak polybases are the two primary classes of pH-responsive polymers. Weak polyacids are typified by poly(acrylic acid), which has pendant carboxylic acid groups. These groups accept protons at low pH and donate protons at elevated pH. Conversely, weak bases are protonated (neutralized) at high pH and ionized at low pH. pH-responsive behavior is effectively a result of electrostatic repulsions between similar charges [17].

1.5 Polymer Solution Thermodynamics: LCST

The presence of hydrogen bonding, a directional specific interaction, in aqueous polymer solutions can lead to LCST phase separation. The change in free energy of the system upon mixing ($\Delta G_M$) is governed by the equation

$$\Delta G_M = \Delta H - T\Delta S$$  (eqn 1)

where $\Delta H$ is the change in enthalpy of the system, $T$ is the temperature, and $\Delta S$ is the change of entropy of the system. The hydrogen bonding that occurs in aqueous polymer solutions causes heat to be released upon mixing. This heat release is associated with a change in system enthalpy, whose contribution to the $\Delta G_M$ is favorable for mixing [18]. Even though the formation of hydrogen bonds promotes
mixing, their formation is coupled to an unfavorable change in system entropy. Hydrogen bonding between water molecules and polymer chains lead to an unfavorable change in entropy because degrees of freedom are constrained by one specific interaction. This change in entropy contributes unfavorably to $\Delta G_M$ and becomes increasingly significant as the temperature increases and can eventually lead to phase separation upon heating (LCST demixing) [19].

Free volume differences between polymer chains and water molecules can also play a role in LCST phase behavior. Water and polymer chains have different thermal expansion coefficients, which is equivalent to different free volumes [20]. When two liquids of differing free volumes are mixed, their net volume decreases. The net volume contraction provides a favorable contribution to the change in system enthalpy, which promotes mixing. However, the volume reduction also leads to a positive contribution to $-T\Delta S$, which does not favor mixing. As the temperature increases, the contribution of the unfavorable change in the system’s entropy to $\Delta G_M$ overwhelms the favorable contribution of the change in the system’s enthalpy, which leads to demixing (LCST phase behavior). The application of high pressures is known to suppress the temperature at which polymer solutions phase separate. This behavior is compatible with the free volume explanation of the LCST in polymer solutions. When aqueous polymer solutions are subjected to increased pressure, the solvent density increases, which decreases the difference in free volume between the water and the polymer chains.

While the Flory-Huggins theory provides a useful jumping off point for understanding polymer solution phase separation, it is imperfect. The theory does not
apply to systems with strong and specific interactions (hydrogen bonding), it neglects compressibility effects, and does not apply to dilute or semi dilute solutions because it assumes random mixing.

The deficiencies of the Flory-Huggins theory are incorporated into the interaction parameter, $\chi$, which describes the difference between the water and polymer interaction energies. The temperature dependence of $\chi$ is frequently described by a combination of an enthalpic (A) and an entropic (B) term in the following equation:

$$\chi(T) \equiv A + \frac{B}{T} \quad \text{(eqn 2)}$$

UCST phase behavior is described by this relation when $B$ is positive; $\chi$ decreases with increasing temperature. However, LCST phase behavior occurs when $B$ is negative and $\chi$ decreases with decreasing temperature. The LCST often occurs near the gas-liquid critical temperature of the solvent, which means that it is often above the normal boiling point. In order to see the LCST of many polymer solutions, pressurized vessels must be used. Although the lower critical solution temperature occurs at a higher temperature than the upper critical solution temperature it is referred to as “lower” because it lies at the bottom of the two phase region of the phase diagram, as depicted in figure 1.5.
Figure 1.5. Schematic phase diagram of a polymer solution that has both an upper critical solution temperature and a lower critical solution temperature.

1.6 Associating Polymers

What makes stimuli-responsive polymers so attractive is that molecular changes can be accompanied by reversible macroscopic property changes such as
solubility, viscosity, and conductivity. This trait allows material for properties to be tailored to specific applications requiring triggered changes. The ability to tune water-soluble polymer properties is of great interest to many fields including surfactants, flocculants, biomedical devices, sensors, actuators and adhesives.

Historically polymers have been synthesized with the intent to utilize the unique and interesting properties that result from many monomers covalently bonded to one another. Recently, noncovalent interactions have also been exploited to create a class of materials that are able to reversibly change structure. Associating polymers are characterized by the presence of groups that attract one another and form physical bonds. This group encompasses ionomers, polyelectrolytes, and hydrogen bonding polymers. The intermolecular attractive interaction between groups leads to the formation of a physical bond or cross-link [21]. Unlike covalent bonds, physical bonds are reversible. While individual covalent bonds are much stronger than physical bonds, the superposition of many physical bonds can be rather strong, for example in high molecular weight polymers. There are two categories of physical bonds: weak and strong. The difference lies in the time scale of the bond. Weak bonds break and form continuously while strong bonds are stable, except when the environment changes drastically [22].

Within the class of associating polymers, there also exist stimuli-responsive polymers. Stimuli-responsive polymers have association changes that are triggered by changes in their environment (temperature, pH, etc) and result in property changes. Synthetic chemistry is a powerful tool that allows polymers with a wide variety of constituents and architectures to be designed and produced. In particular, monomers
with hydrogen bonding moieties and hydrophobic units can be incorporated into a polymer chain, providing associating groups that mediate the formation of physical bonds. While these responsive polymers are designed to emulate natural polymers, they have an added benefit; their conformation changes are reversible.

For example, hydrogen bonding and hydrophobic interactions play pivotal roles in the shape of folded proteins. The shape of a protein determines its function and its shape is determined by its structure. When the hydrophobic/hydrophilic interactions are disrupted the resulting shape change can be irreversible. Synthetic associating polymers, however, can be made to reversibly change shape. For temperature-sensitive polymers, this can mean that water-soluble polymers can precipitate when heated, and subsequently, upon cooling the polymers will redissolve. The temperature at which this transformation occurs can be altered by changing the structure of the polymer. The balance between hydrophobic and hydrophilic interactions can be used to dictate the LCST. By making use of physical bonds (hydrogen bonding, hydrophobic interactions, and van der Waals forces), a new type of material has emerged that mimics biological molecules. (Hydrogen bonding plays a key role in associating polymer water solubility.)

1.6.1 Hydrogen Bonding

Despite its small size, water has very high melting and boiling points, as well as a large heat capacity and high thermal conductivity, often making it a challenge for research. This odd behavior is the result of its hydrogen bonding behavior. The
stability of the 3-D hydrogen bonded network that liquid water molecules form is responsible for water’s high phase transition temperatures. Its high polarity, small size, and high dielectric constant also make water an excellent solvent. Interestingly, water also has a density maximum at 4°C so that it expands upon cooling towards its solid state. Typical substances shrink when solidified [23].

The concept of hydrogen bonding was first formulated in 1920 [24]. Hydrogen has a single valence electron, as such, it is expected to be attracted (or bonded) to just one atom. However, hydrogen is capable of forming a “divalent bond” between two atoms, which is known as hydrogen bonding. For example, in water, hydrogen bonding occurs when hydrogen atoms with partial positive charges (due to polarization through the O-H bond) are attracted to other negatively “charged” oxygen atoms belonging to nearby water molecules. This second bond, a hydrogen bond, is neither covalent nor as strong [24].
Figure 1.6. a) The water molecule. b) The tetrahedral coordination of water. c) A water molecule can participate in up to 4 hydrogen bonds, two as a donor and two as an acceptor.

Beyond oxygen and hydrogen, as in water, other groups can also participate in hydrogen bonding. For instance hydrogen bonds with nitrogen or other electronegative atoms such as fluorine and chlorine atoms. The nature of the donor and acceptor atoms strongly influences the strength of the hydrogen bond. Generally, homoatomic interactions are stronger than heteroatomic interactions [25]. Examples of homoatomic interactions are: O-H---O, and N-H---N. Examples of heteroatomic interactions are: N-H---O, C-H---O, and O-H---N. Strong hydrogen bonds have a bond energy that ranges from 40 to 15 kcal/mol and are often referred to as ionic
hydrogen bonds, because there is either an electron deficiency in the donor group or extra electrons in the acceptor group (F-H---F). The bonding energy of moderate hydrogen bonds ranges from 15 to 4 kcal/mol (O-H---O-H, N-H---O=C, O-H---O=C). These are the most common hydrogen bonds and are also known as “normal” hydrogen bonds. Weak hydrogen bonds have bond energies less than 4 kcal/mol and are characterized by a hydrogen atom being covalently bonded to an atom that is only slightly more electronegative than hydrogen (for example C-H---O) [26].

Liquid water has the strongest hydrogen bonding character of any solvent, because there are nearly as many hydrogen bonds as covalent bonds. In the liquid state there can be up to four hydrogen bonds associated with each water molecule [27]. Clumps of hydrogen bonded water form and these clumps are cooperative in nature. As such, the first hydrogen bond of a cluster is the most difficult to break and each subsequent bond is easier to break. This cooperativity makes the hydrogen bonded network of water molecules; water acts as both a hydrogen donor and acceptor, which is more stable than that of molecules that acts only as a donor or an acceptor. While the hydrogen bonded network is strong, it is also dynamic. The hydrogen bonds are in a constant state of change, they break and reform continuously between the same or different molecules. The lifetime of hydrogen bonds in liquid water ranges from 1 to 20 ps, while the lifetime of a broken bond is only about 0.1 ps [28].

By definition, hydrogen bonds also possess directionality. Strong hydrogen bonding causes the network of water molecules to expand to accommodate the directed bonds [23]. However, when hydrogen bonding is weak, water molecules
crowd together. These changes in the clustering of water are responsible for the differences in hydrogen bonding of hot (weak hydrogen bonding), cold water (strong hydrogen bonding), and ice (well formed hydrogen bonded network). The high boiling point of water is a direct result of the strength of the hydrogen bonds. A great deal of heat is necessary to break enough hydrogen bonds to allow water molecules to evaporate.

1.6.2 Properties that Influence Hydrogen Bonding

In liquid water there exists a delicate balance between van der Waals interactions and directed hydrogen bonds. The strong directionality of the hydrogen bonds gives rise to clustering (or ordering) which influences physical properties such as increasing cohesion, compressibility, and dielectric constant. When the hydrogen bonds are weak the cohesion, compressibility and dielectric constant decrease. The influence of increasing temperature, pressure, or the addition of electrolytes can all disrupt the hydrogen bonding structure in water [23].

The equilibrium of interaction \{O-H---O \leftrightarrow O-H + O\} is endothermic, therefore increasing the temperature of the system reduces the number of hydrogen bonds. At 0°C, the hydrogen bonding energy is about 17 kcal/mol, while at 200°C (under pressure) it is reduced to 13 kcal/mol [29]. In addition to the more energetic conditions at high temperatures, hydrogen bond strength decreases by approximately 10% for a 100°C temperature increase [30].
Hydrogen bonded water has a density that is lower that it would be if no hydrogen bonds existed. The system volume can be reduced by increasing system pressure. Therefore, when water is pressurized the density increases and the hydrogen bond lengths decrease. The decrease in hydrogen bond length increases their strength; however, increased density also bends the hydrogen bonds, which results in many breakages.

There are two primary types of electrolytes when dealing with hydrogen bonding: “structure makers” and “structure breakers”. When an electrolyte is added to water a hydration layer is formed surrounding the solute. When the solute contains a large nonpolar moiety, “hydrophobic hydration” occurs. The network of water molecules rearranges to surround the solute and increases the number of hydrogen bonds near the solute, hence the name structure maker. This rearrangement causes the network to expand which decreases the density of the system. Hydrophobic hydration is caused by the addition of an ionic (or polar) solute. Hydrogen bonds are broken in this scenario, which increases the density and decreases the heat capacity of liquid water.

1.6.3 The Hydrophobic Effect

The hydrophobic effect relates to the incompatibility of substances with water. However, it should be noted that while the term “hydrophobic” literally means water fearing, hydrophobic species and water have attractive dispersive interactions. Nevertheless, the attractive interaction between water molecules is typically much
greater than that of water and hydrophobic species [31], leading to an unfavorable free energy change upon mixing. The result is the sparingly soluble nature of hydrophobic species.

Water’s strong hydrogen bonding interactions also dictate its interactions with nonhydrogen bonding molecules, albeit in an indirect way. Hydrophobic molecules (for example inert atoms, colloidal particles, hydrocarbons, and fluorocarbons) force water molecules that come into contact with them to rearrange in order to accommodate them, and water does so in a manner that minimizes the number of lost hydrogen bonds [32]. When the hydrophobic solute is small, it may be possible for water to surround it in such a way that few hydrogen bonds are sacrificed. The primary energetic implication of bringing together water molecules with nonpolar solutes is due to the reorganization of the water structure, not, as was thought for many years, because the interactions between water and nonpolar molecules is much more unfavorable or repulsive compared to water-water interactions. In fact, the dispersive interactions between such molecules are quite similar [31].

The tetrahedral coordination of the water molecules is a key factor in its role as a solvent. The molecules are able to surround both large and small solutes with minimal disruption to the hydrogen bonding network. Liquid water generally participates in 3-3.5 hydrogen bonds per molecule [23]. When surrounding a nonpolar solute, the water can become more ordered by participating in 4 hydrogen bonds. This ordered water “layer” that surrounds the solute is known as the first hydration shell, and the phenomenon is often referred to as hydrophobic hydration or solvation. Because of the increased order within the water network, the dissolution
process is entropically unfavorable. The entropic penalty associated with solvation of hydrocarbons is the explanation for why hydrocarbons are only sparingly soluble in water. The free energy of transfer of a hydrocarbon from the bulk into water is proportional to the surface area of the hydrocarbons, which relates to the volume of water network that is disrupted, since the number of hydrogen bonds that must be reoriented is controlled by the surface area of the hydrocarbon [31].

1.6.4 Hydrophobic Interaction

The hydrophobic interaction relates to the abnormally strong effective attraction between nonpolar molecules in water, and is a manifestation of the hydrophobic effect. The attraction between the nonpolar molecules in water is most often greater than that in air. The origin of this phenomenon is also entropic. When water molecules rearrange to accommodate the hydrophobic solutes and two solutes are in close proximity, their hydrophobic hydration layers overlap and the solutes are attracted to each other [32]. Eliminating some of the hydration layers between adjacent solutes leads to gain if free energy which is in turn, manifested as an apparent attraction between the solutes. Hydrophobic interaction is critical to many phenomena such as protein folding, micelle aggregation, and molecular self assembly.
1.6.5 Hydrophilicity

While the term “hydrophilic effect” does not exist, the tendency of particular molecules to repel each other in water, but be water-soluble does exist. When water-solute interactions are more favorable than solute-solute interactions a molecule or group is referred to as hydrophilic [23]. For example, groups containing hydrated ions are expected to be hydrophilic, but so are a number of neutral, but polar molecules, and even a few non-polar molecules. All molecules have the proper geometric configuration and have electronegative atoms that are able to participate in hydrogen bonding with water. An example of this is the presence of an oxygen atom in the PEO repeat unit or the nitrogen atom in amines. Interestingly, non-polar groups may be hydrophilic and polar groups may be hydrophobic. As stated above, hydrophobic groups tend to increase the order in the surrounding water network. Inversely, hydrophilic groups can cause disorder [32].

1.7 Poly(ethylene oxide)

PEO is an interesting molecule because it contains both hydrophilic and hydrophobic moieties, which can give rise to versatile behavior and properties; for example, it is soluble in both aqueous and organic solvents, and when in solution it is quite dynamic. However, it can easily form crystallized solids. In solution, it has a high mobility, yet can complex and aggregate and exist in helical structures as well as hydrogen bond or coordinate with other molecules [33]. Its wide applicability in
many commercial products (food, packaging, cosmetics, and medical devices) is a result of its nontoxicity in addition to its versatile properties. Furthermore, it is rather inexpensive and easy to produce.

1.7.1 Water Solubility of PEO

PEO seems like an anomaly in the polyether series, because it is insoluble in water at all molecular weights [34]. The structure of PEO is similar to that of other polyethers such as poly(propylene oxide) (PPO) and poly(methylene oxide) (PMO). However, PPO and PMO are only water-soluble at low molecular weights. The unique solubility properties of PEO are a result of hydrogen bonding between the ether group and water and its molecular architecture. An unstrained and continuous network of water molecules is able to form when water hydrogen bonds with PEO. The distance between neighboring oxygen atoms in PEO (4.7Å), matches the distance between hydrogen bonded oxygen atoms (4.7 to 2.9Å) [35]. Each oxygen atom in PEO can hydrogen bond with two water molecules. While each monomer interacting with two water molecules is not sufficient to form a hydration shell around the polymer, it is possible to form a complete shell when some of the water molecules also form part of the hydration shells of neighboring PEO chains. The hydrogen bonding that occurs between PEO and water, while not markedly disrupting the hydrogen bonded water network, is the reason for PEO’s superior aqueous solubility. The change in enthalpies of dissolution and dilution of PEO in water are both negative, as is the associated change in entropy. The hydrogen bonding that occurs
between water and PEO makes PEO a structure maker for water, therefore the
dissolution process is exothermic. Because water molecules hydrogen bond with the
polymer, the structure of those water molecules become more structured, thereby
reducing the system entropy.

Although PPO and PEO have quite similar structures, only low molecular
weight PPO is water-soluble and only at low temperatures. Interestingly, the phase
diagram of PPO in water is quite similar to that of PEO, except that the miscibility
gap encircles most temperatures where water is liquid [35]. The hydration shell of
ordered water that forms when PPO is mixed with water is associated with negative
excess enthalpy and entropy of mixing. The steric hindrance caused by the methyl
groups in PPO causes the water structure to be strained. As the molecular weight of
PPO increases, so does the number of methyl groups and thus strain of the water
structure increases and the phase transition temperature decreases.

PMO’s water insolubility seems rather surprising at first glance because its
oxygen to carbon ratio is larger than that of PEO. The insolubility of PMO is a direct
consequence of its structural “incompatibility” with the hydrogen bonded water
network, which originates from the difference in distance between oxygen atoms in
PMO and the oxygen atoms in the hydrogen bonded water network.

1.7.2 LCST of PEO

While PEO is soluble in water at low and moderate temperatures, high
molecular weight PEO phase separates from water above 100°C [36]. This LCST
behavior is a result of hydrogen bond reduction due to thermal energy. The LCST of PEO in water can be altered by changing environmental conditions. As discussed above, many factors can influence hydrogen bonding, which in turn influence phase behavior. The presence of electrolytes generally reduces the water solubility of PEO, thus reduces the LCST. Increasing the pressure will also reduce the LCST of PEO. Any change in the system that will disrupt hydrogen bonding will also cause the LCST of PEO in water to shift to lower temperatures.

Water and PEO are soluble at low temperatures because the structured water surrounding the PEO is enthalpically favorable, even though it is entropically unfavorable [35]. The geometric fit between the water and the PEO is the cause of the favorable enthalpy. As the temperature increases, two effects come into play: first, thermal energy will break hydrogen bonds. Independently, the hydrogen bond breakage is not sufficient to cause phase separation, however, as the temperature increases the entropic penalty rises which ultimately results in phase separation. With phase separation, comes water structure destruction. For low molecular weight PEO, the combinatorial entropy is large and at sufficiently high temperatures the PEO and water will become miscible again. As such, the size of this miscibility gap is a function of molecular weight.
1.8 Research Objectives

The research contained in the body of this thesis pertains to the synthesis and phase behavior of regioregular (alternating) copolymers with tunable water solubility. Although a great deal of progress has been made in the field of temperature-responsive polymers, most systems are based on a single, non degradable polymer whose LCST in water is practically not tunable. This work describes the synthesis of a series of linear, segmented polyamide and polyester copolymers based on poly(ethylene oxide) and their aqueous phase behavior.

The tunability of the system was achieved by designing regions/sequences along the copolymers with the proper balance of hydrophobic and hydrophilic components. In each system, the hydrophilic segment was a short chain of poly(ethylene oxide) while the hydrophobic units varied from aliphatic hydrocarbon chains, to aromatic rings, and aromatic rings with pendant carbon trifluoride or carboxylic acid groups. The incorporation of the carboxylic acid moieties rendered the polymer responsive to both temperature and pH changes. Finally, a method to graft these alternating copolymers from a surface using polycondensation was developed.
1.9 References


Chapter 2

Alternating Regioregular Water-Soluble Copolymers: Tuning the LCST

2.1 Summary

Regioregular linear copolymers, with alternating sequences of two different monomers exhibiting tunable water solubility, were prepared using polycondensation synthesis. The copolymers (both polyamide and polyester) consisted of alternating hydrophilic and hydrophobic segments. By varying the relative size of the two segments, the lower critical solution temperature (LCST) was changed. By increasing the size of hydrophobic groups, the LCST was shifted to lower temperatures, while incorporating larger hydrophilic groups shifts the LCST to higher temperatures. To date, the most commonly used method for shifting the LCST of a water soluble temperature-responsive polymer is to graft hydrophilic or hydrophobic groups to poly(n-isopropylacrylamide). While the phase transition temperature of the resulting polymers is shifted, the transition is also broadened by the formation of micelles. By limiting the size of the hydrophobic and hydrophilic segments, as well as arranging them in an alternating manner, the sharpness of the phase transition temperature is maintained because micellization can be prevented. The aqueous phase behavior of
four polyamides and three polyesters is investigated using cloud point measurements. These measurements are used to generate phase diagrams, which can be used to determine the LCST. A relationship between the ratio of hydrophilic to hydrophobic groups and the LCST exists for both the polyamides and the polyesters [1]. These relations are used to predict the LCST of other copolymers.

2.2 Introduction

The class of polymers whose phase behavior changes abruptly in response to small environmental changes is widely referred to as stimuli-responsive polymers. The field has attracted a great deal of attention due to its potential applications. Specifically, polymers that are soluble in water at low temperatures and become insoluble upon heating are known as temperature-responsive (or temperature sensitive) polymers. These systems exhibit lower critical solution temperature (LCST) behavior. The ability to control the temperature at which the polymers become insoluble in water is of great importance for applications.

Chain conformation is influenced by the quality of the solvent. Below the LCST, good solvent conditions exist and the expanded coil conformation allows for the maximum number of polymer-solvent contacts. In aqueous solutions, hydrogen bonding is prevalent and water molecules solvate the polymer chain. As the temperature increases, the solvent quality decreases and hydrogen bonds are broken, water is expelled from the coil and interactions between hydrophobic moieties increase. For an infinitely long chain, an abrupt phase transition occurs at the theta
temperature and the chains form globules. With increasing temperature, hydrophobic interactions between the globules cause them to aggregate and the chains phase separate from the solvent. The result is a two phase system where one phase is polymer rich and solvent poor and the other is polymer poor and solvent rich. The LCST in aqueous polymer solutions has been attributed to a number of phenomena: hydrogen bonding between polymer and water, hydrophobic interactions, greater entropy in the two phase system than the single phase region, and excluded volume effects [2].

The aqueous solution LCST can be tuned by balancing hydrophobic and hydrophilic moieties within the polymer. This concept was taken advantage of as early as 1935 by Heymann, who studied the water solubility of methylcelluloses (considered copolymers with a random distribution of hydrophobic and hydrophilic segments) [3]. In 1951, Timasheff, Bier, and Nord [4] investigated the aqueous phase behavior of copolymers containing poly(vinyl acetate), as did Sakurada in 1957 [5]. The concept of copolymerizing hydrophilic and hydrophobic monomers to produce polymers with LCST phase behavior in water was popularized by Taylor and Cerankowski in 1975 in the form of a rule. “As a polymer which is soluble in water at all temperatures is made increasingly hydrophobic, before complete water insolvency is reached, a range of composition will be found which will have temperature inverse solubility and the more hydrophobic the increment, the lower the LCST” [6]. Taylor and Cerankowski recognized that it is possible to develop numerous temperature-responsive polymers by copolymerizing hydrophobic monomers with more water soluble monomers. They also proposed building a monomer that would have a
balance of hydrophobic and hydrophilic interactions that would allow one to homopolymerize it to form a temperature-responsive polymer. However, Taylor and Cerankowski failed to realize that the distribution of the comonomers is of great importance. When large segments of hydrophobic and hydrophilic monomers exist, LCST phase behavior does not occur because micelles form when the aqueous polymer solution is heated and the phase separation can not be predicted.

Many groups have since utilized the hydrophilic/hydrophobic balance to create temperature-responsive polymers. The most popular thermosensitive polymer is PNIPAM. Its LCST is approximately 32 °C [7]. At temperatures below 32 °C the polymer is soluble in water because of hydrogen bonds between water and polar groups on the polymer chain. Above 32 °C, the hydrogen bonds break and are not sufficient to maintain the polymer in solution, which causes the chains to aggregate.

2.2.1 Shifting the LCST

One method to shift phase transition temperatures of polymer solutions has been to graft PEO to a PNIPAM backbone. While this method does cause cloud point temperatures to increase with increasing PEO grafting density, the phase separation is a result of a coil-to-micelle transition rather than PNIPAM’s LCST. The PNIPAM backbone becomes hydrophobic above its LCST, however, the chains do not collapse and aggregate. Instead, micelles are formed with hydrophobic PNIPAM cores, while the hydrophilic grafted PEO segments remain solvated by water. The phase separation is a result of light scattered by the micelles, not a genuine LCST phase
transition. As the grafting density increases, the cloud point transition broadens further, which limits applications [8]. Similar behavior is seen for hydrophobic grafts on PNIAPAM [9]. An additional complication that results from the coil-to-micelle transition is that it is difficult to predict and control the phase behavior in aqueous solutions [10]. However, it is possible to theoretically predict phase behavior based on the relative size of the hydrophilic and hydrophobic components when a proper LCST transition exists.

Another method used to change the hydrophilic/hydrophobic balance within a polymer was to replace hydroxyl groups in linear polyglycidol with hydrophobic ester groups. By varying the number of esterfied hydroxyl groups, the LCST was tuned between 4 and 100 °C in water [11].

While designing monomers with appropriate hydrophobic/hydrophilic balance has been successful for PNIPAM (as well as other poly(N-alkylacrylamides)), this approach has also been use to develop other thermosensitive polymers such as: poly(vinyl ethers) [6], poly(N-vinyl alkylamides) [7], and poly(N-vinyl caprolactam) [8]. However, there is a limit in the number of polymers that can be developed in this manner and tuning their LCSTs has proven to be difficult [10]. The existence of many hydrophilic and hydrophobic monomers allows for the possibility of a large number of combinations that will yield polymers with temperature-responsive behavior. The LCST can then be tweaked by choosing monomers with slightly different hydrophilicities or hydrophobicities. This concept is tremendously useful, as it allows polymers with specific temperature-sensitive solubilities to be conceived.
A number of research groups have copolymerized hydrophobic monomers with acrylamides [6] and dimethylacrylamides [15]. Mori et al. [16] were able to generate a series of temperature-responsive polymers with sharp aqueous solution LCSTs. Random copolymers were produced by copolymerizing N-dimethylacrylamide (hydrophilic) with N-phenylacrylamide (hydrophobic). The LCST ranged from 5 to 55 °C in water by incorporating 15-27% N-phenylacrylamide. Lutz and Hoth [17] prepared tunable thermoresponsive PEG based random copolymers of 2-(2-methoxyethoxy)ethyl methacrylate and oligo(ethylene glycol) using controlled radical polymerization. By adjusting the comonomer composition and using small PEG units that prevent micellization, polymers with sharp LCSTs ranging from 28-90 °C were achieved in water.

As Taylor and Cerankowski [6] state, the proper balancing of hydrophilic and hydrophobic components of polymer is necessary to yield LCST behavior. By controlling the relative sizes of those components it is possible to tune the LCST. Most applications of temperature-sensitive polymers rely on a fast phase transition that occurs over a narrow temperature range. In order to achieve this, a polymer with linear architecture and hydrophilic and hydrophobic moieties that are distributed randomly or evenly across the chain is required. If the monomers are not distributed evenly (i.e. they are lumped together in a blocky manner) a coil-to-micelle transition may result.

Poly(ethylene oxide) (PEO) is a prominent biocompatible polymer that exhibits LCST behavior in water at temperatures ranging from 100-150°C, depending on molecular weight [18,19]. The biocompatibility offered by PEO is attractive for
applications in biotechnology. However, its temperature sensitivity in water occurs at temperatures too high to be relevant for biological applications. By introducing additional hydrophobic ethylene units to PEO, the LCST in water is expected to decrease \[20\], as predicted by the Taylor and Cerankowski solubility rule.

Also from the solubility rule, it is expected that increasing the size of the hydrophobic ethylene units while maintaining the same number of hydrophilic ethylene oxide will result in a decreased LCST in water. This was demonstrated by others for both polyesters and polyamides \[20\]. The aim of this work is to design and synthesize linear copolymers with tunable water solubility that is achieved by balancing hydrophilic and hydrophobic components. Two polymer series were synthesized and studied with controlled relative size of ethylene oxide (hydrophilic) and ethylene (hydrophobic) units; one with ester linkage groups and the other with amide linkage groups.

2.3 Experimental Methods

2.3.1 Polyamide Synthesis

A schematic of the polyamide and polyester synthesis scheme is presented in figure 2.1. The structures and CAS numbers of all of the monomers are listed in Appendix B. Poly(ethylene glycol) bis(carboxymethyl) ether (PEG Mw 600, Sigma Aldrich) was heated to 80°C and vacuum dried for 2 hours. Dichloromethane (DCM) and 4 times the stoichoimetric amount of thionyl chloride (thionyl chloride) was
added and refluxed at 80°C for 4 hours under argon. The resulting PEG diacid chloride (PEG-Cl) was vacuum dried at 40°C to remove the solvent and excess thionyl chloride (SiCl₂). DCM was added to the PEG-Cl and the resulting solution was 25wt% PEG-Cl. An α,ω alkane diamine (1,6-Hexanediamine (C₆), 1,8-Diaminoctane (C₈), 1,10-Diaminodecane (C₁₀), or 1,12-Diaminododecane (C₁₂), all from Sigma Aldrich) was dissolved in DCM, the solution was then filtered. The residue was discarded and the filtrate dried. The resulting diamine was then dried under vacuum for 30 minutes before dried DCM and 2 times the stoichiometric amount of pyridine was added, resulting in a 20wt% diamine solution. To the diamine solution, 80% of the PEG-Cl solution was added in a dropwise fashion over 2 hours. The reaction was done under argon at room temperature. After 6 hours the remaining diamine was dropped in over 2 hours. The solution was filtered to remove the pyridine hydrochloride that was formed during the reaction. The polymer was then precipitated with ether, filtered and vacuum dried. To increase the molecular weight further, the polymer was dissolved again in dry DCM and pyridine was added. The PEG-Cl and diamine solutions were alternately dropped in. The polymer solution was then precipitated with ether, filtered again and the filtrate was dried.

The resulting polymer was dissolved in water and underwent dialysis to remove the residual pyridine hydrochloride and any unreacted molecules. A dialysis membrane with a size exclusion limit of 1000 g/mol was used. The water was then evaporated under a stream of air and samples were vacuum dried. Fractionation by reprecipitation was used to isolate narrower molecular weight samples. The polymer solution was transferred to an Erlenmeyer flask; ether was added to the
dichloromethane polyeamide solution until the solution became turbid. The flask was held at a 45° angle, allowing the precipitate to collect at the bottom corner. After 24 hours, the solute was carefully removed. The precipitate was redissolved in dichloromethane and fractionated again using hexane. The solute was also fractionated again by adding hexane. This procedure was repeated 6 times.

Figure 2.1. Polyamide and polyester synthesis scheme. The reactions was carried out at 25 °C in dichloromethane in the presence of pyridine and under argon.

### 2.3.2 Polyester Synthesis

Polycondensation was also employed to prepare a series of polyesters. Polyethylene glycol with molecular weights of 400, 600, and 900 g/mol (PEG 400, 600, 900) were vacuum dried at 80°C for 1 hour to remove water. The dried PEG was dissolved in dichloromethane (DCM) and kept under argon. In a separate flask, dichloromethane and pyridine were added. To this flask, 75% of a stoichiometric solution PEG was added. Next, 75% of an acid chloride (sebacoyl chloride, suberoyl
chloride, or adipoyl chloride; structures and cas numbers listed in Appendix B) was
added in a drop-wise fashion. The reaction was kept under argon and stirred for 2
hours. Subsequently, the remaining PEG and acid chloride solutions were added
alternately in a dropwise manner. The solution then stirred for another 2 hours. A
white precipitate formed during the reaction. This precipitate was pyridinium
hydrochloride and was removed by vacuum filtration.

Fractionation by reprecipitation was used to isolate narrower molecular
weight samples. Hexane was added to the dichloromethane polyester solution until
the solution became turbid. After 24 hours, the solute was carefully removed. The
precipitate was redissolved in dichloromethane and fractionated again using hexane.
The solute was also fractionated again by adding hexane. This procedure was
repeated 6 times.

2.3.3 Molecular weight determination

Polyamide copolymers: The molecular weight and molecular weight distribution of
the copolymers were determined by gel permeation chromatography (GPC) using a
Waters 410 GPC with a refractive index detector with PEO molecular weight
standards. The measurements were taken at 60°C using dimethyl formamide as the
solvent and a mobile phase flow rate of 0.6 ml/min.

Polyester copolymers: The molecular weight and molecular weight distribution of the
copolymers were determined by gel permeation chromatography (GPC) using a
Waters 1515 HPLC pump and a Waters 2414 refractive index detector with
polystyrene molecular weight standards. The measurements were taken at 37°C using tetrahydrofuran as the solvent and a mobile phase flow rate of 1.0 ml/min.

2.3.4 Cloud Point Determination

A polymer solution (1 ml) sample is placed in a glass vial immersed in a water bath. At low temperatures, when the solution is transparent, a laser beam travels through the sample and enters a photometer at a 0° angle where its transmitted intensity is recorded as a voltage. As the temperature rises, the solution becomes turbid causing the laser beam to scatter and the transmitted intensity to decrease. A temperature probe connected to a hot plate is placed directly in polymer solution to record the instantaneous temperature, and is also used to control the heating/cooling rate. The temperature and voltage are recorded simultaneously using serial port data collection software. The phase transition temperature (cloud point) is defined to be the temperature at which 60% of the maximum laser power is recorded.

2.4 Results and Discussion

Three polyamides were synthesized, where the ethylene oxide unit remained constant with a length of (CH$_2$CH$_2$O)$_{12}$ and the hydrophobic segment was varied from 3 to 6 ethylene units. Each polymer was fractionated and phase diagrams were generated for each molecular weight.

The most common technique used to generate phase diagrams of polymer solutions is the cloud point method. Several polymer solution samples are prepared at
different concentrations. In the case of polymer solutions that demonstrate LCST behavior, when the solution is heated it becomes turbid when the coexistence curve is crossed. The onset of turbidity indicates the change from a one-phase system to a two-phase system. The temperature at which this change occurs is the cloud point temperature. The turbidity is a result of microscopic heterogeneity; the polymer chains collapse and form a second, polymer rich phase. The difference in refractive indices between the polymer rich and polymer poor phases causes light to scatter and the solution to appear cloudy. When several aqueous solutions with different copolymer concentrations are prepared and their cloud points measured, a plot of cloud point temperature versus concentration can be generated (a coexistence curve). The minimum of the curve is the LCST.

The molecular weights and LCSTs of the eleven polyamides are presented in table 2.1. The name of each sample is divided into three sections. The first two letters are either PA or PE, which refer to polyamide or polyester, respectively. The numbers in the parentheses are the number of hydrophilic PEO units and the number of hydrophobic ethylene units, respectively. Finally, the last number is the LCST of the sample. For example, PA(12/3) 60 is a polyamide composed of hydrophilic segments that have 12 ethylene oxide units and hydrophobic segments that have 6 carbons and has an LCST in water at 60 °C.
Table 2.1. Molecular weight, polydispersity and LCST data for polyamide series.

<table>
<thead>
<tr>
<th>Sample</th>
<th>LCST (°C)</th>
<th>Mn (g/mol)</th>
<th>Mw (g/mol)</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA(12/3) 60</td>
<td>59.5</td>
<td>17600</td>
<td>26900</td>
<td>1.5</td>
</tr>
<tr>
<td>PA(12/4) 50</td>
<td>50.4</td>
<td>3900</td>
<td>6600</td>
<td>1.7</td>
</tr>
<tr>
<td>PA(12/4) 45</td>
<td>45.1</td>
<td>17400</td>
<td>23100</td>
<td>1.3</td>
</tr>
<tr>
<td>PA(12/4) 38</td>
<td>38.2</td>
<td>18500</td>
<td>27800</td>
<td>1.5</td>
</tr>
<tr>
<td>PA(12/5) 28</td>
<td>27.6</td>
<td>1400</td>
<td>4200</td>
<td>3.0</td>
</tr>
<tr>
<td>PA(12/5) 21</td>
<td>21</td>
<td>7300</td>
<td>12200</td>
<td>1.7</td>
</tr>
<tr>
<td>PA(12/5) 20</td>
<td>19.9</td>
<td>7700</td>
<td>17300</td>
<td>2.2</td>
</tr>
<tr>
<td>PA(12/5) 17</td>
<td>16.9</td>
<td>12800</td>
<td>22400</td>
<td>1.8</td>
</tr>
<tr>
<td>PA(12/6) 25</td>
<td>25.3</td>
<td>1400</td>
<td>2800</td>
<td>2.0</td>
</tr>
<tr>
<td>PA(12/6) 13</td>
<td>12.7</td>
<td>5600</td>
<td>11700</td>
<td>2.1</td>
</tr>
<tr>
<td>PA(12/6) 11</td>
<td>11.4</td>
<td>7200</td>
<td>14900</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Three polyesters of various molecular weights were synthesized and aqueous cloud point measurements were made to determine their phase diagrams. The molecular weights and LCSTs in water of the polymers are presented in table 2.2.

Table 2.2. Molecular weight, polydispersity and LCST data for polyester series.

<table>
<thead>
<tr>
<th>Sample</th>
<th>LCST</th>
<th>Mn (g/mol)</th>
<th>Mw (g/mol)</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE(20/3) 52</td>
<td>52</td>
<td>4100</td>
<td>13600</td>
<td>3.3</td>
</tr>
<tr>
<td>PE(20/3) 50</td>
<td>50.3</td>
<td>13300</td>
<td>20600</td>
<td>1.5</td>
</tr>
<tr>
<td>PE(20/3) 44</td>
<td>44.4</td>
<td>20200</td>
<td>35300</td>
<td>1.7</td>
</tr>
<tr>
<td>PE(20/4) 50</td>
<td>50</td>
<td>4300</td>
<td>9000</td>
<td>2.1</td>
</tr>
<tr>
<td>PE(20/4) 38</td>
<td>38</td>
<td>3800</td>
<td>13900</td>
<td>3.7</td>
</tr>
<tr>
<td>PE(20/4) 35</td>
<td>35</td>
<td>6100</td>
<td>16300</td>
<td>2.7</td>
</tr>
<tr>
<td>PE(20/4) 28</td>
<td>27.7</td>
<td>12200</td>
<td>22000</td>
<td>1.8</td>
</tr>
<tr>
<td>PE(13/3) 33</td>
<td>32.9</td>
<td>2000</td>
<td>3700</td>
<td>1.9</td>
</tr>
<tr>
<td>PE(13/3) 29</td>
<td>28.8</td>
<td>2300</td>
<td>5300</td>
<td>2.3</td>
</tr>
<tr>
<td>PE(13/3) 26</td>
<td>25.7</td>
<td>15700</td>
<td>33200</td>
<td>2.1</td>
</tr>
</tbody>
</table>
2.4.1 Polyamide Phase Diagrams

The phase diagrams of all of the polyamide samples are presented in figure 2.2. PA(12/3) had a molecular weight of 26,900 and an LCST of 59.5 °C. The molecular weights PA(12/4) ranged from 6,600 to 27,800 g/mol and had LCSTs in water ranging from 50.5-38.2 °C.

The molecular weights PA(12/5) ranged from 4,200 to 17,300 g/mol and had LCSTs ranging from 27.6-16.9 °C. The molecular weights PA(12/6) ranged from 2,800 to 14,900 g/mol and had LCSTs ranging from 25.3-11.4 °C.
2.4.2 Polyester Phase Diagrams

The aqueous solution phase diagrams of the polyester samples are presented in figure 2.3. The molecular weights of the PE(20/3) samples ranged from 13,600 to 35,300 g/mol and had LCSTs ranging from 52.0 to 44.4 °C. The molecular weights of the PE(20/4) samples ranged from 9,000 to 22,000 g/mol and had LCSTs ranging from 50.0 to 27.7 °C. The molecular weights of the PE(13/3) samples ranged from 3,700 to 33,200 g/mol and had LCSTs ranging from 32.9 to 25.7 °C.

Figure 2.3. Phase diagrams of several molecular weights of three polyesters in water: PE(20/3) circles, PE(20/4) squares, and PE(13/3) triangles.

The aqueous solution cloud point measurements for the sample PA(12/5)17 are plotted in figure 2.4.
Figure 2.4. Raw data from cloud point measurements of six concentrations of PA(12/5) 17 in water, heated at 1 °C/min.

Six aqueous solution samples with concentrations ranging from 6.5 wt% to 1 wt% were heated at a rate of 1 °C/min. The phase transitions are as sharp as expected from a LCST phase behavior. The phase transition of the 6.5 wt% sample had a breadth of 0.5 C. The 1 wt% solution experienced at 80% reduction in relative laser intensity in a 2°C region. This data is representative of the whole series, even at elevated temperatures. From this, it can be strongly suggested that a true LCST phase transition exists, as opposed to a coil-to-micelle transition, in which phase transitions are much broader (over 5-15°C in breadth). The phase diagram in figure 2.5 was generated from the cloud point data shown in figure 2.4.
Figure 2.5. Phase diagram of PA(12/4) 17 in water.

The aqueous solution cloud point decreased upon dilution from 18.5 to 16.9 °C and then increased to 18.7 °C. The minimum, 16.9 °C, corresponds to the 1 wt% sample and is taken as the LCST.

Figure 2.6 shows the cloud point curves for PE(20/4) 28 (Mw 21,900 g/mol, PDI 1.8) in water. The concentration of polymer in water ranges from 1-20 wt% and the corresponding cloud points range from 28 to 38 °C. All of the polyesters demonstrate similarly sharp phase transitions. It should be noted that the lower concentrations of polymer in water have broader cloud point curves. This is a manifestation of the kinetics of aggregation, which are slower in dilute solutions than in semi-dilute and concentrated solutions.
Figure 2.6. Cloud point measurements of 1-20 wt% aqueous solution of PE(20/4) 28. Heating rate 1 °C/min.

Figure 2.7 depicts the aqueous solution phase diagram that is generated for the cloud point data in figure 2.6.

Figure 2.7. Phase diagram of PE(20/4) 28 in water generated from cloud point curves in figure 2.2.
The cloud point temperature was taken as the temperature at which the laser intensity was 60% of the maximum. The minimum temperature on the phase diagram is considered to be the LCST at 28°C.

It should be noted that when the copolymer aqueous solutions are held at temperatures above their cloud point temperatures a long time, the system will macroscopically phase separate into two phase (one polymer rich and one polymer poor) and each phase will be homogenous, therefore, optically transparent. This macroscopic phase separation indicates that micellization is not occurring [9]. If micelles had formed, the micellar structures would be stable in water and would not precipitate.

2.4.3 Influence of Heating Rate

The influence of the heating rate on the aqueous solution cloud point temperature was explored by studying the cloud point curve of a 3 wt% aqueous solution of PE(20/4) 28 at two heating rates: 0.1 and 1°C/min. The corresponding cloud point curves are presented in figure 2.8. When the heating rate increased by an order of magnitude, the cloud point increased by just 1 °C. It is clear that the cloud point is not markedly dependent on heating rate with in the range of 0.1 to 1 °C/min, as expected from genuine LCST phase behavior.
For the rest of the results presented in this thesis, the experimental heating rate used to generate phase diagrams was 1 °C/min. Several other groups [21,22] have studied the influence of heating rate on cloud point and also found that increasing the heating rate slightly increases the cloud point. This is a direct manifestation of the limitations of heat transfer to the solution and the kinetics of phase separation for polymer solutions.
2.4.4 Cloud Point on Heating and Cooling

In figure 2.9, the heating and cooling cloud point curves for PE(20/4) 28 in water are presented. Upon heating, the cloud point (at 60% intensity) is 27.5 °C. When the turbid solution is cooled, the mixing temperature (at 60% intensity) is 27.3°C.

![Figure 2.9. Relative laser intensity as a function of temperature on heating and cooling at 0.1 °C/min for a 3wt% aqueous solution of PE(20/4) 28.](image)

The slightly lower (0.2 °C) mixing temperature is likely the result of intra and interchain hydrogen bonding that forms in the collapsed aggregates that must be broken in order for remixing to occur [23], and is in agreement with genuine LCST phase behavior studied via turbidity measurements [for example, 17].
2.4.5 Shifting the LCST

2.4.5.1 Polyamides

The focus of this chapter is tuning the LCST in water by varying the ratio of hydrophilic to hydrophobic units in the polymer. Chapter 3 will explore the influence of the molecular weight on the LCST. Therefore the discussion in this chapter will be mainly concentrating on the polyamides listed in table 2.3, which are the highest molecular weight polymers from each chemical composition.

Table 2.3. The LCST and $m/n_{\text{real}}$ and $m/n_{\text{reactant}}$ in each series.

<table>
<thead>
<tr>
<th>polyamides</th>
<th>LCST °C</th>
<th>$(m/n)_{\text{real}}$</th>
<th>$(m/n)_{\text{reactant}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA(12/3) 60</td>
<td>59.5</td>
<td>3.9</td>
<td>4.0</td>
</tr>
<tr>
<td>PA(12/4) 38</td>
<td>38.2</td>
<td>2.9</td>
<td>3.0</td>
</tr>
<tr>
<td>PA(12/5) 17</td>
<td>16.9</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>PA(12/6) 11</td>
<td>11.4</td>
<td>1.9</td>
<td>2.0</td>
</tr>
<tr>
<td>PE(20/3) 44</td>
<td>44.4</td>
<td>6.5</td>
<td>6.7</td>
</tr>
<tr>
<td>PE(20/4) 28</td>
<td>27.7</td>
<td>5.2</td>
<td>5.0</td>
</tr>
<tr>
<td>PE(13/3) 26</td>
<td>25.7</td>
<td>4.2</td>
<td>4.3</td>
</tr>
</tbody>
</table>

At high molecular weights the ratio of hydrophilic to hydrophobic units ($m/n$) is constant and equal to that of the reactants. However, at lower molecular weight the terminal monomer influences the overall ratio $m/n$ of the polymer. To account for this, $(m/n)_{\text{real}}$ is defined. The total number of PEO and ethylene units was determined using the polymer molecular weight from gpc data along with knowledge of the terminal monomers. Once the total number of hydrophobic and hydrophilic groups in
each polymer was determined, \((m/n)_{\text{real}}\) was calculated. While the polymers presented here are not of exceptionally high molecular weight, changing the end groups does not alter the \((m/n)\) ratio more than +/- 5% from the \((m/n)_{\text{reactant}}\) (i.e. from the \(m/n\) of the reactants).

The aqueous solution phase diagrams for the four highest molecular weight polyamides are plotted in figure 2.10. The polyamide series nicely demonstrates that the LCST is reduced by increasing the number of ethylene units. PA(12/3) 60 has an LCST of 60°C. By increasing the ethylene unit from 4 to 5 the LCST decreased from 38.2 to 16.9°C. When the ethylene unit was increased to 6 the LCST fell to 11.4 °C. The respective \(m/n\) ratios were 3.9, 2.9, 2.3, and 1.9.

![Figure 2.10. The phase diagrams of four polyamides with different \((m/n)\) ratios in water.](image)

For this series of \(m/n\) and molecular weights, a linear relation exists between the aqueous solution LCST and \((m/n)_{\text{real}}\), as plotted in figure 2.11.
Figure 2.11. The LCSTs of aqueous solutions of PA(12/3), PA(12/4), PA(12/5), and PA(12/6) plotted as a function of (m/n)\text{\_real}. The resulting linear relation is used to predict the LCSTs of polyamide copolymers with different m/n ratios.

Assuming this simple mathematical correlation between the observed LCST and (m/n)\text{\_real}, the LCST can be predicted using the simple linear equation (equation 1):

\[
LCST = 25.1 \left( \frac{m}{n} \right) - 37.8 
\]  

(eqn 1)

This equation can be used to predict the phase behavior of other polyamide copolymers that have 12 ethylene oxide units and various lengths of ethylene. The four polyamides studied here had \( n = 3, 4, 5, 6 \). Equation 1 can be used to predict the LCST of 3 additional polyamides that can be synthesized with commercially available diamines (\( n = 2.5, 3.5, 4.5 \)). The (m/n)\text{\_reactant} values of all possible polyamides and their corresponding LCSTs calculated using equation 1 are also plotted in figure 2.11. According to equation 1, it is possible to shift the LCST from 83 to 13°C by varying the size of the number of ethylene units in the diamine comonomer.
### 2.4.5.2 Polyesters

Three polyesters were synthesized: PE(13/3), PE(20/3) and PE(20/4). The aqueous solution phase diagrams of the highest molecular weight samples of these three polyesters are plotted in figure 2.12. PE(20/3) has a LCST of 44.4 °C. When the number of ethylene groups was increased from 3 to 4 and the number of ethylene oxide remained constant at 20, the LCST dropped by 16°C to 27.7 °C. When the number of ethylene oxide units decreased from 20 to 13 and the number of ethylene units remained constant at 3, the LCST decreased by 18°C, to 25.7 °C.
Figure 2.12. Aqueous solution phase behavior of the copolymers PE(20/3)44, PE(20/4)28, and PE(13/3)26. The phase diagrams were generated from cloud point measurements.

The relationship among these three polyesters is more complex than that of the polyamides. In the m/n ratio, m denotes the hydrophilic contributions of the polymer while n represents the hydrophobic contributions. In the polyamide series, the only variable was the number of ethylene units (n). The three polyesters vary the number of ethylene oxide units (m) and the number of ethylene units (n). It is important to recall that the ester linkage groups, as well as the amides, participate in hydrogen bonding with water. For the amides, only the number of ethylene groups varied, allowing the contribution of linkage groups to the m/n ratio to be “ignored” (it was effectively incorporated into the 12 ethylene oxide sequence). However, the LCST is only loosely a linear function of the m/n ratio for the three polyester samples. The ester groups must be accounted for explicitly or must be added to the ethylene oxide contribution in a weighted manner for a more accurate prediction [1]. However, with only three polyester copolymers, only a linear relation can be used to
predict LCST values. Additional copolymers with different m/n ratios need to be synthesized and their aqueous phase behavior studied to develop a more accurate empirical relationship between m and n when both segment lengths are varied. However, the LCSTs of the three copolymers can be used to loosely predict the LCST of other polyester copolymers. The LCST of the three polyester copolymers, whose aqueous phase behavior is shown in figure 2.13, is plotted as a function of $(m/n)_{\text{real}}$ in figure 2.13.

![Figure 2.13](image)

Figure 2.13. The LCST is plotted as function of $(m/n)_{\text{real}}$ for PE(20/3), PE(20/4) and the resulting linear relation is used to predict the LCST of polyester copolymers with various m/n ratios.

Equation 2 expresses the linear relation of the LCST and $(m/n)_{\text{real}}$ for the polyester copolymers in water

\[
\text{LCST} = 8.4 \left(\frac{m}{n}\right) - 11.7 \quad (\text{eq} \ 2)
\]
LCST values of 71.9, 60.7, 55.2, 36.1, 25.4, 21.7, and 15.5°C are obtained when m/n values of 10, 8.7, 8, 5.7, 4.4, 4, and 3.3, respectively, are used in equation 2.

The role of the linkage group in the phase behavior of these copolymers is clear when the aqueous solution LCST of PA(12/3)60 is compared to that of PE(13/3)26. The weight average molecular weights of the copolymers are similar, 26,900 and 33,200 g/mol, respectively, as is the composition; the polyamide copolymer has 12 ethylene oxide sequences alternating with 3 ethylene sequences, while the polyester copolymer has 13 ethylene oxide sequences alternating with 3 ethylene sequences. However, the aqueous solution LCST of the polyester copolymer is 34°C lower than that of the polyamide copolymer. The extra ethylene oxide unit in the polyester provides an addition hydrogen bonding site, therefore, acts to increase the LCST. Therefore, the lower LCST of the polyester copolymer solution is a direct consequence of the hydrogen bonding strength of the ester linkage groups. The amide linkage groups participate in stronger hydrogen bonds than the esters, resulting in a higher LCST of the aqueous polyamide copolymer solution.

2.4.6 Hydrolysis

The polyester and polyamide copolymers are subject to hydrolysis when dissolved in water. Both the ester and amide linkage groups are susceptible to hydrolysis. The cloud point is sensitive to changes in molecular weight, as the molecular weight decreases, the cloud point increases. Therefore, cloud point
measurement is an excellent method for monitoring the molecular weight changes of a polymer that is a result of hydrolysis in an aqueous solution.

Two 3wt% aqueous copolymer solutions were prepared; one polyamide and one polyester. The copolymers were of similar molecular weight. The polyamide, PA(12/4)38, had a molecular weight of 27,800 g/mol and an LCST of 38°C. The polyester, PE(13/3)26, had a molecular weight of 33,200 g/mol and a LCST of 26°C. As shown in figure 2.14, the cloud point of both aqueous polymer solutions was measured over a 60 day period. The cloud point temperature of the PA(12/4)38 aqueous solution increased only 4.5 °C in 60 days; while the cloud point of an aqueous solution of PE(13/3)26 increased a mere 3.6 °C.

![Figure 2.14](image-url)

Figure 2.14. Cloud point temperatures of 3wt% aqueous solutions of PA(12/4)38 and PE(13/3)26 over a 60 day period.

Although the cloud point of the aqueous solution of PA(12/4)38 increased slightly more than that of PE(13/3)26, ester bonds typically hydrolyze faster than amide bonds. This curious result merits further research.
2.5 Conclusions

Polycondensation synthesis (peptide chemistry or esterification) was used to prepare regioregular alternating linear copolymers with tunable water solubility. Two types of polymers were realized: one with amide linkages and the other with ester linkages. By copolymerizing a hydrophobic monomer with a hydrophilic monomer, a series of polymers that exhibit inverse temperature solubility in water (LCST) were made. To shift the LCST to higher temperatures a larger hydrophilic monomer was used. Conversely, a larger hydrophobic monomer was incorporated to shift the LCST to lower temperatures. The aqueous phase behavior of the polymers was studied using cloud point measurements. These measurements were used to generate phase diagrams in order to establish the LCST.

For a small range of polymer molecular weight, an almost linear relationship between the ratio of hydrophilic to hydrophobic groups and the LCST exists for both the polyamides and the polyesters. These relations can be used to predict the LCST of other polymers empirically, without the need for complicated theoretical approaches.
2.6 References


Chapter 2 Supplemental Information A. Polyamide and Polyester Copolymers:
Structure, Molecular Weight, and Aqueous Cloud Point Measurements
PE(13/3) 33  Mn 2000 Mw 3700

Cloud point Temperature C
Weight percent polymer in water

Relative Laser Intensity
Temperature C

Cloud point Temperature C
Weight percent polymer in water
PE(13/3) 29 Mn 2300 Mw 5300

Relative Laser Intensity

Temperature C

Cloud point temperature C

Weight percent polymer in water
PE(13/3) 26  Mn 15700  Mw 33200

Cloud point temperature C

Weight percent polymer in water

Relative Laser Intensity

Temperature C
PE(20/3) 52  Mn 4100  Mw 13600
PE(20/3) 50  Mn 13300 Mw 20600

Cloud point temperature C

Weight percent polymer in water
PE(20/3) 44  Mn 20200  Mw 35300

![Chemical structure of PE(20/3) 44]

![Graph showing relative laser intensity vs. temperature for different weight percent polymer in water]

![Graph showing cloud point temperature vs. weight percent polymer in water]

- 20 wt%
- 15 wt%
- 10 wt%
- 7 wt%
- 5 wt%
- 3 wt%
- 1.8 wt%
PE(20/4) 28  Mn7000 Mw 11100
PE(20/4) 31 Mn 4200 Mw 5700

Cloud point temperature C

Weight percent polymer in water

Relative Laser Intensity

Temperature
PE(20/4) 38 Mn 3700 Mw 4700

![Chemical structure of PE(20/4) 38 Mn 3700 Mw 4700]

**Graphs:**
- **Temperature vs. Weight percent polymer in water**
- **Cloud point temperature vs. Weight percent polymer in water**

Legend:
- 19 wt%
- 15 wt%
- 12 wt%
- 9 wt%
- 7 wt%
- 5 wt%
- 4 wt%
- 3 wt%
- 1 wt%
PE(20/4) 28  Mn 12200 Mw 22000

Cloud point temperature C

Weight percent polymer in water

Relative laser intensity

Temperature C
E(20/4) 35  Mn 6100 Mw 16300

Relative Laser Intensity

Temperature C

Cloud point temperature C

Weight percent polymer in water
PE(20/4) 38 Mn 3800 Mw 13900

![Chemical structure diagram](image)

**Graph 1:**
- **X-axis:** Temperature (°C)
- **Y-axis:** Relative Laser Intensity
- **Legend:**
  - 18.5 wt%
  - 10 wt%
  - 5 wt%
  - 4 wt%
  - 3 wt%
  - 2 wt%
  - 1 wt%

**Graph 2:**
- **X-axis:** Weight percent polymer in water
- **Y-axis:** Cloud point temperature (°C)
PE(20/4) 50  Mn 4300 Mw 9000

Cloud point temperature (°C)

Weight percent polymer in water

Relative Laser Intensity vs. Temperature

9 wt% 7 wt% 4 wt% 3 wt% 2 wt% 1 wt%
PE(20/benzene)  Mn 8700 Mw 15000

Cloud point temperature C

Weight percent polymer in water

Relative Laser Intensity

Temperature C
PA(12/4) 50  Mn 3900 Mw 6600

Cloud point temperature

Weight percent polymer in water
PA(12/4) 45     Mn 17400 Mw 23100

![Chemical structure of PA(12/4) 45](image)

**Graphs:**

1. **Relative Laser Intensity vs. Temperature C**
   - X-axis: Temperature C
   - Y-axis: Relative Laser Intensity
   - Legend: 10 wt%, 7 wt%, 5 wt%, 4 wt%, 3 wt%, 2 wt%, 1 wt%

2. **Cloud point temperature C vs. Weight percent polymer in water**
   - X-axis: Weight percent polymer in water
   - Y-axis: Cloud point temperature C
   - Data points for various weight percent concentrations
PA(12/4) 38  Mn 18500 Mw 27800

![Chemical Structure](image)

**Graph 1:**
- X-axis: Temperature (°C)
- Y-axis: Relative laser intensity
- Data points for different weight percent polymer in water:
  - 9.8 wt%
  - 6.9 wt%
  - 5.0 wt%
  - 3.9 wt%
  - 3.0 wt%
  - 2.0 wt%
  - 1.0 wt%

**Graph 2:**
- X-axis: Weight percent polymer in water
- Y-axis: Cloud point temperature (°C)
PA(12/5) 28  Mn 1400 Mw 4200

Cloud point temperature C

Weight percent polymer in water

Relative laser intensity

Temperature C
PA(12/5) 21  Mn 7300  Mw 12200

![Chemical structure of PA(12/5) 21](image)

![Graph showing relative laser intensity vs. temperature](image)

![Graph showing cloud point temperature vs. weight percent polymer in water](image)
PA(12/5) 20  Mn 7700 Mw 17300

![Chemical Structure](image)

![Graph 1](image)

![Graph 2](image)
PA(12/5) 17  Mn 12800 Mw 22400

[Chemical structure image]

![Graph showing relative laser intensity vs. temperature C with different weight percent polymer in water.

*6.4 wt%*  *4.8 wt%*  *4 wt%*  *3 wt%*  *2 wt%*  *1 wt%*

![Graph showing cloud point temperature C vs. weight percent polymer in water.]

*14 16 18 20 22 24*  *1 2 3 4 5 6 7*
PA(12/6) 25  Mn1400 Mw 2800

[Chemical structure image]

[Graph with data points and lines indicating temperature versus relative laser intensity for different weight percentages of polymer in water.]

[Graph showing cloud point temperature C versus weight percent polymer in water.]
PA(12/6) 13 Mn 5600 Mw 11700

Relative Laser Intensity

Temperature C

Cloud point temperature C

Weight percent polymer in water
PA(12/6) 11 Mn 7200 Mw 14900

[Chemical structure image]

[Graph 1: Relative Laser Intensity vs. Temperature C]

[Graph 2: Cloud point temperature C vs. Weight percent polymer in water]
PA(12/benzene)  Mn 18400 Mw 34000

- 5 wt%
- 4 wt%
- 3 wt%
- 2 wt%
- 1 wt%

Cloud point temperature C

Weight percent polymer in water
PA(12/benzene CF3)  Mn 3300 Mw 5600

Cloud Point Temperature °C

Weight percent polymer in water

PA(12/benzene CF3)  Mn 3300 Mw 5600
Chapter 2 Supplemental Information B. NMR Spectra
Current Date Parameters
NAME
EXPGD
PROCNG

F2 - Acquisition Parameters
Date_ 20080305
Time 15:00
INSTRUM spect
POLTMOD 5 mm 0DI 1H-2
PULPROG zg40
TD 65536
SOLVENT DDI13
VS 10
DS 5
SNH 0.278 146 Hz
FIDRES 0.12633 kHz
AG 3.5564243 sec
RD 200.1
DW 60.400 us
DE 60.00 us
TE 300.0 ms
DT 1.00000000 sec

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NLC1
PH 6.45 us
PL 1.00 us
SPE1 400.1324 MHz

F2 - Processing parameters
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SF 400.1320 MHz
WM DM
SSB 0
LB 0.30 Hz
DD 0
DC 1.00

2D NMR plot parameters
CH 20.00 cm
F6P 10.000 ppm
F1 4001.30 Hz
FDP 0.000 ppm
FO 0.00 Hz
PPMCM 0.03000 ppm/cm
H2CM 200.09500 Hz/cm0
Chapter 3

Regioregular Alternating Copolymers with Tunable Water Solubility: Molecular Weight and Terminal Monomer Effects on the LCST

3.1 Summary

A series of linear regioregular alternating copolymers with tunable water solubility were prepared by polycondensation. The influence of molecular weight on the lower critical solution temperature (LCST) was investigated by studying the aqueous phase behavior of various molecular weight fractions of three polyamides and three polyesters. For all polymers, it was determined that as the molecular weight increased, the LCST decreased, in concert with normal solution behavior.

The aqueous solution phase diagrams of both the series of polyamides and the polyesters were used to estimate the temperature dependence of the Flory-Huggins chi parameter as a function temperature. Shultz-Flory plots were then used to estimate the theta temperature of each copolymer composition.

The influence of the hydrophilic or hydrophobic nature of the terminal monomer on the aqueous phase behavior of the copolymers was also determined, and was shown to be significant for low molecular weight polymers. When the terminal
monomers were hydrophilic, the resulting copolymer was more hydrophilic. Conversely, when the terminal monomers were hydrophobic, the copolymers were more hydrophobic. The affect of the terminal monomer was shown to be most pronounced at molecular weights less than 5,000 g/mol.

3.2 Introduction

Water-soluble temperature-sensitive polymers are used in many applications, however many questions regarding the parameters that influence the phase transition temperature still remain. As discussed in Chapter 2, the hydrophilic/hydrophobic (m/n) ratio within a polymer is important in determining the LCST of their aqueous polymer solution. In addition, there are two more parameters that need to be considered: the molecular weight and the nature of the terminal monomers (hydrophilic or hydrophobic). Theoretically, when the molecular weight increases, the LCST decreases, although this has been a topic of much debate [1-8]. The Flory-Huggins theory predicts that as molecular weight increases, the critical chi parameter decreases, which in the case of the LCST corresponds to a lower phase transition temperature. The nature of the terminal monomer is also important at low molecular weights, primarily because it alters the m/n ratio of the copolymer. The combined influence of the molecular weight, m/n ratio, and the nature of the terminal monomer will be discussed in this chapter.
Many environmental changes have been employed to alter the LCST of water-soluble temperature-responsive polymers, for example: salts, surfactants, cosolvents, and pressure. When salts are added to aqueous solutions of thermosensitive polymers, the LCST typically decreases [9-11]. This “salting out” effect is a result of the ions disrupting the structure of the water molecules that solvate the polymer chains. The ions compete with the water to solvate the chains, and also the ions are themselves hydrated because of their favorable charged-dipole interactions with water. The increased intrachain and intermolecular hydrophobic interactions lead to a decreased LCST. Conversely, the addition of surfactants generally causes the LCST to increase [12]. The amphiphilic structure of surfactants solubilize the polymer in water by associating to the hydrophobic segments, separating them from the water molecules. The LCST is raised by minimizing hydrophobic interactions. Cosolvents can be used to increase or decrease the LCST [13] since the polymer/water interactions are altered by the addition of a cosolvent, which in turn changes the LCST. Pressure increase is often used to depress the LCST [14,15] because volumetric compression acts to break hydrogen bonds, which in turn lowers the LCST. While all of these parameters are important for applications and fundamental understanding, the most important parameters to consider here are the effects of molecular weight and end groups. Their influence on the LCST in an aqueous solution must first be understood, before the effect of other environmental changes can be further explored.

While poly(N-isopropylacrylamide) (PNIPAM) has been actively studied for nearly 40 years [16], the influence of the molecular weight on its LCST in water has not been elucidated. This question remains debated for all temperature-responsive
polymers. Many research groups have reported that the LCST of PNIPAM has an inverse dependence on the molecular weight [1-4], while others have reported either a direct dependence [5] or no dependence at all [6-8]. Recently two groups [4,17] performed thorough studies on both the effect of molecular weight on the aqueous LCST as well as the influence of the polarity of the end groups of PNIPAM. Furyk et al. showed that at molecular weights greater than 50,000 g/mol, the LCST of aqueous solutions of PNIPAM does not depend on molecular weight. At molecular weights less than 50,000 g/mol small changes (approximately 1°C) were seen in the LCST due to changes in the polarity and structure of the end group. Their samples ranged in molecular weight from 46,000 to 380,000 g/mol. Xia et al. also studied the importance of the molecular weight and end group with regards to the LCST of PNIPAM. They studied much lower molecular weights (3,000 to 50,000 g/mol) with low polydispersities (less than 1.2) and found that hydrophilic end groups increased the LCST and hydrophobic end groups decreased the LCST. The most significant change (8 °C) was seen at the lowest molecular weights. Above 10,000 g/mol the effect of the end group vanished quickly. Both studies propose that the discrepancy in the role of molecular weight on the LCST of aqueous solutions of PNIPAM reported in earlier works was a result of endgroup differences resulting from different synthetic methods (i.e. initiators, terminators, and chain transfer agents). Examining earlier work on LCST of PNIPAM aqueous solutions, it can be seen that, generally, when the end groups are hydrophobic, the LCST is either independent of molecular weight, or increases with increasing molecular weight. It can also be seen that when the LCST decreases with increasing molecular weight, the endgroups are hydrophilic.
From these studies one can conclude that what was previously reported as differences in the LCST due to molecular weight effects in PNIPAM aqueous solutions can be attributed to the polarity of the end group, especially at lower molecular weights and that the Flory-Huggins theory prediction of an inverse relation between temperature and molecular weight probably holds true for PNIPAM’s LCST in water.

The polyamides and polyesters studied in this work have an additional variable related to the aqueous solution LCST. Unlike PNIPAM which has the hydrophilic/hydrophobic (m/n) balance within each monomer, these polymers incorporate the hydrophilic/hydrophobic balance within regions (a “macromonomer”) consisting of 12, 13, or 20 polyethylene oxide monomers and 3-6 ethylene monomers. These “macromonomers” (or sequences) have molecular weights that range from 716 to 1044 g/mol. At low molecular weights the m/n ratio is strongly dependent on the nature of the terminal sequence. As a result, low molecular weight polymers have a different m/n ratio than the reactants or the theoretical (infinite molecular weight) ratio. Figure 3.1 depicts the structure of the alternating copolymers which can have terminal sequences that are either hydrophilic or hydrophobic.
Figure 3.1 Hydrophobic and hydrophilic sequences (or macromonomers) are polymerized to form alternating regioregular copolymers with ester and amide linkages. The nature of the terminal “group” influences the m/n ratio that is set by the reactants.

There are three factors that influence the aqueous solution LCST of these copolymers: molecular weight, nature of terminal sequence, and the real m/n ratio of the copolymer. Increasing the molecular weight decreases the LCST, as expected by normal solution theory. The m/n ratio is used to control the hydrophilic/hydrophobic balance within the polymer; however, it is constant and equal to that of the reactants only at high copolymer molecular weights. At low copolymer molecular weights, the nature of the terminal sequence directly influences the \( (m/n)_{\text{real}} \) ratio of the polymer, and thus its LCST in water. The polymer fractions presented here are all of low
enough molecular weight that all three factors can contribute to the LCST of the copolymers in water.

3.3 Experimental Methods

The same approaches, methods, and experimental setups used in Chapter 2 are also employed for the synthesis, characterization, and study of the aqueous copolymer LCST phase behavior in this chapter.

3.4 Results and Discussion

Three polyesters and three polyamides with different m/n ratios were synthesized using polycondensation synthesis schemes (peptide chemistry and esterification). Fractional precipitation was used to isolate samples with different molecular weights. Tables 3.1 and 3.2 list the number and weight average molecular weights determined by gpc, and the aqueous solution LCST data for the fractionated samples. Phase diagrams of the fractionated samples were generated by measuring the cloud points of aqueous polymer solutions with varying concentrations. The LCST was determined by plotting the cloud point temperature versus the polymer concentration, and the minimum of that curve was the LCST. The number of ethylene oxide and ethylene units in each sequence determines $(m/n)_{\text{reactant}}$. While $(m/n)_{\text{real}}$ is calculated by taking into account the influence of the terminal sequence. The weight average molecular weight is used to determine the number of sequences in the
polymer when calculating (m/n)_{real}. The weight average molecular weight was divided by the molecular weight of the sequences to determine the number of repeated sequences in each chain. An equivalent PEO molecular weight was then calculated by multiplying the number of repeated segments by 12 (the number of ethylene oxide sequences in each segment) and then multiplying by 44 g/mol (the molecular weight of each ethylene oxide unit).

Table 3.1. LCST and molecular weight data for fractioned samples of polyesters: PE(20/4), PE(20/3), and PE(13/3). Hydrophilic terminal sequences are indicated with*.

<table>
<thead>
<tr>
<th>Polymers</th>
<th>LCST (°C)</th>
<th>Mn (g/mol)</th>
<th>Mw (g/mol)</th>
<th>Equivalent PEO Mw</th>
<th>(m/n)_{real}</th>
<th>(m/n)_{reactant}</th>
<th>(m/n)<em>{real} / (m/n)</em>{reactant}</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE(20/4) 28</td>
<td>27.6</td>
<td>7000</td>
<td>11100</td>
<td>9235</td>
<td>4.6</td>
<td>5</td>
<td>0.91</td>
</tr>
<tr>
<td>PE(20/4) 31</td>
<td>31.1</td>
<td>4200</td>
<td>5700</td>
<td>4683</td>
<td>4.2</td>
<td>5</td>
<td>0.84</td>
</tr>
<tr>
<td>PE(20/4) 38</td>
<td>38.1</td>
<td>3700</td>
<td>4700</td>
<td>3840</td>
<td>4.1</td>
<td>5</td>
<td>0.81</td>
</tr>
<tr>
<td>PE(20/4) 28*</td>
<td>27.7</td>
<td>12200</td>
<td>22000</td>
<td>18665</td>
<td>5.2</td>
<td>5</td>
<td>1.05</td>
</tr>
<tr>
<td>PE(20/4) 35*</td>
<td>34.5</td>
<td>6100</td>
<td>16300</td>
<td>13861</td>
<td>5.3</td>
<td>5</td>
<td>1.07</td>
</tr>
<tr>
<td>PE(20/4) 38*</td>
<td>37.5</td>
<td>3800</td>
<td>13900</td>
<td>11838</td>
<td>5.4</td>
<td>5</td>
<td>1.08</td>
</tr>
<tr>
<td>PE(20/4) 50*</td>
<td>49.7</td>
<td>4300</td>
<td>9000</td>
<td>7708</td>
<td>5.6</td>
<td>5</td>
<td>1.13</td>
</tr>
<tr>
<td>PE(20/3) 44</td>
<td>44.4</td>
<td>20200</td>
<td>35300</td>
<td>30448</td>
<td>6.5</td>
<td>6.7</td>
<td>0.98</td>
</tr>
<tr>
<td>PE(20/3) 50</td>
<td>50.3</td>
<td>13300</td>
<td>20600</td>
<td>17732</td>
<td>6.4</td>
<td>6.7</td>
<td>0.96</td>
</tr>
<tr>
<td>PE(20/3) 52</td>
<td>52</td>
<td>4100</td>
<td>13600</td>
<td>11660</td>
<td>6.2</td>
<td>6.7</td>
<td>0.93</td>
</tr>
<tr>
<td>PE(13/3) 26</td>
<td>25.7</td>
<td>15700</td>
<td>33200</td>
<td>26430</td>
<td>4.2</td>
<td>4.3</td>
<td>0.98</td>
</tr>
<tr>
<td>PE(13/3) 29</td>
<td>28.8</td>
<td>2300</td>
<td>5300</td>
<td>4141</td>
<td>3.8</td>
<td>4.3</td>
<td>0.88</td>
</tr>
<tr>
<td>PE(13/3) 33</td>
<td>32.9</td>
<td>2000</td>
<td>3700</td>
<td>2863</td>
<td>3.6</td>
<td>4.3</td>
<td>0.83</td>
</tr>
</tbody>
</table>
Table 3.2. Aqueous LCST and molecular weight data for fractioned samples of polyamides copolymers: PA(12/4), PA(12/5), and PA(12/6).

<table>
<thead>
<tr>
<th>Polyamides</th>
<th>LCST (°C)</th>
<th>Mn (g/mol)</th>
<th>Mw (g/mol)</th>
<th>Equivalent PEO Mw</th>
<th>(m/n)_real</th>
<th>(m/n)_reactant</th>
<th>(m/n)_real / (m/n)_reactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA(12/3) 60</td>
<td>59.5</td>
<td>17600</td>
<td>26900</td>
<td>19751</td>
<td>3.9</td>
<td>4</td>
<td>0.97</td>
</tr>
<tr>
<td>PA(12/4) 38</td>
<td>38.2</td>
<td>18500</td>
<td>27800</td>
<td>19627</td>
<td>2.9</td>
<td>3</td>
<td>0.97</td>
</tr>
<tr>
<td>PA(12/4) 45</td>
<td>45.1</td>
<td>17400</td>
<td>23100</td>
<td>16291</td>
<td>2.9</td>
<td>3</td>
<td>0.97</td>
</tr>
<tr>
<td>PA(12/4) 50</td>
<td>50.4</td>
<td>3900</td>
<td>6600</td>
<td>4582</td>
<td>2.7</td>
<td>3</td>
<td>0.90</td>
</tr>
<tr>
<td>PA(12/5) 17</td>
<td>16.9</td>
<td>12800</td>
<td>22400</td>
<td>15203</td>
<td>2.3</td>
<td>2.4</td>
<td>0.97</td>
</tr>
<tr>
<td>PA(12/5) 20</td>
<td>19.9</td>
<td>7700</td>
<td>17300</td>
<td>11714</td>
<td>2.3</td>
<td>2.4</td>
<td>0.96</td>
</tr>
<tr>
<td>PA(12/5) 21</td>
<td>21</td>
<td>7300</td>
<td>12200</td>
<td>8226</td>
<td>2.3</td>
<td>2.4</td>
<td>0.94</td>
</tr>
<tr>
<td>PA(12/5) 28</td>
<td>27.6</td>
<td>1400</td>
<td>4200</td>
<td>2755</td>
<td>2.0</td>
<td>2.4</td>
<td>0.84</td>
</tr>
<tr>
<td>PA(12/6) 11</td>
<td>11.4</td>
<td>7200</td>
<td>14900</td>
<td>9702</td>
<td>1.9</td>
<td>2</td>
<td>0.95</td>
</tr>
<tr>
<td>PA(12/6) 13</td>
<td>12.7</td>
<td>5600</td>
<td>11700</td>
<td>7590</td>
<td>1.9</td>
<td>2</td>
<td>0.93</td>
</tr>
<tr>
<td>PA(12/6) 25</td>
<td>25.3</td>
<td>1400</td>
<td>2800</td>
<td>1716</td>
<td>1.5</td>
<td>2</td>
<td>0.76</td>
</tr>
</tbody>
</table>

3.4.1 Influence of Molecular Weight on the LCST

Figures 3.2 to 3.7 present the aqueous solution phase diagrams of different molecular weight fractions of PA(12/4), PA(12/5), PA(12/6), PE(13/3), PE(20/3), PE(20/4). The cloud points are plotted as a function of molecular weight for the polyamide copolymers in figures 3.2-3.4 and the polyester copolymers in Figures 3.5-3.7. For the PA(12/4) samples the molecular weight increases from 6,600 to 27,800 g/mol and the corresponding LCST decreases from 50.4 to 38.2°C, as shown in figure 3.2. For the PA(12/5) series, the molecular weight increases from 4,200 to 22,400 g/mol and the corresponding LCST decreases from 27.6 to 10.0°C, which is presented in figure 3.3. For the PA(12/6) samples the molecular weight increases from 2,800 to 14,900 g/mol and the corresponding LCST decreases from 25.3 to 11.4°C, as shown in the phase diagrams in figure 3.4. For the PE(13/3) samples the molecular weight increases from 3,700 to 33,200 g/mol and the phase diagrams presented in figure 3.5 show that the corresponding LCST decreases from 32.9 to 25.7°C. For the three
PE(20/3) fractions the molecular weight increases from 13,600 to 35,300 g/mol and the corresponding LCST decreases from 52.0 to 44.4°C, as shown in figure 3.6. For the three PE(20/4) fractions the molecular weight increases from 3,700 to 11,100 g/mol and, as shown in figure 3.7, the corresponding LCST decreases from 38.1 to 27.6°C.

Figure 3.2. Cloud point temperature versus polymer concentration in water for PA(12/4) for 3 molecular weights and a heating rate of 1°C/min.
Figure 3.3. Cloud point temperature versus polymer concentration in water for PA(12/5) for 4 molecular weights and a heating rate of 1°C/min.

Figure 3.4. Cloud point temperature versus polymer concentration in water for PA(12/6) for 3 molecular weights and a heating rate of 1°C/min.
Figure 3.5. Cloud point temperature versus polymer concentration in water for PE(13/3) for 3 molecular weights and a heating rate of 1°C/min.

Figure 3.6. Cloud point temperature versus polymer concentration in water for PA(20/3) for 3 molecular weights and a heating rate of 1°C/min.
Figure 3.7. Cloud point temperature versus polymer concentration in water for PE(20/4) with hydrophobic terminal monomers for 3 molecular weights and a heating rate of 1°C/min.

The LCST is an entropically driven phase transition; therefore the LCSTs inverse molecular weight dependence can be described by a greater $\Delta S$ of the phase transition for low molecular weight polymers. The LCSTs inverse dependence on molecular weight can be explained in terms of free volume. The free volume difference between the water molecules and the polymer chains is larger for high molecular weight polymers than for low molecular weight polymers, therefore the “driving force” for phase separation is larger for long polymer chains. Qualitatively, this phenomenon can be described by ordered water molecules that solvate the polymer chains. The entropy change associated with the phase transition is smaller for large molecules than it is for shorter polymers. In order to be solvated, a large solute will interact with more water molecules than a small solute. Therefore, as the length of a polymer chain increases, the number of water molecules that are forced to change their hydrogen bonding networks to accommodate the solute also increases,
which results in a decrease in the system’s entropy. A solvated short chain is more entropically favorable than a solvated long chain.

The influence of the molecular weight on the critical point is also predicted by Flory-Huggins theory [9,18,19] where

\[ \chi_c = \frac{1}{2}\left(1 + \frac{1}{\sqrt{r}}\right)^2 \]  

(eqn 1)

with \( r \) being the polymer to solvent molar volume ratio, \( N \) the degree of polymerization and \( \chi_c \) the Flory critical chi parameter. As the molecular weight of the polymer increases, \( r \) increases resulting in a decrease in \( \chi_c \). The Flory chi parameter is proportional to the enthalpic energy of the solvent-polymer interactions, therefore, a decrease in \( \chi_c \) results in a decrease in LCST. The second equation clearly demonstrates that as the degree of polymerization increases \( \chi_c \) approaches \( \frac{1}{2} \), which corresponds to the theta temperature (the lower limit of the LCST).

The temperature dependence of \( \chi \) was estimated using the equation

\[ \chi(T) \approx A + \frac{B}{T} \]  

(eqn 2)

The molecular weight of each copolymer was used to estimate \( \chi_c \) using the equation

\[ \chi_c = \frac{1}{2} + \frac{1}{\sqrt{N}} + \frac{1}{2N} \]  

(eqn 3)

By plotting \( \chi_c \) versus \( T_{\text{LCST}}^{-1} \), shown in figures 3.8 and 3.9 for the polyester and polyamide copolymers, the parameters \( A \) and \( B \) in eqn 2 were determined and are presented in tables 3.3 and 3.4.
Figure 3.8. The Flory-Huggins critical chi parameter is plotted as a function of the inverse of the critical temperature for aqueous solutions of PE(13/3), PE(20/4), and PE(20/3). The slope and intercept yield the parameters A and B, which are needed to estimate the temperature dependence of the Flory-Huggins chi parameter.

Figure 3.9. The Flory-Huggins critical chi parameter is plotted as a function of the inverse of the critical temperature for aqueous solutions of PA(12/6), PA(12/5), and PA(12/4). The slope and intercept yield the parameters A and B, which are needed to estimate the temperature dependence of the Flory-Huggins chi parameter.
Table 3.3. The parameters A and B used to predict the temperature dependence of the Flory-Huggins chi parameter for aqueous solutions of the polyester copolymers PE(20/4), PE(20/3), and PE(13/3).

<table>
<thead>
<tr>
<th>Polyesters</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE(20/4)</td>
<td>0.60</td>
<td>-1.7</td>
</tr>
<tr>
<td>PE(20/3)</td>
<td>0.67</td>
<td>-6.9</td>
</tr>
<tr>
<td>PE(13/3)</td>
<td>0.90</td>
<td>-9.1</td>
</tr>
</tbody>
</table>

Table 3.4. The parameters A and B used to predict the temperature dependence of the Flory-Huggins chi parameter for aqueous solutions of the polyamide copolymers PA(12/4), PA(12/5), and PA(12/6).

<table>
<thead>
<tr>
<th>Polyamide</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA(12/4)</td>
<td>0.71</td>
<td>-6.5</td>
</tr>
<tr>
<td>PA(12/5)</td>
<td>0.56</td>
<td>-0.030</td>
</tr>
<tr>
<td>PA(12/6)</td>
<td>0.57</td>
<td>-0.10</td>
</tr>
</tbody>
</table>

For aqueous solutions of the polyester copolymers, the values of B are all negative, which is indicative of LCST phase behavior. As the hydrophilic/hydrophobic ratio decreases, B becomes more negative, decreasing from -1.7 to -9.1. For the aqueous solutions of the polyamide copolymers, all of the B values are also negative. However, there is no trend relating the value of B to the hydrophobic/hydrophilic ratio.

High molecular weight PEO has an LCST in water at approximately 100°C. As shown in Chapter 1, by copolymerizing PEO with ethylene units, the aqueous phase behavior of the copolymers is still described by an LCST, but shifted to lower temperatures. Interestingly, the nature of the phase transition of PEO is not altered by introducing hydrophobic groups across the polymer. The ethylene units act to shift
the phase temperatures to lower critical temperatures, but do not shift the LCST to lower critical concentrations.

The aqueous solution theta temperature of the copolymers can be estimated using the equation:

\[
\frac{1}{T_c} = \frac{\chi_c - A}{B} = \frac{1}{T_\theta} + \frac{1}{B \left( \frac{1}{\sqrt{N}} + \frac{1}{2N} \right)} \quad \text{(eqn 4)}
\]

For aqueous solutions of each of the copolymer series, plotting the inverse of the critical temperature as a function of \((1/\sqrt{N}) + 1/2N\) (as shown in figures 3.10 and 3.11, along with PEO) yields the theta temperature as well as the parameter B (which was also used in eqn 2). The slope of each line corresponds to the inverse of B, while the intercept is the inverse of the theta temperature. The values of B and the theta temperature are presented in tables 3.5 and 3.6.

Figure. 3.10. A Shultz-Flory plot of the aqueous phase behavior of the polyester copolymers PE(20/3), PE(20/4), and PE(13/3) as well as that of PEO [data from 3].
Figure 3.11. A Shultz-Flory plot of the aqueous phase behavior of the polyamide copolymers PA(12/4), PA(12/5), and PA(12/6) as well as that of PEO [PEO data Saeki 1976].

Table 3.5. The theta temperature and parameter B from the Shultz-Flory plot of the aqueous phase behavior of the polyester copolymers PE(20/3), PE(20/4), and PE(13/3) as well as that of PEO [PEO data Saeki 1976].

<table>
<thead>
<tr>
<th>Polyester</th>
<th>T (°C)</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE(20/4)</td>
<td>-2.7</td>
<td>-0.13</td>
</tr>
<tr>
<td>PE(20/3)</td>
<td>30</td>
<td>-0.33</td>
</tr>
<tr>
<td>PE(13/3)</td>
<td>21</td>
<td>-1.3</td>
</tr>
<tr>
<td>PEO</td>
<td>97</td>
<td>-0.37</td>
</tr>
</tbody>
</table>

Table 3.6. The theta temperature and parameter B from the Shultz-Flory plot of the aqueous phase behavior of the polyamide copolymers PA(12/4), PA(12/5), and PA(12/6) as well as that of PEO [PEO data Saeki 1976].

<table>
<thead>
<tr>
<th>Polyamide</th>
<th>T (°C)</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA(12/4)</td>
<td>33</td>
<td>-0.63</td>
</tr>
<tr>
<td>PA(12/5)</td>
<td>23</td>
<td>-0.71</td>
</tr>
<tr>
<td>PA(12/6)</td>
<td>2</td>
<td>-0.59</td>
</tr>
<tr>
<td>PEO</td>
<td>97</td>
<td>-0.37</td>
</tr>
</tbody>
</table>
The estimated theta temperatures shown in tables 3.5 and 3.6 confirm that as the hydrophobic sequences of the PEO based copolymers get larger, their aqueous solution theta temperatures decrease. As expected, the aqueous solution theta temperatures of all of the copolymers are less than that of PEO. For the aqueous solution polyester copolymers, the B values determined using the Shultz-Flory plots are within an order of magnitude of those determined using eqns 2 and 3. They also show the same trend of decreasing in value as the hydrophilicity decreases. However, neither the aqueous polyamide copolymer solution B values generated from Shultz-Flory nor those generated from eqns 1 and 2 follow a trend.

### 3.4.2 Influence of the Nature of the Terminal Group on the Hydrophilic/Hydrophobic Balance of the Copolymer

For low molecular weights, the phase behavior of these copolymers is further complicated by the nature of the terminal sequence. At low molecular weights the hydrophilicity or hydrophobicity of the terminal sequence can influence the m/n ratio of the copolymer, resulting in an “effective” m/n \[(m/n)_{\text{real}}\], different than the theoretical value determined from the number of ethylene oxide and ethylene units in each macromonomer (reactants). In order to elucidate the effect of the terminal sequence, the polyester PE(20/4) was synthesized twice: once with hydrophobic terminal sequences and once with hydrophilic terminal sequences. The phase diagrams for different molecular weight fractions of these two polyesters (with
hydrophilic terminal sequences and with hydrophobic terminal sequences) are plotted in figures 3.12 and 3.13.

Figure 3.12. Cloud point temperature versus polymer concentration in water for PE(20/4) with hydrophilic terminal sequences for four molecular weights and a heating rate of 1°C/min.

Figure 3.13. Cloud point temperature versus polymer concentration in water for PE(20/4) with hydrophobic terminal sequences for four molecular weights and a heating rate of 1°C/min.
The complexity of the relationship between LCST, molecular weight, m/n ratio and terminal sequence is exemplified by comparing the phase behavior the PE(20/4) molecular weight fractions. The polymers with hydrophobic terminal sequences have an \((m/n)_{\text{real}}\) that is lower than \(m/n\) value of the reactants, while those with hydrophilic terminal sequences have higher \((m/n)_{\text{real}}\) values. Interestingly, the hydrophilically terminated polymer with a molecular weight of 13,900 g/mol has an aqueous solution LCST of 37.5 °C and the hydrophobically terminated polymer with a molecular weight of just 4,700 g/mol has an LCST of 38.1 °C in water. While both polymers are alternating regioregular copolymers of the same chemistry, they have similar LCSTs, but at vastly differing molecular weights. This effect can also be seen at higher molecular weights. For the hydrophilically terminated polymer with a molecular weight of 22,000 g/mol has an LCST of 27.7 °C in water and the hydrophobically terminated polymer with a molecular weight of just 11,100 g/mol has an LCST of 27.6 °C.

The \((m/n)_{\text{real}}\) for PE(20/4) with hydrophobic and hydrophilic terminal sequences as a function of copolymer molecular weight is plotted in figure 3.14. As expected, the effect of the terminal sequence is most pronounced at low molecular weights. This is intuitively expected because the end sequence makes up a greater portion of the copolymer and thus alters the m/n ratio to a greater extent.
The polymers with hydrophobic terminal sequences have a \((m/n)_{\text{real}}\) ratio that is lower than that of the reactant \(m/n\) ratio, while the polymers with hydrophilic terminal sequences have \(m/n\) ratios that are greater than the reactant value. Figure 3.13 shows that as the molecular weight increases the \((m/n)_{\text{real}}\) ratios converge to the reactant \(m/n\) value of 5. Hydrophobic sequences act to depress the aqueous solution LCST while hydrophilic sequences raise the LCST. These effects could be accounted for by considering the ordering of the water solvating the chain; for example, hydrophobic segments enhance the water molecules ordering, while the hydrophilic segments decrease the order of the molecules. Interestingly, following similar free volume arguments, it has been proposed that hydrophobic or hydrophilic groups have a greater influence on solution phase transition behavior when they are at the end of the chains, as compared to being located midchain [20].
The samples of PE(13/3) and PE(20/3) were also synthesized with hydrophobic end sequences. The dependence of m/n on the molecular weight of these polymers is plotted in Figure 3.15. \((m/n)_{\text{real}}\) is again sensitive to molecular weight, and especially important at molecular weights less than 5,000 g/mol. Also of note is that \((m/n)_{\text{real}}\) of PE(20/3) is more sensitive to molecular weight than PE(13/3). This is because the macromonomer of PE(20/3) is much larger than that of PE(13/3), 1016 g/mol as opposed to 716 g/mol. This causes the \((m/n)_{\text{real}}\) to be skewed more by the larger polyethylene oxide units of PE(20/3).

![Figure 3.15. The influence of molecular weight on \((m/n)_{\text{real}}\) for PE(13/3).](image)

When \((m/n)_{\text{real}}\) ratio is normalized with respect to \((m/n)_{\text{reactant}}\) value and plotted against the molecular weight, data from the entire set of polymers overlay, as shown in Figure 3.16. At molecular weights greater than 15,000 g/mol \((m/n)_{\text{real}}\) is within 5% of \((m/n)_{\text{reactant}}\) values for all of the copolymers.
3.5 Conclusions

A series of polyamide and polyester regioregular copolymers of ethylene oxide and ethylene were synthesized and their aqueous phase behavior was studied with cloud point measurements. Phase diagrams were generated from the cloud point data. It was determined that the LCST of all of the copolymers in water decreased with increasing molecular weight. It was also shown that the aqueous copolymer solutions behaved in a manner consistent with aqueous solutions of PEO, with respect to molecular weight, as shown by comparing the molecular weight dependence of the LCST for the PEO component of the copolymers against that of aqueous PEO solutions. The copolymers are composed of rather large sequences, particularly the
ethylene oxide regions. At high molecular weights, the balance of hydrophilic to hydrophobic units within the polymer is determined by the reactants; however, at low molecular weights, this balance can be substantially skewed by the terminal groups, which were chosen to be either hydrophilic or hydrophobic. When the terminal monomers were hydrophilic, the resulting polymer was more hydrophilic, and accordingly, when the terminal monomers were hydrophobic, the polymers were more hydrophobic. The effect of the terminal monomer was shown to be pronounced at copolymer molecular weights less than 5,000 g/mol.
3.6 References


[14] K. Otake, R. Karaki, T. Ebina, C. Yokoyama, S. Takahashi. Pressure effects on the aggregation of poly(N-isopropylacrylamide) and poly(N-


Chapter 4

Aqueous Phase Behavior of Regioregular Copolymers with Aromatic Hydrophobic Units

4.1 Summary

Linear, regioregular copolymers with tunable water solubility tailored by alternating regions of hydrophobic and hydrophilic groups were synthesized with polycondensation. As before, ethylene oxide units were chosen as the hydrophilic units. In this chapter, the hydrophobic unit was an aromatic ring instead of aliphatic hydrocarbons, with no pendant functional group, a pendant CF$_3$, or a pendant ionizable carboxylic acid. The single polyester was composed of ethylene oxide units as well as an unfunctionalized aromatic ring. The aqueous phase behavior of the aromatic group containing polymers was compared to that of the copolymers with aliphatic hydrophobic segments. It was determined that the aromatic group imparts more hydrophobicity than any of the aliphatic groups previously studied [(CH$_2$CH$_2$)$_{3-6}$].

One of the polyamide copolymers contained an ionizable carboxylic acid group. The incorporation of this group rendered the polymer pH-responsive. The
aqueous solution LCST shifted from 8 to 41°C when the pH of the solution was changed from 3.7 to 4.2 (carboxylic acid is expected to ionize at pH 4). Above pH 4.5 the polymer was soluble at all temperatures.

4.2 Introduction

As presented in Chapters 2 and 3, linear regioregular copolymers of alternating ethylene oxide and short alkyl chain sequences show reversible phase separation in water. The copolymerization of PEO with other hydrophobic groups, such as aromatics, is also expected to yield polymers with temperature-sensitive behavior, as long as the proper balance between hydrophobic and hydrophilic segments in the copolymer exists. The addition of an ionizable group to the copolymer, whose ionization state influences solubility, would lead to a dually responsive system, where both temperature and pH changes could induce phase transitions.

Many polymers have been synthesized that are able to respond to either temperature or pH. However, it is of particular interest when a single polymer is able to respond to more than one stimulus, for instance temperature and pH, because the properties of a polymer can be altered by changing multiple environmental conditions [1]. Temperature- and pH-responsive polymers are of particular interest to the life sciences because proteins, which demonstrate temperature-sensitive folding, are composed of hydrophilic, hydrophobic, and, sometimes, charged segments. It is
assumed that the hydrophobic interactions due to the presence of aliphatic and aromatic groups in a protein are responsible for maintaining its native state.

Hydrophobic molecules (such as aliphatic and aromatic hydrocarbons) are less soluble in water than polar molecules (such as ethylene oxide) because non-polar solutes do not have favorable interactions with the polar water [2]. Unfavorable hydration entropies and favorable, but small, hydration enthalpies characterize hydrophobic hydration of non-polar molecules. The hydrogen bonded structure of water molecules surrounding non-polar solutes reorients so that O-H bonds are tangential to the non-polar surface, which maximizes the number of hydrogen bonds in the surrounding water network. The solvation of the non-polar molecules is not favorable because a large entropic penalty is required to form this highly ordered network [2], whereas the reorientation does not offer comparable increase in the number hydrogen bonds, i.e. in the system enthalpy.

Both aromatic and aliphatic hydrocarbons are hydrophobic, however, the nature of their hydrophobicity differs, and thus aliphatic and aromatic hydrocarbons have vastly different solubilities in water. For example, n-hexane has a solubility that is 20 times less than that of benzene, even though the molecules are both composed of six carbons and are of comparable molecular weight and size [3]. While the interactions between water and aromatic compounds are favorable, they are less favorable than the interactions between aromatic compounds themselves. This is the origin of the low solubility of aromatics in water [3]. Additionally, the pi electron system of benzene, the quintessential aromatic hydrocarbon, makes it a slightly polar molecule [2], which can act as a hydrogen bond acceptor [4]. This hydrogen bonding
capability also explains the greater aqueous solubility of aromatic groups than comparable aliphatic groups.

4.2.1 pH Sensitivity.

Polyelectrolytes are a broad class of polymers (both synthetic and natural) that contain charged groups. A sub-class of polyelectrolytes is pH-responsive polymers, which change from neutral to ionized over a range of pH. These polymers have ionizable pendant groups, whose ionization state strongly influences the aqueous solubility of the polymer. The ionizable groups can either accept (acid) or donate (base) protons when the pH of the system is altered. The water solubility change of the polymer is a result of the ionization change, which is an effect of electrostatic interactions and the osmotic pressure from the neutralization of charges by mobile counter ions.

In the case of the ionization of an acid-bearing polymer, the ionization is changed from a neutral state at low pH to a negatively charged state above the critical pH. When weak acids are fully protonated (neutral), electrostatic repulsion disappears. In the absence of charged repulsion, hydrophobic interactions dominate and cause aqueous phase separation. An additional mechanism for phase separation is inter- and intra-chain hydrogen bonding that may exist when the ionizable groups are uncharged.

Weak polyacids often contain carboxylic acid pendant groups. These polymers have pKa between approximately 5 and 6, since the pKa of carboxylic acid
is about 4. These polyacids are deprotonated (charged) at high pH and protonated (neutral) at low pH. Their charged state at moderate pHs allows them to behave as polyelectrolytes. The negative charge of the carboxylate anion causes electrostatic repulsions between chains. This repulsion dominates the solubility of chains at high pH in water.

Hydrophobically modified pH-responsive polymers have stirred interest as well [5]. There is a delicate balance between electrostatic repulsions and hydrophobic interactions within pH-sensitive water-soluble polymers. For example, the phase transition of polyacrylic acid in water is broad (continuous) while that of polymethacrylic acid in water is sharp (discontinuous). The extra methyl group in polymethacrylic acid results in stronger hydrophobic interactions and increases the driving force for aggregation. Integrating larger hydrophobic groups into a pH-sensitive polymer results in increasingly discontinuous phase transitions, as well as a more compact neutral state conformation.

The critical pH is a function of the pKa, however it is not the sole contributor [6]. There are two primary variables that influence the critical pH: the pKa of the ionizable group and the nature and amount of the hydrophobic moieties. The pKa is defined as the pH at which half of the ionizable groups are ionized. The pH at which the phase transition occurs is dictated by the balance between charged repulsions (a result of the pKa) and hydrophobic interactions. Incorporating hydrophobic segments into a polyacid typically increases the critical pH, since a greater electrostatic repulsion is needed to cause a phase change, which shifts the critical pH to a higher
value [5]. The opposite is true for weak polybases, where adding hydrophobic components will shift the critical pH to lower values [7].

Water-soluble polymers that respond to two stimuli, particularly temperature and pH, have attracted a great deal of attention. A number of studies have focused on the aqueous phase behavior of random and graft copolymers of PNIPAM and acrylic acid [1]. While the temperature sensitivity is due to the presence of PNIPAM, the stimulus for the phase transition is a combination of both temperature and pH changes. The mutual influence of temperature and pH on the aqueous solution LCST is the result of the change in solubility due to ionization. For example, carboxylate anions are more soluble in water than carboxylic acid groups. The increase in solubility of the ionizable group at high pH alters the hydrophilic/hydrophobic balance within the polymer that dictates the LCST.

4.3 Experimental Methods

Five amphiphilic copolymers were synthesized with polycondensation: two polyesters and three polyamides, as shown in figure 4.1.
Figure 4.1. Synthesis scheme for the synthesis of polyamide and polyester alternating copolymers via polycondensation. a: PA(12/benzene COOH), b: PA(12/benzene CF3), c: PA(12/benzene), and d: PE(20/benzene).

4.3.1 Polyamide Synthesis

Poly(ethylene glycol) bis(carboxymethyl) ether (PEG Mw 600, Sigma Aldrich) was heated to 80°C and vacuum dried for 2 hours. Dichloromethane (DCM) and four times the stoichiometric amount of thionyl chloride was added and refluxed...
at 80ºC for 4 hours under argon. The resulting PEG diacid chloride (PEG-Cl) was vacuum dried at 40ºC to remove the excess thionyl chloride. A diamine (m-phenylene diamine, 3,5-diaminobenzotri fluoride, or methyl 3,5-diaminobenzoate) was dissolved in DCM and filtered. The filtrate was then dried under vacuum for 30 minutes the resulting solids were weighed. DCM and two times the stoichiometric amount of pyridine were added to the diamine. To the diamine solution, 80% of the PEG-Cl solution was added dropwise over 2 hours. The reaction was carried out under argon at room temperature. After 6 hours the remaining diamine was dropped in over 2 hours. Finally, an excess of diamine was added to ensure all end groups are amines. The solution was filtered to remove the pyridine hydrochloride that was formed during the reaction. The polymer was then precipitated from the filtrate with hexane and vacuum dried.

To deprotect the carboxylic acid of the methyl 3,5-diaminobenzoate unit, the polyamide was dissolved in ethanol, where NaOH was subsequently added and the solution was stirred for 24 hours. Acetic acid was then added and the solution stirred for another 4 hours. The ethanol was evaporated and the polymer was dissolved in DCM and filtered to remove precipitates.

Polycondensation yields a polymer with a broad molecular weight distribution. Fractionation by reprecipitation (dichloromethane and hexane) was used to isolate narrower molecular weight samples. The molecular weight and molecular weight distribution of the copolymers were determined by gel permeation chromatography (GPC) using a Waters 410 GPC with a refractive index detector with
PEO molecular weight standards. The measurements were taken at 60°C using dimethyl formamide as the solvent and a mobile phase flow rate of 0.6 ml/min.

4.3.2 Polyester Synthesis

Polyethylene glycol (Mw 900) was heated to 80°C and vacuum dried for 2 hours. DCM was to the dried PEG added. In a separate flask, an acid chloride (terephthaloyl chloride) and DCM was added. To a third flask, DCM and pyridine was added. Over a 12 hour period, portions of the PEG and acid chloride solutions were alternately added to the pyridine containing flask while the solution was stirred and under argon. The resulting polymer solution was filtered. The filtrate was then fractionated to reduce the polydispersity of copolymer using DCM and hexane. The molecular weight and molecular weight distribution of the copolymers were determined by gel permeation chromatography (GPC) using a Waters 1515 HPLC pump and a Waters 2414 refractive index detector with polystyrene molecular weight standards. The measurements were taken at 37°C using tetrahydrofuran as the solvent and a mobile phase flow rate of 1.0 ml/min.

4.4 Results and Discussion

Cloud point measurements were used to determine the LCST of each sample in water. Their molecular weight and LCST data, along with those of copolymers with aliphatic hydrophobic segments, are presented in Table 1. The first two letters in
sample names denote the linkage groups (PA for polyamide and PE for polyester); the first number inside the brackets is the number of hydrophilic ethylene oxide monomers in each repeat unit; and the second number or word represents the hydrophobic units (the numbers refer to the number of ethylene groups in each repeat unit, while the words express which aromatic monomer was used).

Table 4.1. Molecular weight and LCST data for PE(20/benzene), PE(20/benzene CF₃), PA(12/benzene), PA(12/benzene CF₃), and PA(12/benzene COOH).

<table>
<thead>
<tr>
<th>Sample</th>
<th>LCST °C</th>
<th>Mn g/mol</th>
<th>Mw g/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA(12/3)</td>
<td>59.5</td>
<td>17600</td>
<td>26900</td>
</tr>
<tr>
<td>PA(12/4)</td>
<td>38.2</td>
<td>18500</td>
<td>27800</td>
</tr>
<tr>
<td>PA(12/5)</td>
<td>16.9</td>
<td>12800</td>
<td>22400</td>
</tr>
<tr>
<td>PA(12/6)</td>
<td>11.4</td>
<td>7200</td>
<td>14900</td>
</tr>
<tr>
<td>PA(12/benzene)</td>
<td>16.4</td>
<td>18400</td>
<td>34000</td>
</tr>
<tr>
<td>PA(12/benzene)</td>
<td>-</td>
<td>43700</td>
<td>63000</td>
</tr>
<tr>
<td>PA(12/benzene CF₃)</td>
<td>13.3</td>
<td>3300</td>
<td>5600</td>
</tr>
<tr>
<td>PA(12/benzene CF₃)</td>
<td>-</td>
<td>10400</td>
<td>20800</td>
</tr>
<tr>
<td>PA(12/benzene COOH)</td>
<td>variable</td>
<td>38600</td>
<td>56500</td>
</tr>
<tr>
<td>PE(20/3)</td>
<td>44.4</td>
<td>20200</td>
<td>35300</td>
</tr>
<tr>
<td>PE(20/4)</td>
<td>27.7</td>
<td>12200</td>
<td>22000</td>
</tr>
<tr>
<td>PE(20/benzene)</td>
<td>21.9</td>
<td>8700</td>
<td>15000</td>
</tr>
</tbody>
</table>

The LCST phase transition of the polyamide and polyesters aqueous solutions was studied by monitoring the cloud point. The polymer aqueous solution sample was placed in a glass vial immersed in a water bath. At low temperatures, when the solution was transparent, a laser beam is transmitted through the sample and enters a photometer at 0°, where it is recorded as a voltage. As the temperature rose, the solution became turbid causing the laser beam to scatter and the transmitted intensity (voltage) to decrease. A temperature probe connected to a hot plate was placed
directly in the sample vial and recorded the instantaneous temperature. The
temperature and voltage were recorded simultaneously using serial port data
collection software. The phase transition temperature is defined to be the temperature
at which 60% of the maximum transmitted intensity is recorded.

4.4.1 Polyester Phase Behavior

Cloud point measurements were performed to generate phase diagrams for the
three polyamide and two polyester samples in aqueous solutions. Figure 4.2 presents
the cloud point measurements for PA(12/benzene) in water.

![Figure 4.2](image_url)

Figure 4.2. Cloud point data of PA(12/benzene) for five aqueous solution samples
with varied polymer concentrations ranging from 5 to 1 wt%. The heating rate was
1°C/min.

Five aqueous solution samples ranging in concentration from 5 to 1 wt% were
prepared. Each solution was heated at a rate of 1°C/min. The cloud point temperature
decreased with decreasing concentration from 17.9°C at 5 wt% to 16.4°C at 2 wt%. The cloud point temperature then increased from 2 to 1 wt% to 17.5°C. The LCST, the minimum cloud point temperature is 16.4°C, which corresponds to the 2 wt% solution.

Phase diagrams were generated from cloud point data for aqueous solutions of three polyamides and one polyester. The phase behavior of PE(20/benzene) is compared to that of PE(20/3) and PE(20/4) in figure 4.3.

![Figure 4.3. Phase diagrams of polyesters in water: PE(20/3), PE(20/4), and PE(20/benzene).](image)

The LCSTs of PE(20/3) and PE(20/4) are 44.4°C and 27.7°C respectively, these are higher than 21.9°C, which corresponds to PE(20/benzene). PE(20/3) has a 6 carbon hydrocarbon chain in each repeat unit while PE(20/benzene) has 6 carbons in an aromatic ring. Even though the size and compositions of the hydrophobic groups are similar, the hydrophobicity they impart to the polymer differs. It is clear from
figure 4.3 that the aromatic group imparts more hydrophobicity to the polyester copolymer than either the (CH$_2$CH$_2$)$_3$ or (CH$_2$CH$_2$)$_4$ aliphatic units. The molecular weight of the PE(20/benzene) copolymer is 15,000 g/mole, which is much lower than both of the aliphatic copolymers PE(20/3) and PE(20/4) that have molecular weights of 35,300 g/mol and 20,000 g/mol, respectively. A sample of PE(20/benzene) with a molecular weight of 20,000-35,000 g/mol is expected to have an LCST even lower than 16.4°C (because of the inverse relationship between LCST and molecular weight). Figure 4.3 clearly shows that incorporating aromatic rings as hydrophobic units will result in a polyester with a greater degree of hydrophicity than a polyester containing similarly sized (6 and 8 carbon) aliphatic hydrophobic units. Interestingly, benzene is 20 times less soluble in water than n-hexane [3], but this solubility difference is not reflected in the copolymers. Benzene packs well with itself, which results in its low water solubility. However, when it is incorporated into a copolymer, it no longer packs well. This causes the copolymer to dissolve better in water than expected. By incorporating additional small groups into the hydrophobic units of the polymer chains, the properties of the polymer can be further altered.

4.4.2 Polyamide Phase Behavior

Phase diagrams of PA(12/benzene) and PA(12/benzene CF$_3$) in water were also generated using cloud point measurements and are plotted in figure 4.4.
The LCST of PA(12/benzene) is 16.4°C and the LCST of PA(12/benzene CF₃) is 13.3°C. Two samples of PA(12/benzene) and two samples of PA(12/benzene CF₃) were prepared, however, only the lower molecular weight samples were soluble in water. The highest molecular weight samples likely have an LCST in water below 0°C. The sample PA(12/benzene CF₃) with a molecular weight of 20,800 g/mol was insoluble at all temperatures, as was PA(12/benzene) with a molecular weight of 63,000 g/mol. The phase diagram of PA(12/benzene) with a molecular weight of 34,000 g/mol is much flatter than that of PA(12/benzene CF₃) with a molecular weigh of only 5,600 g/mol, a behavior which is consistent with molecular weight dependence of the LCST on phase behavior. The difference in cloud point temperatures only varies by 1.5 °C when the concentration changes from 4.7 to 2 wt% for PA(12/benzene). However, for PA(12/benzene CF₃), the cloud point decreases by 3.2 °C when the concentrations decreases from 5 to 2 wt%. This is a
manifestation of the molecular weight difference between the two copolymers [8]. The polyamides demonstrate the expected behavior of the PA(12/benzene CF₃) having a lower LCST than PA(12/benzene), despite having a molecular weight that is 6 times lower. The aromatic ring with a pendant CF₃ group is more hydrophobic than the unfuctionalized aromatic ring, resulting in a lower aqueous LCST for a low molecular weight sample of PA(12/benzene CF₃). Like hydrocarbons, fluorinated compounds force water molecules to order around them, resulting in negative entropies of solvation [9]. However, fluorocarbons have more hydrophobic character than hydrocarbons, which is reflected in their low values of cohesive energy density and surface energy [10].

The phase behavior of PA(12/benzene) in water is plotted along with that of PA(12/3), PA(12/4), PA(12/5), and PA(12/6) in figure 4.5. The LCSTs of PA(12/benzene) and PA(12/5) are almost the same, 16.4 and 16.9 °C, respectively (the molecular weights of the copolymers are 34,000 g/mol and 22,400 g/mol, respectively). However, the PA(12/benzene) sample with a molecular weight of 63,000 g/mol is insoluble in water at all temperatures, in contrast with PA(12/alkyls) of similar molecular weight.
Figure 4.5. Phase diagrams aqueous polyamide copolymer solutions.

For both the polyester and polyamide copolymers, using benzene as the hydrophobic unit yields a polymer with a lower LCST than the respective copolymers with aliphatic hydrocarbons (6-12 carbons). When incorporated into a polymer, the hydrophobic nature of the benzene seems to be altered; it no longer behaves more hydrophilic than similarly sized aliphatic groups, an effect that is probably related to the neighboring linkage groups (esters or amides).

4.4.3 Temperature- and pH-Responsive Properties

In pH-responsive polymer systems, the balance between hydrophobic interactions and charge repulsions is altered by the environmental pH, yielding a pH sensitivity, where pH changes can act as an on/off switch for polymer solubility in water. A dually responsive polymer can be obtained by combing the elements of
temperature and pH-sensitive systems; specifically, a proper hydrophilic/hydrophobic balance and ionizable groups.

The PEG/diaminobenzoate copolymer is hydrolyzed to form ionizable carboxylic acid groups. The pH of the aqueous solution influences the protonation of PA(12/ring COOH). An increase in pH leads to a deprotonation (ionization) of the carboxylic acid group. As the carboxylic acid becomes ionized it becomes more soluble in water. The phase diagram of PA(12/ring COOH) at pH 3.7 is plotted in figure 4.6 and demonstrates the polymer’s thermosenstivity.

Figure 4.6. Phase diagram of PA(12/benzene COOH) at pH 3.7 in water.

Five aqueous solution samples were prepared with copolymer concentrations ranging from 7 to 0.5 wt%. The LCST is 8 °C, which corresponds to concentration between 2 and 4 wt%. At pH 3.7 the carboxylic acid groups are mostly protonated (neutral), therefore there are fewer electrostatic interactions present to influence the phase behavior. In addition to the hydrogen bonding sites provided by PEO,
protonated (neutral) carboxylic acid groups can also participate in hydrogen bonding. These added sites increase the water solubility of the polyamide. PA(12/benzene) copolymers differs from PA(12/benzene COOH) by the existence of a single carboxylic acid group in each repeat unit. The PA(12/benzene) sample with a molecular weight of 63,000 g/mol is not soluble in water at any concentration. However, the presence of the carboxylic acid group in the PA(12/benzene COOH) sample (MW 56,500 g/mol) increases the aqueous solubility sufficiently for the sample to be soluble in water, and undergo a phase transition with a LCST of 8 °C.

The LCST of the aqueous polymer solution increases dramatically with pH. The water solubility of the copolymer is dependent on both the system temperature and pH. At low pH, the solubility is almost entirely dependent on the hydrophilic/hydrophobic balance within the polymer. This balance dictates the temperature at which a LCST phase separation occurs. However, as the pH is raised, carboxylic acid groups become ionized carboxylate anions, pushing the LCST to higher temperatures. The hydrophobic interactions of the polymer must overwhelm the electrostatic interactions for phase separation to occur. Increasing the degree of ionization eventually reaches a point where the electrostatic interactions overwhelm the hydrophobic interactions and no phase separation occurs.

Figure 4.7 shows the cloud point of a 3 wt% aqueous solution of PA(12/ring COOH) at 3 pHs: 3.7, 4.0, and 4.2. At pH 3.7 the cloud point is 8 °C, at pH 4.0 the cloud point is 26 °C, and at pH 4.2 the cloud point is 41 °C.
No phase separation occurs at pH above 4.5, and the polymer is water-soluble at all temperatures and compositions studied. The LCST likely moved above the temperature range of the experimental setup (90 - 100°C). A pressurized vessel could be used to determine the LCST at pH 4.5 and higher pHs. It is clear from figure 4.7 that the phase transition broadens at the pH as increased. This can be attributed to the incomplete ionization of the copolymer chains. The degree to which each chain is ionized may be varied, therefore the hydrophilic/hydrophobic balance of the copolymers may have a wide distribution. This will result in chains collapsing and aggregating at different temperatures, depending on their ionization state, which broadens the transition of the solution. Several factors contribute to the increase of the LCST when pH is increased. First, the hydrogen bonding within and between the polymer chains is disrupted by the ionization of carboxylic acids as pH increases. The polymer chains are then forced into a more swollen state because of electrostatic
repulsions. Second, polymer-water interactions are enhanced upon ionization, and the anions effectively suppress the hydrophobic character of the groups.

4.5 Conclusions

Three polyamide and one polyester copolymers containing alternating ethylene oxide sequences and aromatic groups were synthesized. The hydrophobic units of the three polyamides had different small groups attached to the aromatic ring; one had no functional groups, one had a pendant CF$_3$, and one had a pendant ionizable carboxylic acid. The single polyester’s hydrophobic unit was an unfuctionalized aromatic ring. Aqueous solutions of these polymers show aqueous solution LCSTs that correlate with the hydrophobicity of the aromatic groups. By increasing the hydrophobicity of the polymer, the LCST was pushed to lower temperatures. The LCST behavior of the aromatic containing polymers were also compared to that of homologous copolymers that contain aliphatic hydrocarbons as the hydrophobic groups. High molecular weight copolymers of the polyamides with unfuctionalized aromatic groups, as well as CF$_3$ functionalized aromatic groups, were not water-soluble at any temperature or composition studied. A dramatic increase in LCST was seen with the ionization of the hydrophobic segment (i.e. when the pH of a solution of carboxylic acid containing copolymer was increased from 3.7 to 4.2). For these ionomers, above pH 4.5, no phase transition occurred at any temperature or composition studied.
4.6 References


Chapter 5

Method for End Tethering Regioregular Copolymers to a Silicon Wafer

5.1 Summary

A regioregular polyamide composed of alternating ethylene oxide and ethylene sequences (PA(12/4)) was end-tethered to a silicon wafer. Vapor deposition of silanes was used to decorate the silicon surface with mixed silane SAMs containing reactive end groups. A “grafting from” approach employing peptide polycondensation was used to produce a surface coated with grafted polymer. Two samples with different molecular weights were prepared: 18,600 and 74,400 g/mol. Contact angle measurements were used to monitor the wettability of the surface throughout the synthesis process. Atomic force microscopy was utilized to obtain topography images of both surfaces.

5.2 Introduction

End-tethered polymers have many potential applications, particularly in colloids and surface modification problems. There are two extreme regimes that exist
when polymers are end-grafted to a surface, as shown in figure 5.1. First, there is the
so-called “mushroom” regime, where the grafting density is low enough for the
chains to be isolated. The second regime ("brush") is characterized by high grafting
densities, where the chains stretch away from the surface due to steric hindrance.

![Figure 5.1](image)

**Figure 5.1.** a) “mushroom” regime; isolated polymer chain. b)"brush” regime;
densely grafted polymer chains.

When polymer chains are end-tethered to a surface or at an interface and the
grafting density is sufficiently high for steric hindrance to overwhelm the
conformational entropy, the chains stretch normal to the surface, like the bristles of a
brush [1]. The altered conformation of the tethered chains results in the unique
properties of polymer brushes. The behavior of densely grafted polymer chains differs
considerably from that of surface physisorbed or free polymer chains, especially in
solution. When in good solvent, the chains stretch even more normal to the surface
because the chains have an affinity for the solvent. Even in the absence of a good
solvent, the chains still stretch away from the surface, but only enough to avoid overlapping [2].

Polymer brushes can also offer a model system for studying other systems, such as polymer micelles, diblock copolymers in the melt, and block copolymers at the interface of two fluids. Polymer brushes can be synthesized by covalently bonding or adsorbing polymer chains to a solid surface. Alternatively, block copolymers are used to make polymer brushes using physisorption where only one block has favorable interactions with the surface. Alternatively, when polymer brushes are formed at the interface between two fluids, one block will preferentially dissolve in one solvent while the other block(s) will only dissolve in other solvent.

Polymers that are covalently bonded to surfaces fall into any of the following categories: homopolymers, mixed homopolymers, random copolymers, and block copolymers. The presence of an interface limits the number of possible conformations of tethered polymer chains. Their conformations are dictated by a delicate balance between configurational entropy and steric interactions [3]. Dense grafting forces the chains to overlap, which increases the number of monomer-monomer contacts. In the presence of a good solvent, the osmotic pressure within the brush causes the chains to stretch away from the surface, which lowers the monomer concentration and results in an increased brush thickness. The interplay of the elastic free energy, the entropic restoring forces, and the steric and enthalpic interaction energies of the chains determine brush thickness. However, the single most important parameter that influences the brush thickness is the molecular weight ($\sigma N$) [2]. At high grafting densities the height varies with $N(\sigma)^{1/3}$ in a good solvent where $N$ is the degree of
polymerization and $\sigma$ is the grafting density. (For free chains in a good solvent, the radius of gyration scales as $N^{3/5}$ [3].)

In the absence of good solvent, the radius of gyration varies with $N^{1/3}$ for free chains and the height of a polymer brush varies with $N^{2/3}$ [2]. This behavior confirms that densely tethered polymer chains are deformed, which is the source of the unique behavior of polymer brushes. Deformed conformations exist regardless of the quality of the solvent. Although, the extent of deformation of the tethered polymer chains is related to the environment (for example the solvent quality) to which the chains are exposed. Therefore, it is possible for the same end-tethered polymer system (same $\sigma$, $N$) to exist in different regimes in different solvents.

When tethering chains to a surface, chemisorption is preferable to physisorption. The covalent bond employed by chemisorption is far more robust than the physical bond utilized in physisorption and can be defined to a single-point (e.g. end-tethered chains). There are two methods available for covalently grafting polymer chains to solid surfaces: “grafting to” and “grafting from” [4]. In the “grafting to” method, polymers with a functionalized terminal group react with the substrate to form a covalent bond. The substrate is first treated so that appropriate reactive groups are present on the surface with a surface density of $\sigma$. The primary drawback to using the grafting to approach is that only a small number of chains can be attached to the surface; once chains begin to attach to the surface, any further chains must diffuse through the polymers already attached [3]. As substantially more polymers attach to the surface, the barrier to diffusion becomes large, which limits the grafting density. To overcome this steric limitation, the “grafting from” approach was
developed. As with the “grafting to” approach, the surface is decorated with reactive
groups that can be used to end-tether polymers; however, instead of attaching pre-
formed polymer chains to the surface, the polymerization is initiated from the surface.
The surface functional groups act as initiators and the polymer grows from the
surface monomer by monomer. By diffusing monomers, as opposed to polymers, the
barrier to diffusion is dramatically reduced [3].

In the 1950s polymer brushes first garnered attention when it was discovered
that grafting colloidal particles with polymer chains prevents aggregation [5]. Since
then, polymer brushes have been utilized in a number of applications such as protein
resistant surfaces [6], chromatography [7], polymer surfactants [1], adhesives [8], as
well as temperature- [9], pH- [10], and photo- responsive [11] surfaces. Surfaces that
exhibit thermally sensitive behavior in a solvent are created, for example, by grafting
polymers that possess LCST behavior in this solvent.

When an environmentally responsive polymer is tethered to a surface, its
responsive properties are largely maintained. For example, PNIPAM is the most
commonly used polymer to create temperature-sensitive brushes. When attached to a
surface and exposed to a good solvent, the polymer chains will be swollen. If the
solvent quality becomes poor, the chains collapse, resulting in a brush height
reduction. These phenomena result in surfaces with reversible switching of properties
such as surface energy (adhesion) and roughness as the temperature crosses the
LCST. These changes allow the utilization of contact angle, AFM adhesion and
topography measurements to be used to investigate the LCST of polymer brushes.
5.3 Experimental Methods

PEG 600 acid chloride was synthesized starting with dicarboxylic acid terminated PEG 600. A 10 wt% solution in dichloromethane was made and to that 4 times the stoichiometric amount of thionyl chloride was added. (Thionyl chloride is a highly toxic substance. Precautions should be taken to avoid skin contact and inhalation.) The reaction proceeded under argon and was refluxed at 80°C for 4-6 hours. A vacuum was used to remove the excess thionyl chloride and the dichloromethane. Fresh dichloromethane was added to the diacid-chloride-PEG 600.

A silicon wafer was rinsed with acetone and wiped with a kim wipe before it was UV ozone cleaned (Novascan PSD-UVT) at 60°C for 5 minutes. This process removes any organic material from the surface of the wafer, as well as frees pendant hydroxyl groups on the SiO$_x$ surface [12]. This occurs because ozone absorbs UV light and dissociates into atomic oxygen. Organic materials are turned into volatile oxidation products and reactive silanols are produced. While piranha etch will also remove organics from the surface as well as free hydroxyl groups on the surface of silicon wafers, it is not an ideal cleaning method. It is quite dangerous (it has been known to explode) and often residues remain on the surface after cleaning, which makes it difficult to subsequently functionalize these surfaces reproducibly.

After cleaning, vapor deposition of 3-aminopropyltriethoxysilane (APTES), the structure of which is depicted in figure 5.2, was done in a closed Petri dish that contained a open dsc pan (diameter of 5 mm, height of 2 mm). Into the pan, 2 drops of paraffin oil were added, followed by 2 drops of APTES. (The paraffin oil is used to
reduce the diffusion rate of the APTES.) The cover was placed on the Petri dish and the wafer was exposed to the APTES/oil mixture for 10 minutes. As the APTES evaporated, it diffused in the vapor phase and deposited on the substrate. After 10 minutes, the wafer was removed and subsequently placed in a new Petri dish that contained another open dish where four drops of octyldimethylchlorosilane (ODS), the structure of which is presented in figure 5.2, were added and the Petri dish was covered.

![Figure 5.2. Structures of 3-aminopropyltriethoxysilane (APTES), above, and octyldimethylchlorosilane (ODS), below.](image)

The ODS was allowed to deposit for 30 minutes, which should completely backfill any unreacted hydroxyl groups on the silicon surface. Monofunctional chlorosilanes are attractive because of their reproducibility; there is only one possible reaction when in the presence of a hydroxyl decorated surface, unlike di- and
trichlorsilanes which can react with each other in the vicinity of the surface and polymerize vertically and horizontally [13]. The amine terminated silanes attached to the surface act as polymerization initiators to end-tether the polyamide copolymers. While the methyl terminated silanes prevent further reactions with the substrate and are thus used to control the polymer’s grafting density.

After both silanes were deposited, the SAM bearing silicon wafer was immersed in a dichloromethane solution of chlorinated PEG 600 chloride and pyridine for 10 seconds, as depicted in figure 5.3. The wafer was rinsed in dichloromethane and immersed in a dichloromethane solution of amine terminated (CH$_2$)$_8$ and pyridine and then rinsed again. This procedure was repeated either 25 or 100 times to produce two copolymer samples. With each cycle, the molecular weight grows by one PEG and one alkyl sequence. The acid chloride functional groups on the PEG react with the amine functional groups on the aliphatic hydrocarbon. The resulting polymer is a PA(12/4), the LCST of which is 38.2°C in water for a polymer with a molecular weight of 27,800 g/mol and whose aqueous solution properties are presented in Chapters 2 and 3.

This monomer-by-monomer polycondensation reaction allows for good control of polymer molecular weight. This process yields monodisperse end grafted copolymers. When care is taken, acid chloride groups do not react with ambient water molecules to form carboxylic acid. (Carboxylic acid does not react with amine at room temperature, which prevents additional monomers from attaching to the polymer.) The sample with 25 cycles had an expected molecular weight of 18,600 g/mol, while the sample with 100 cycles has an expected molecular weight of 74,400 g/mol.
5.4 Results and Discussion

5.4.1 Contact Angle

Static contact angle measurements were performed using the sessile drop method. A 5μl DI water droplet was placed on the sample surface at room temperature. The droplet was photographed and the static contact angle measured.
The static contact angle is a simple characterization technique that provides a direct measurement of wetting, and thus, an indirect measurement of the surface tension.

Contact angles were measured during the end-tethered polymer synthesis process as shown in figure 5.4. After UV/ozone cleaning, the contact angle was 8°; the UV/ozone treatment renders the surface hydrophilic by generating surface hydroxyl groups. After the APTES deposition the contact angle increased to 50°. Since the surface is only partially covered with APTES, the diffusion time is an important parameter when vapor deposition of APTES is used. In diffusion times less than 7 minutes, a gradient of APTES on the surface formed. This is agreement with the work of Chaudhry and Whitesides [14]. A 10 minute diffusion time was used to ensure uniform coverage (which was confirmed with contact angle measurements made at various spots along the substrate). Once the ODS was deposited and the SAM was completely formed, the contact angle increased further to 84°. Finally, after the polymers were grafted, the contact angle of the 25 cycle sample was 67° and the 100 cycle sample was 69°. In the range of molecular weights studied, the wettability of the surface is independent of chain length, as expected.
Figure 5.4. Contact angle measurements of surface after silane modification and brush synthesis. A: UVO cleaned silicone wafer. B: Silicon wafer after exposure to APTES (partial coverage). C: Silicon wafer after exposure to ODS (a full mixed-SAM of APTES and ODS is expected at this point). D: PA(12/4) copolymer with 25 cycles. E: PA(12/4) copolymer with 100 cycles
Table 5.1. Sessile deionized water drop contact angle measurements of the surface throughout the synthesis procedure. The measurements were performed at 25°C.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Contact Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) UVO cleaned silicone wafer</td>
<td>8</td>
</tr>
<tr>
<td>b) 10 minute vapor deposition of APTES</td>
<td>50</td>
</tr>
<tr>
<td>c) 30 minute vapor deposition of ODS</td>
<td>84</td>
</tr>
<tr>
<td>d) PA(12/4) end-tethered polymer 25 cycles</td>
<td>67</td>
</tr>
<tr>
<td>e) PA(12/4) end-tethered polymer 100 cycles</td>
<td>69</td>
</tr>
</tbody>
</table>

5.4.2 Atomic Force Microscopy

Atomic force microscopy (AFM), also known as scanning force microscopy, produces high resolution images of surfaces using a scanning stylus technique. Attached to a cantilever spring is a sharp tip. The forces between the tip and the sample surface deflect the cantilever according to Hooke’s law. A laser beam and a photodetector are used to measure the cantilever deflections. A piezo crystal is used in conjunction with a feedback system to control the vertical position of the sample during scanning and the output signal can be transformed into topography as well as amplitude, and phase images when a vibrating tip is used.

A Digital Instruments Multimode AFM, controlled by the Nanoscope IIIa Scanning Probe Microscope Controller with a Nanoscope extender was used to perform atomic force microscopy. AFM topography imaging was done on both the 25 cycle and 100 cycle samples under air. Prior to imagining, the samples were placed in an 80°C oven for 30 minutes to dry.
Figure 5.5a shows a 1 μm 3D topography image in air of the 25 cycle sample. The corresponding 2D image is shown in figure 5.5b. The height profile along a typical scan line is shown in figure 5.5c. Figure 5.6 presents 2.5 μm and 600 nm 3D topography images and corresponding 2D images for the 25 cycle sample. The height data scale for each of the 3D images is 10 nm (600 nm), 8 nm (1 μm), and 13 nm (2.5 μm). All the measurements were performed with tapping mode AFM at a scanning frequency of 0.25 Hz and an amplitude set point ratio of 0.4. Figure 5.7a presents a 1 μm² 3D topography image of the 100 cycle sample performed in air. Figure 5.7b shows the corresponding 2D image and figure 5.7c is the height profile along a typical scan line. The 3D topography image and 2D image of a 600 nm² section of the 100 cycle sample is shown in figures 5.8a and b. The height scale for each of the 3D images is 20 nm. Both images were scanned at a rate of 1 Hz and the amplitude set point ratio was 0.5.
Figure 5.5. (a) AFM 3-D topography image of a 1 square micron area of a sample with 25 cycles of PA(12/4) end grafted from a silicon wafer. (b) 2-D plot of same image. (c) Height profile along typical scan line.
Figure 5.6. (a) AFM 3-D topography image of a 2.5 square micron area of a sample with 25 cycles of PA(12/4) end grafted from a silicon wafer. (b) 2-D plot of same image. (c) AFM 3-D topography image of a 600 square nanometer area of a sample with 25 cycles of PA(12/4) end grafted from a silicon wafer. (d) 2-D plot of same image.
Figure 5.7. (a) AFM 3-D topography image of a 1 square micron area of a sample with 100 cycles of PA(12/4) end grafted from a silicon wafer. (b) 2-D plot of same image. (c) Height profile along typical scan line.
Figure 5.8. (a) AFM 3-D topography image of a 600 square nanometer area of a sample with 100 cycles of PA(12/4) end grafted from a silicon wafer. (b) 2-D plot of same image.
By comparing the 600 nm² and 1 μm² scans of both samples, it is clear that the features of the 100 cycle sample are much larger. This is to be expected because of the higher molecular weight copolymer grown on the 100 cycle sample. The features in both samples are aggregates of polymer chains, however, in the 100 cycle sample, there are longer chains, and perhaps more chains, in each aggregate. At low grafting densities, polymer chains are isolated, as shown in figure 5.9a.

![Figure 5.9a](image.png)

Figure 5.9. Schematic drawing if a) polymer chains tethered to a surface at low grafting densities; b) “pinned” micelles formed by polymers with moderate grafting densities.

However, at moderate grafting densities, the structure is determined by two competing factors: the constraint of the tethers and inter- and intrachain attraction. The result is the formation of “clusters” on the surface, shown in figure 5.9b, which have been labeled “surface octopus micelles” [15] and “pinned micelles” [16]. These structures are known to form in bad solvent conditions and in air. The images
presented in figures 5.5-5.8 were performed in air, which is effectively a very bad solvent. It is likely that the features seen in these images are pinned micelles.

5.5 Conclusions

Polycondensation peptide chemistry was successfully used to create a surface covered with end-tethered temperature-sensitive polymer chains. A “grafting from” approach was used to grow the polymer chains one monomer at a time by dipping a silicon surface decorated with a mixed silane SAM that contain reactive amine endgroups alternately into two monomer solutions. The resulting regioregular alternating copolymer has the structure of PA(12/4), a polymer that demonstrates temperature sensitivity in water. Surfaces with two different molecular weight were prepared: 18,600 and 74,400 g/mol. Sessile static water drop contact angle was used to characterize the wetting ability of the surface throughout the surface preparation. Tapping mode AFM in air was used to obtain topography images of both surfaces. The images show large, regular features on the surface that are likely “pinned micelles”, or clusters of polymer chains.
5.6 References


Chapter 6

Conclusions and Suggestions for Further Research

6.1 Future Work

The purpose of this work was to develop a series of copolymers, whose solubility in water can be tailored by copolymerizing hydrophobic and hydrophilic units. The temperature sensitivity of these copolymers relates to their ability to phase separate from water abruptly above a specific temperature. A series of polyamides and polyesters was developed, where the lower critical solution temperature (LCST) was controlled by the balance of hydrophobic and hydrophilic segments in the polymer. It was shown that by changing the size of either component, the aqueous solution LCST could be shifted to higher or lower temperatures by design. In order to maintain a sharp phase transition, the hydrophilic and hydrophobic segments were connected in an alternating manner across a linear copolymer. This avoids “blockyness” within the backbone which would result in micellization and a broad phase transition. PEO was chosen as the hydrophilic component in all of the copolymers because of its LCST behavior in water and its proven utility in biological applications. Short, difunctional aliphatic hydrocarbon chains were chosen as the hydrophobic segment. They are commercially available in a number of lengths, which
permits the formation of many polymers with different compositions and varied aqueous phase behaviors.

While the choice of comonomers is an important factor in determining the LCST of the resulting copolymers, several other variables can influence the aqueous solution behavior. It was shown that the molecular weight influence on the LCST is marked at low and moderate molecular weight. As the molecular weight of the copolymers increased, their LCSTs decreased. It was also demonstrated that at low and moderate copolymer molecular weights the hydrophobic or hydrophilic nature of the end group must be considered. At high molecular weights the hydrophilic/hydrophobic balance within the polymer is solely dependent on the relative sizes of the reactant comonomers. However, at low copolymer molecular weights, the nature of the endgroup will alter the hydrophilic/hydrophobic balance of the copolymer. This is a direct consequence of the size of the comonomer (which was as much as 900 g/mol). While the choice of comonomers determines a range in which the LCST will exist, both the molecular weight and the endgroup can be used to “fine tune” the LCST.

The concept of adjusting the LCST of water-soluble polymers by alternating hydrophilic and hydrophobic segments of different lengths was first carried out with linear alkyls. This design scheme was further extended to aromatic hydrophobic groups, and it was shown that the aromatic groups are far more hydrophobic than the respective aliphatic groups of similar molecular weight. Additionally, the hydrophobicity of the aromatic group increased dramatically with the addition of a pendant fluorinated group.
A dually responsive polyamide that demonstrates both temperature- and pH-responsive properties was formed by selecting an aromatic group that contained a pendant carboxylic acid as the hydrophobic comonomer. The role of the acid was twofold: it increased the water solubility of the hydrophobic segment by providing additional hydrogen bonding sites and upon pH change its ionization change rendered the polymer more hydrophilic. Thus, the temperature-responsive characteristics of the aqueous copolymer solution changed with pH.

Finally, a method to covalently attach temperature-sensitive polymers to a silicon wafer was devised. By using the “grafting from” approach in conjunction with polycondensation peptide chemistry, a temperature-sensitive polyamide was grown from a silicon wafer. The wafer was first decorated with end-functionalized silane SAMs using silane vapor deposition. The modified wafer was then dipped in two monomer solutions in an alternating sequence. The surface was characterized with contact angle and AFM topography imaging.

While the concept of producing temperature-sensitive tunable water-soluble copolymers has been shown to be effective, much work remains. A series of samples need to be produced with very low (1.1) polydispersities and high molecular weights. These samples can be studied with light scattering. The aggregation kinetics and the copolymer size a function of temperature can be investigated easily with dynamic light scattering. It would be of particular interest to compare the behavior of a
copolymers with hydrophobic groups that are: aliphatic, aromatic (with no pendant
groups), and aromatic with a pendant group.

There is a great deal yet to be done with copolymers that exhibit both
temperature- and pH-responsiveness. A natural progression from the work presented
in chapter 4 is to make copolymers with 2 different hydrophobic groups: one with a
pH-sensitive moiety and one without. For example, instead of using equamolar
amounts of PEG and the aromatic with carboxylic acid, a mixture of hydrophobic
units could be used, for example 75\% ((\text{CH}_2\text{CH}_2)_3 and 25\% aromatic with carboxylic
acid. This system would have two variables: the length of the aliphatic unit and the
molar fraction of hydrophobic comonomers with ionizable acid groups. In this case
the pH sensitivity would be altered by the percent of carboxylic acid containing
hydrophobic groups, while the temperature sensitivity can be tuned by choosing the
appropriate ratio of aliphatic to ethylene oxide units. The synthetic method used
throughout this thesis could be used. However, a higher molecular weight polymer
would likely result if the PEG was purified with column chromatography and or
fractionation to reduced the polydispersity and nmr was done to determine the true
molecular weight.

End-tethered polymers present an excellent opportunity to study the surface
properties of temperature-sensitive polymers. Of particular interest would be to study
the aqueous solution LCST of end-tethered polymers that have the same composition
as those presented in this work. The influence of the molecular weight and terminal
monomer nature would make for an interesting study as well. Another study could
focus on mixed end-tethered polymer chains with two chemical compositions. For
instance, a 100 cycle sample would be produced, but 50 cycles in, the hydrophobic comonomer would be changed. Two samples could be made, one with the lower LCST on the top layer and other with the lower LCST on the bottom. The use of polycondensation peptide chemistry for the synthesis of end-tethered polymer chains is ideally suited for studying pH sensitivity. A primary hurdle for studying pH responsiveness is the inability to control where on the chain the pH-responsive moiety is. The monomer by monomer synthesis scheme presented in this work would allow the pH-sensitive monomer to be placed with great accuracy.
Appendix A. Monomer CAS Numbers, Names and Structures
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<td>Poly(ethylene glycol)</td>
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<tr>
<td></td>
<td>Mw 600 and 900</td>
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<tr>
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<td>Poly(ethylene glycol) bis(carboxymethyl) ether</td>
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<tr>
<td></td>
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<tr>
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<td>---------------------</td>
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VITA

Theresa Foley was born and raised in the great state of Minnesota. The University of Wisconsin-Madison greeted her warmly in the fall of 1998. In August 2002, she earned a B.S. in Chemical Engineering from UW. She then made her way to Pennsylvania in September where she began her graduate studies in the Department of Materials Science and Engineering at Penn State in the group of Evangelos Manias. Five and a half years later, she found herself with a PhD and free time to travel the world.