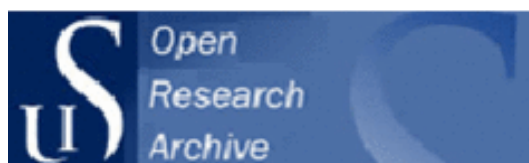




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Tuning the Thermoresponsive Properties of Hyperbranched Poly(ester amide)s Based on Diisopropanolamine and Cyclic Dicarboxylic Anhydrides

Malcolm A. Kelland

ABSTRACT: A range of water-soluble hyperbranched poly(ester amide)s has been synthesized with a view to studying their thermoresponsive behavior in water. Poly(ester amide)s with lower critical solution temperature (LCST) values around physiological temperatures are of interest for biological and medical applications, whereas poly(ester amide)s with high LCST values may be useful as kinetic hydrate inhibitors for high salinity produced fluids in the oil and gas industry. The LCST of these polymers was measured as the optical cloud point. The LCST can be tuned in various ways for these applications, for example, by varying the hydrophobicity of the groups on the cyclic anhydride monomer or by adjusting the hydrophilicity of the imine used to make the peripheral groups of the polymer.

Key words: hyperbranched; phase behavior; water-soluble polymers; lower critical solution temperature; kinetic hydrate inhibitors

INTRODUCTION

In the last 15 years, there has been much focus on the thermoresponsive properties of polymers for use in such fields as drug delivery,¹⁻³ biomaterials,^{4,5} nanomaterials,⁶ filtration,^{7,8} supported catalysts,⁹ and microfluidics.¹⁰ By far, the most studied poly-mers are linear polyvinyl polymers exemplified by poly(N-isopropylacrylamide)(PNIPAM), which has a lower critical solution temperature (LCST) of about 32 C, close to physiological temperatures.¹¹⁻¹⁵ Other linear polymers with LCSTs in water include other poly(N-alkylacrylamides),¹⁶⁻¹⁹ poly(N-vinylcaprolactam),²⁰ poly(2-alkyl-2-oxazoline)s,^{21,22} polyethers,²³ polyvinyl ethers,^{24,25} poly(dimethylaminoethylmethacrylate),²⁶ polylactides,²⁷ and copoly(oligoethylene oxide)acrylates.^{28,29}

More recently, water-soluble hyperbranched polymers and dendrimers have been synthesized and studied as thermoresponsive materials.³⁰⁻⁴⁰ Some have been investigated for controlled-release drug delivery systems.^{41,42} Dendrimers can be made water-soluble primarily through the peripheral groups being hydrophilic even when the core is hydrophobic.⁴³ By varying the hydrophobicity of the peripheral groups, one can obtain dendrimers with LCST values in water. These include poly(amido-amine) dendrimers with peripheral N-isopropylamide or N-isobutylamide groups.⁴⁴ Hyperbranched polymers have a more open structure and the whole polymer can take part in hydrogen-bonding in aqueous media if water-soluble. Examples are polyamides,^{45,46} polyglycerols,^{47,48} aliphatic polyesters,^{49,50} poly(ethyleneimine)s,⁵¹ poly(ester amide)s,⁵² and polyethers.^{30,53-55}

One class of hyperbranched poly(ester amide)s are those made using cyclic carboxylic anhydrides and dialkanolamines and discovered by DSM.⁵⁶⁻⁵⁸ The mechanism of their formation has been investigated previously.⁵⁹ In a one-pot procedure, the dialkanolamine molecules react preferentially via the secondary amine group with the cyclic anhydride, forming *in situ* a bis(hydroxyalkyl)amide group (AB₂) containing carboxylic acid (Fig. 1).⁶⁰ Because of the known high reactivity of 2-hydroxyalkylamide groups toward esterification with carboxylic acids, a fast and efficient polycondensation at temperatures of 140–200° C without the addition of a catalyst can be performed. The preferred dialkanolamine is diisopropanolamine; diethanolamine leads to unwanted coupled products via side-reactions giving gelled, high molecular weight polymers. The esterification of the bis(hydroxyalkyl)amide proceeds via an oxazolinium–carboxylate ion pair intermediate; ring opening of the oxazolinium species via nucleophilic attack of the associated carboxylate finally affords the ester (Fig. 2). The end product is a hyper-branched poly(ester amide) (Fig. 3). The theoretical ratio of cyclic anhydride to dialkanolamine is $n : n + 1$ giving polymers with specific molecular weights, although several structures are possible.

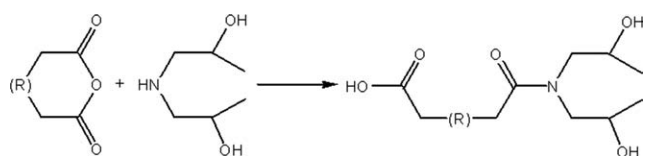


Figure 1 Formation of a bis(hydroxyalkyl)amide from a cyclic anhydride and a dialkanolamine.

Using diisopropanolamine as the sole secondary amine leads to polymers with peripheral hydroxyl groups. By adding a second secondary amine (but with no hydroxyl groups), one can produce a polymer with peripheral groups that are derived from this amine. The theoretical ratio of alkanolamine to secondary amine to cyclic anhydride is then $n : n + 2 : 2n + 1$. An example using 3,3-iminobis(*N,N*-dimethylpropylamine) as the second secondary amine is given in Figure 4.

Water-soluble hyperbranched poly(ester amides) are now used in paper coatings⁵⁹ and as kinetic hydrate inhibitors (KHIs) for the oil and gas industry⁶¹ and may have possible applications in biology and medicine, for example, if the LCST can be adjusted to physiological temperatures. For use as KHIs, hyperbranched poly(ester amides) need to be water-soluble in produced or completion fluids of high salinity but at the same time containing hydrophobic groups that can disturb gas hydrate formation.⁶²⁻⁶⁴ The main salt in oil and gas multiphase pipeline fluids is sodium chloride, which originates either from formation water or injected seawater. Thus, as is typical of thermoresponsive polymers, a high LCST in distilled water is needed for some KHIs as the LCST will decrease as the sodium chloride salinity increases.

We decided to carry out a study to determine the range of hyperbranched poly(ester amides) that could be made water-soluble given changes in the structures of the two or three reactants. One way to modify the LCST which we did not explore is to react peripheral hydroxyl groups on a poly(ester amide) of the type in Figure 3 with varying amounts of ethylene oxide to make the peripheral groups more hydrophilic.⁵⁷ This would raise the molecular weight of the polymer significantly, which is detrimental for kinetic hydrate inhibition because a higher wt % concentration in aqueous solution will then be needed to obtain the same inhibition performance.

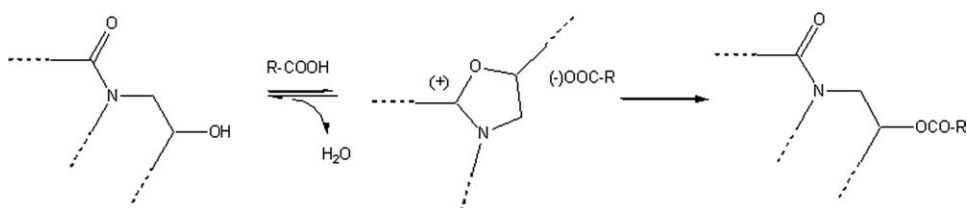


Figure 2 Reaction mechanism for the esterification of 2-hydroxyalkylamides.

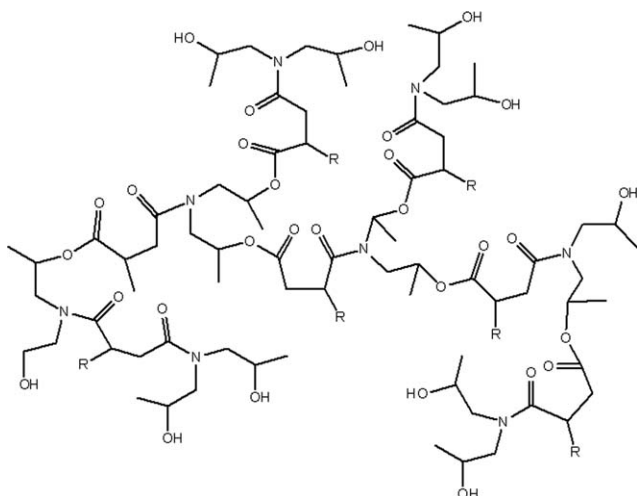


Figure 3 Example of a hyperbranched poly(ester amide) structure formed from an alkylsuccinic anhydride and diisopropanolamine.

EXPERIMENTAL SECTION

Polymer synthesis

All chemicals were obtained from Sigma-Aldrich Company except *cis*-1,2-cyclohexane-dicarboxylic anhydride (HHPA), 3-methyl-*cis*-1,2-cyclohexane-dicarboxylic anhydride, *cis*-1,2-cyclohex-4-ene-dic-arboxylic anhydride, and 1-oct-2-ene-succinic anhydride which were obtained from Dixie Chemical Company. Other 1-alkylsuccinic anhydride derivatives were prepared by the literature method.^{65,66} An example preparation is given below for 1-isobutyl-succinic anhydride. Poly(ester amide)s were prepared according to the literature method.⁶⁷ A typical synthesis of a poly(ester amide) is given below for PEA39.

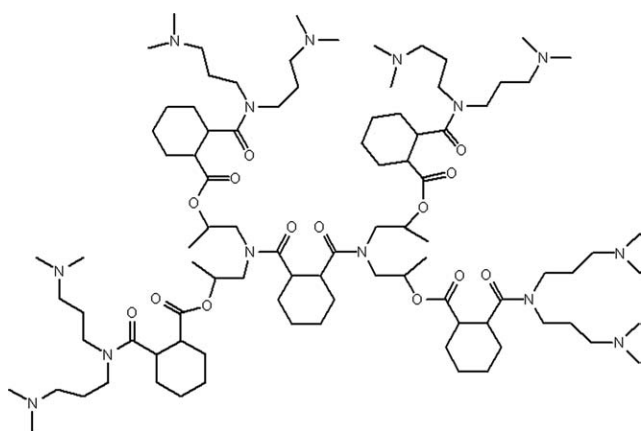


Figure 4 Example of a hyperbranched poly(ester amide) structure formed from *cis*-1,2-cyclohexane-dicarboxylic anhydride, diisopropanolamine, and 3,3-iminobis(*N,N*-dimethylpropylamine).

The NMR spectra were obtained using a Varian 300 MHz instrument. IR spectroscopy was carried out on selected polymers using a Perkin Elmer Spectrum One fourier transform infra red (FTIR) spectrometer. We conducted gel permeation chromatography (GPC) using a 1100 series Agilent HPLC system equipped with a refractive index detector (Agilent 1313A). Manual injection of 50 μ L sample (Rhyodyne valve) was used onto an Aquagel-OH 30 column (Polymer Labs, USA) kept at 30° C, isocratically loaded with 1.0 mL/min deionized water (mobile phase) with a phosphate buffer. We also had a few of the same polymer samples investigated at Warwick University, U.K., on a PL GPC 50 Integrated GPC system with a PL-AS RT autosampler and a Varian 390-LC detector suite with differential refractive index (DRI). Three mixed D, 5 μ m columns (one guard and two main) were used at 50° C with a dimethylformamide (DMF) flow rate of 1.0 mL/min. Molecular weights obtained were relative to polymethyl methacrylate standards using a refractive index detector.

1-Isobutylsuccinic anhydride

A total of 100 mL dry methanol was placed in a stirred three-neck flask under nitrogen. Sodium (2.00 g, 86.9 mmol) was added in pieces until the solution began to reflux. Triethyl 1,1,2-ethanetricarboxylate (17.18 g, 69.85 mmol) was added and the solution stirred for 20 min at 50–60° C. Then, isobutyl bromide (11.905 g, 86.9 mmol) was added and the solution refluxed for 16 h. Most of the methanol was distilled off and 150 mL distilled water added to the residue. The mixture was extracted with three portions of diethyl ether (50 mL each) and dried over MgSO₄. The solvent was then removed to leave a pale yellow oil of the isobutyl triester. Concentrated hydrochloric acid (50 mL) was added and the mixture refluxed for 3 days. The solution was cooled to 5° C and the white crystals of 1-isobutylsuccinic acid filtered off and dried overnight. Yield 7.045 g (64.7%). All the 1-isobutylsuccinic acid was refluxed in acetic anhydride (50 mL) for 6 h. The solvent was removed on a rotary evaporator and then on a high vacuum line to leave pure 1-isobutylsuccinic anhydride as a pale yellow oil, 6.31 g (99%). The ¹H- and ¹³C-NMR data agreed with the literature values.⁶⁵

Preparation of poly(ester amide) PEA39

HHPA (4.787 g, 31.09 mmol) was added slowly to a mixture of melted diisopropanolamine (1.772 g, 13.32 mmol) and 3,3-iminobis(*N,N*-dimethylpropyl-amine) (4.150 g, 22.20 mmol) under nitrogen. An exothermic reaction takes place and the viscous liquid was stirred at 170–180°C for 16 h. A gentle flow of nitrogen gas was used after 1–2 h to ensure removal of all the formed water. The viscous pale brown liquid was cooled to room temperature to give a glassy mass of the polymer in quantitative yield. Other polymers were prepared similarly.

Apparatus for the measurement of cloud points

A total of 10 mL of a 1 wt % solution of the polymer was placed in a large test tube, which was placed in a stirred oil bath on a heat regulator. The oil bath was heated at ca. 1°C/min but near the cloud point it was heated at ca. 0.2°C/min (Cloud point work on PNIPAM at 10 mg/mL has shown that increasing the heating rate from 0.1°C/min to 5°C/min increased the observed cloud point by only about 0.5°C).⁶⁸ The cloud point was determined as the temperature at which the first sign of appreciable turbidity was detected, which was observed as a large and sharp change.⁶⁹ The solution was cooled below the cloud point and the solution reheated and the cloud point determined again. The repeated cloud point values were all within 60.5°C of the first values. Using light scattering as the detection method, the change in signal intensity from 0–90% is often within the range of 1°C and different research groups choose different percentage changes in signal intensity to determine the LCST, some choosing 10%, some 50%. For our study, it was not critical to obtain extremely accurate LCST measurements but to demonstrate to a value of approximately 60.5°C the changes in LCST that can be accomplished by varying the structure of hyperbranched polyesteramides. In one study on PNIPAM solutions, differential scanning calorimetry, optical cloud point, and UV turbidimetry gave comparable LCST values, provided that the time scale of the experiments was large enough to ensure close to equilibrium conditions.⁷⁰

RESULTS AND DISCUSSION

Table I lists the poly(ester amide)s that were synthesized, their calculated molecular weights, and their observed cloud points in pure water at a concentration of 10 mg/mL. IR spectroscopy was carried out on selected polymers. In all cases, this showed typical stretching vibrations for C=O from the amide or ester groups at 1720–1620 cm⁻¹ bands to be found in the hyperbranched poly(ester amide)s. Most of the vibration adsorption bands of the C=O of the ester group are at 1740–1720 cm⁻¹. Therefore, we attribute the band at 1640–1620 cm⁻¹ to the C=O from amide groups.⁷¹

As observed previously, using low values of “*n*” (see also “Introduction” Section) in the monomer ratios, the polymer is a manageable viscous liquid at elevated temperatures but at high values of “*n*” the polymerization mixture becomes an unmanageable solid with possible incomplete polymerization due to the lack of stirring.⁵⁷ The molecular weight will increase as “*n*” in the monomer ratios $n : n + 1$ or $n : n + 2 : 2n + 1$ increases and from this theoretical molecular weight values can be calculated. Polymerizations were conducted for ~ 16 h at 170–180°C to ensure complete polymerization and removal of water had taken place, although the literature suggest that 4–6 h is normally adequate.^{58,67}

Size exclusion chromatography (or GPC) is often not very helpful in determining molecular weights of hyperbranched polymers because calibration standards for this analysis technique, such as polystyrenes or polyethyleneglycols, are linear polymers, whereas our polymers are hyperbranched and of low molecular weight.⁵⁹ Workers at DSM found that the measured number-average molecular weights (M_n) using GPC analysis of their poly(ester amide)s based on diisopropanolamine and hexahydrophthalic anhydride were lower than those based on theoretical calculations when using ratios of 1.15 to 1.10, which gives molecular weights in the same window as we have used.⁵⁷ However, at ratios of 1.5 to 1.2, which gives lower molecular weight polymers, the measured M_n values were higher than the calculated values. We observed a similar result with related poly(ester amide)s using poly(methyl methacrylates) in DMF as calibrants and solvent, respectively. The workers at DSM used tetrahydrofuran (THF) as solvent and linear polystyrene as standard calibrant, respectively. These results are in accordance with what would be expected for an average increasingly branched structure. We have conducted GPC analysis on a selection of our polymers and a similar trend was found. The results are given in Table II. The same general trend was observed using both GPC methods described in the experimental section, using calibrants going down to around 800 Da.

The difficulty in characterization by NMR of hyperbranched poly(ester amide)s, such as this and other classes, has been discussed previously.⁷² The original inventors of this class of poly(ester amide)s did not use NMR either for polymer characterization, but for determining the polymerization mechanism. ¹H- and ¹³C-NMR spectra of the polymers has been taken and although it is possible to show that starting materials have been used up, it is not possible to determine whether 100% polymerization to the expected theoretical molecular weights has been obtained because the peaks are so broad.

At temperatures above the cloud point (LCST), intermolecular and intramolecular hydrogen-bonding, such as between C=O and N-H groups within the poly(ester amide)s, may cause a transition to a collapsed or aggregated polymer conformation leading to its insolubility in water. In all, 45 polymers were prepared with a wide range of observed cloud points. This behavior and mechanism has been proposed for other amide-containing thermoresponsive polymers such as poly(*N*-isopropylacrylamide).⁷³ For the simplest polymers, PEA01-04, made from succinic anhydride and diisopropanolamine the cloud point varies from about 45 to 55 °C increasing with “*n*” in the monomer ratio and therefore also the molecular weight. The same trend of increasing cloud point with increasing molecular weight is seen for polymers PEA11-14 made from 1-methylsuccinic anhydride and diisopropanolamine. For these two polymer series, the number of peripheral hydroxyl groups increases with increasing molecular weight with less increase in the number of small hydrophobic methyl groups derived from the 1-methylsuccinic anhydride or diisopropanolamine. For polymers PEA05 and PEA06, the cloud point drops with increasing polymer molecular weight, indicating that the increase in the number of cyclic ether groups from the peripheral morpholine groups does not give the polymer sufficient hydrophilicity to increase the cloud point. For polymers PEA38-40, we observed a similar trend with the cloud point decreasing with increasing molecular weight. In the case, the increase in the number of large cyclohexyl hydrophobic groups in the polymer now has more effect than the increase in peripheral dimethylamino groups.

For a series of polymers at constant monomer ratio, we found a decrease in cloud point as the size of the hydrophobic group attached to the succinyl units increased. Examples are PEA03, which has a higher cloud point than PEA13, and the series PEA10, PEA16, PEA25, PEA27, PEA31, and PEA34, which show decreasing cloud points as the hydrophobic groups become larger. Increasing hydrophobicity can also be accomplished by placing an extra methylene group in the succinyl chains by using glutaric anhydride. The additional hydrophobicity of the methylene group lowers the polymer cloud point as judged by PEA03 versus PEA18 and by PEA06 versus PEA17. However, if the extra methylene group in the glutaric units is exchanged with an oxygen atom to provide diglycolic units, the cloud is significantly raised. For example, no cloud point was observed for polymer PEA20 up to 100 °C, whereas the equivalent polymer PEA03 made with succinic anhydride instead of diglycolic anhydride had a cloud point of 54 °C.

TABLE I
Cloud Points (T_{cl}) of Poly(ester amide)s as 10 mg/mL Solutions in Pure Water

| Polymer | Anhydride | Alkanol amine | Imine | Monomer Ratio | Theoretical M_n | T_{cl} (°C) |
|--------------------|--------------|---------------|--------------|---------------|-------------------|---------------|
| PEA01 | SA | DIPA | | 3 : 4 | 728 | 45 |
| PEA02 | SA | DIPA | | 5 : 6 | 1136 | 50 |
| PEA03 | SA | DIPA | | 7 : 8 | 1548 | 54 |
| PEA04 | SA | DIPA | | 9 : 10 | 1960 | 55 |
| PEA05 | SA | DIPA | Morpholine | 7 : 3 : 5 | 1318 | 36 |
| PEA06 | SA | DIPA | Morpholine | 9 : 4 : 6 | 1684 | 33 |
| PEA07 | SA | DIPA | Pyrrolidine | 9 : 4 : 6 | 1588 | 16 |
| PEA08 | SA | DIPA | Diethylamine | 9 : 4 : 6 | 1600 | <0 |
| PEA09 | SA | DIPA | MePiperazine | 9 : 4 : 6 | 1762 | >100 |
| PEA10 | SA | DIPA | IBDMPA | 7 : 3 : 5 | 1818 | 98 |
| PEA11 | MSA | DIPA | | 3 : 4 | 866 | 21 |
| PEA12 | MSA | DIPA | | 5 : 6 | 1206 | 25 |
| PEA13 | MSA | DIPA | | 7 : 8 | 1646 | 26 |
| PEA14 | MSA | DIPA | | 9 : 10 | 2086 | 27 |
| PEA15 | MSA | DIPA | MePiperazine | 7 : 3 : 5 | 1481 | 62 |
| PEA16 | MSA | DIPA | IBDMPA | 7 : 3 : 5 | 1916 | 66 |
| PEA17 | GA | DIPA | Morpholine | 9 : 4 : 6 | 1810 | 12 |
| PEA18 | GA | DIPA | | 7 : 8 | 1646 | 42 |
| PEA19 | GA | DIPA | MePiperazine | 9 : 4 : 6 | 1888 | 78 |
| PEA20 | DGA | DIPA | | 7 : 8 | 1660 | >100 |
| PEA21 | DGA | DIPA | MePiperazine | 7 : 3 : 5 | 1495 | >100 |
| PEA22 | DGA | DIPA | IBDMPA | 7 : 3 : 5 | 2030 | >100 |
| PEA23 | DGA | DIPA | Pyrrolidine | 7 : 3 : 5 | 1450 | 47 |
| PEA24 | ESA | DIPA | MePiperazine | 7 : 3 : 5 | 1679 | 36 |
| PEA25 | ESA | DIPA | IBDMPA | 7 : 3 : 5 | 2214 | 55 |
| PEA26 | <i>n</i> PSA | DIPA | IBDMPA | 5 : 2 : 4 | 1616 | 35 |
| PEA27 | <i>n</i> PSA | DIPA | IBDMPA | 7 : 3 : 5 | 2312 | 37 |
| PEA28 | iPSA | DIPA | IBDMPA | 5 : 2 : 4 | 1616 | 35 |
| PEA29 | iPSA | DIPA | IBDMPA | 7 : 3 : 5 | 2312 | 35 |
| PEA30 | iPSA | DIPA | MePiperazine | 7 : 3 : 5 | 1667 | 20 |
| PEA31 | iBSA | DIPA | IBDMPA | 7 : 3 : 5 | 2210 | 29 |
| PEA32 | CyPeSA | DIPA | IBDMPA | 7 : 3 : 5 | 2294 | 26 |
| PEA33 | PhSA | DIPA | IBDMPA | 7 : 3 : 5 | 2350 | 21 |
| PEA34 | OSA | DIPA | IBDMPA | 7 : 3 : 5 | 2600 | 19 |
| PEA35 | THPA | DIPA | IBDMPA | 5 : 2 : 4 | 1612 | 40 |
| PEA36 | THPA | DIPA | IBDMPA | 7 : 3 : 5 | 2182 | 34 |
| PEA37 | HHPA | DIPA | MePiperazine | 7 : 3 : 5 | 1847 | <0 |
| PEA38 | HHPA | DIPA | IBDMPA | 5 : 2 : 4 | 1626 | 37 |
| PEA39 | HHPA | DIPA | IBDMPA | 7 : 3 : 5 | 2196 | 34 |
| PEA40 | HHPA | DIPA | IBDMPA | 9 : 4 : 6 | 2788 | 32 |
| PEA41 ^a | HHPA | DIPA | IBDMPA | 7 : 3 : 5 | 2356 | >100 |
| PEA42 | MHHPA | DIPA | IBDMPA | 5 : 2 : 4 | 1692 | 25 |
| PEA43 | MHHPA | DIPA | IBDMPA | 7 : 3 : 5 | 2294 | 20 |
| PEA44 | NDCA | DIPA | IBDMPA | 9 : 4 : 6 | 2878 | 16 |
| PEA45 | MNDCA | DIPA | IBDMPA | 9 : 4 : 6 | 3004 | <0 |

IBDMPA, 3,3-iminobis(*N,N*-dimethylpropylamine); DIPA, diisopropanolamine; MePiperazine, 1-methylpiperazine; SA, succinic anhydride; DGA, diglycolic anhydride; GA, glutaric anhydride; MSA, 1-methylsuccinic anhydride; ESA, 1-ethylsuccinic anhydride; *n*PSA, *n*-propylsuccinic anhydride; iPSA, 1-isopropylsuccinic anhydride; iBSA, 1-isobutylsuccinic anhydride; CyPeSA, 1-cyclopentylsuccinic anhydride; PhSA, 1-phenylsuccinic anhydride; OSA, 1-oct-2-ene-succinic anhydride; HHPA, *cis*-1,2-cyclohexane-dicarboxylic anhydride; THPA, *cis*-1,2-cyclohex-4-ene-dicarboxylic anhydride; MHHPA, 3-methyl-*cis*-1,2-cyclohexane-dicarboxylic anhydride; NDCA, norbornene-2,3-dicarboxylic anhydride; MNDCA, methyl-5-norbornene-2,3-dicarboxylic anhydride.

^a Amine oxide of PEA39.

TABLE II
Theoretical and Measured (GPC) Molecular Weights of Selected Poly(ester amide)s

| Polymer | Anhydride | Alkanol amine | Imine | Monomer Ratio | Theoretical M_n | Measured M_n |
|---------|-----------|---------------|-------------|---------------|-------------------|----------------|
| PEA01 | SA | DIPA | | 3 : 4 | 728 | 940 |
| PEA02 | SA | DIPA | | 5 : 6 | 1136 | 1210 |
| PEA03 | SA | DIPA | | 7 : 8 | 1548 | 1650 |
| PEA04 | SA | DIPA | | 9 : 10 | 1960 | 1810 |
| PEA07 | SA | DIPA | Pyrrolidine | 9 : 4 : 6 | 1588 | 1670 |
| PEA10 | SA | DIPA | IBDMPA | 7 : 3 : 5 | 1818 | 1730 |
| PEA11 | MSA | DIPA | | 3 : 4 | 866 | 1010 |
| PEA12 | MSA | DIPA | | 5 : 6 | 1206 | 1540 |
| PEA13 | MSA | DIPA | | 7 : 8 | 1646 | 1670 |
| PEA14 | MSA | DIPA | | 9 : 10 | 2086 | 1880 |
| PEA38 | HHPA | DIPA | IBDMPA | 5 : 2 : 4 | 1626 | 1590 |
| PEA39 | HHPA | DIPA | IBDMPA | 7 : 3 : 5 | 2196 | 1960 |
| PEA40 | HHPA | DIPA | IBDMPA | 9 : 4 : 6 | 2788 | 2160 |
| PEA42 | MHHPA | DIPA | IBDMPA | 5 : 2 : 4 | 1692 | 1770 |
| PEA43 | MHHPA | DIPA | IBDMPA | 7 : 3 : 5 | 2294 | 1840 |

IBDMPA, 3,3-iminobis(*N,N*-dimethylpropylamine); DIPA, diisopropanolamine; SA, succinic anhydride; MSA, 1-methylsuccinic anhydride; HHPA, cis-1,2-cyclohexane-dicarboxylic anhydride; MHHPA, 3-methyl-cis-1,2-cyclohexane-dicarboxylic anhydride.

By varying the size of the hydrophobic group on the anhydride monomer and the hydrophilicity of the peripheral groups of the polymer derived from the imine as well as the molecular weight, one can tune the polymer cloud point to be at physiological temperatures of $\sim 35\text{--}38^\circ\text{C}$. Examples are PEA05, PEA24, PEA27-28, and PEA38. For KHIs in highly saline brines, the requirement is a polymer with hydrophobic groups, usually adjacent to amide groups, but with a cloud point above the hydrate formation temperature which can be about $12\text{--}20^\circ\text{C}$. A preferred hydrophobic group is that found in polymers PEA37-41 derived from HHPA. The only imine we found that would make such polymers with water-solubility even at room temperature was 3,3-iminobis(*N,N*-dimethylpropylamine). Depending on the molecular weight, these polymers, PEA38-40, had cloud points in the range $32\text{--}37^\circ\text{C}$. However, we found that in 10 wt % NaCl solutions the cloud point of these polymers drops to below 0°C . We further found two ways to raise the cloud point of this polymer class. First, all the peripheral dimethylamino groups could be derivatized to dimethylamineoxide groups by simple reaction with the stoichiometric amount of hydrogen peroxide. Polymer PEA41 is an example of this that we synthesized from PEA39. No cloud point is observed with PEA41 in pure water but in 10 wt % NaCl the cloud point is 30°C , well above hydrate formation temperatures. Thus, dimethylamineoxide groups have higher hydrophilicity compared with dimethylamino groups. The same derivation procedure could be carried out for other polymers containing hydrophobic anhydride monomers.

Another way to raise the cloud point of polymers with peripheral amino groups is to quaternize the groups to produce a cationic polymer. The simplest way is to protonate the dimethylamino groups using a Brønsted acid, but quaternization by reaction with alkyl halides could also be carried out. For example, if polymer PEA39 is derivatized to the hydrochloride salt by reaction with hydrochloric acid, the resulting quaternized polymer shows no cloud point in 10 wt % NaCl up to 100°C . We investigated the change in cloud point as a function of pH for some polymers with peripheral amino groups. Examples are given in Figure 5 for polymers PEA34 and PEA42. The cloud point increases as the pH drops and the amino groups become partially quaternized until at and below about pH 6.3 a cloud point is no longer observed.

We also investigated the variation in cloud point with polymer concentration. Examples for polymers PEA15, PEA24, and PEA30 are shown in Figure 6. Here, we see that as the polymer concentration is increased from 1 wt % to 20-30 wt %, the cloud point increases. PEA15 shows the most dramatic cloud point increase, reaching to over 100°C at a polymer concentration of 21 wt %, from an initial cloud point of 62°C at 1 wt % polymer concentration. This effect of increasing cloud point with increasing polymer concentration was observed with all the polymers investigated. These results can be rationalized that as the polymer concentration increases, there is a concomitant decrease in water-polymer hydrogen-bonding interactions. However, studies on other polymer classes, such as 2-(2-methoxyethoxy)ethyl methacrylate copolymers, have shown that the cloud point may decrease at increasing polymer concentrations.²⁹ This article also reports another way to vary the LCST by incorporating polyglycol chains into the polymer side chains. This could also be applied to poly(ester amide)s by reaction of peripheral amine groups with ethylene oxide or using bis-ethoxylated diisopropanolamines but this was not investigated in this study.

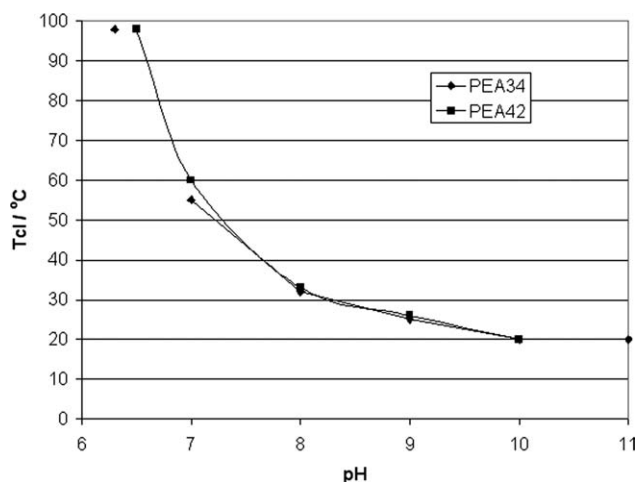


Figure 5 Variation of cloud point (T_{cl}) with pH for a 10 mg/mL solution of poly(ester amide)s PEA34 and PEA42.

Finally, as there are few studies reported on the cloud point (or LCST) of hyperbranched polymers, we investigated the cloud point of the poly(ester amide)s in a few salt solutions to determine if they conformed to the Hofmeister series.⁷⁴ The results are given in Figures 7 and 8 for polymers PEA03 and PEA10. These figures show that cloud points drop as the concentration of the salts sodium chloride or sodium sulfate increase. However, for calcium chloride, we observed higher cloud points for the polymers than with the sodium salts at all but the lowest concentrations investigated. As the higher calcium chloride concentration was increased above about 5 wt %, the polymer cloud points decreased somewhat, but then increased at very high salts concentrations above 10–20 wt % depending on the polymer.

Ions can be classified into a Hofmeister series according to their hydrated radius and salting-out strength.^{75–78} In general, monovalent anions have less effect on the cloud point than divalent anions. This was confirmed for both polymers in that sodium sulfate had a much bigger effect at lowering the cloud point than sodium chloride at equivalent salt concentrations. Divalent cations are known to have less salting-out effect on polymers than monovalent cations.^{79,80} This was confirmed by our studies on hyperbranched poly(ester amide)s. The cloud point of PEA03 or PEA10 decreased in solutions of calcium chloride but not as significantly as in sodium chloride solutions at equivalent concentrations. An interesting observation was that the cloud point of both polymers actually increased at very high Ca^{2+} concentrations. We have also observed this behavior for other classes of polymer including some *N*-vinyl lactam polymers and amide derivatives of maleic anhydride copolymers.⁸¹ We speculate that this is because of Ca^{2+} -polymer interactions becoming favorable at high concentrations making the polymer more hydrophilic. The higher cloud points in calcium chloride brines may make the polymers suitable as KHIs in calcium chloride-based drilling or completion fluids, which often have a high pH and would not have peripheral quaternized amino groups to help the water-solubility.^{82–84}

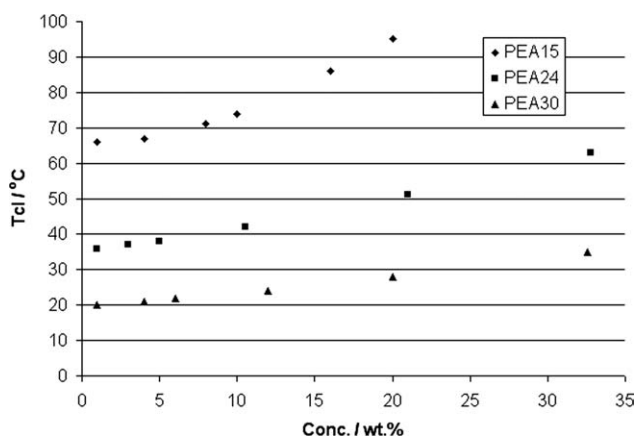


Figure 6 Variation of cloud point with polymer concentration in water for PEA15, PEA24, and PEA30.

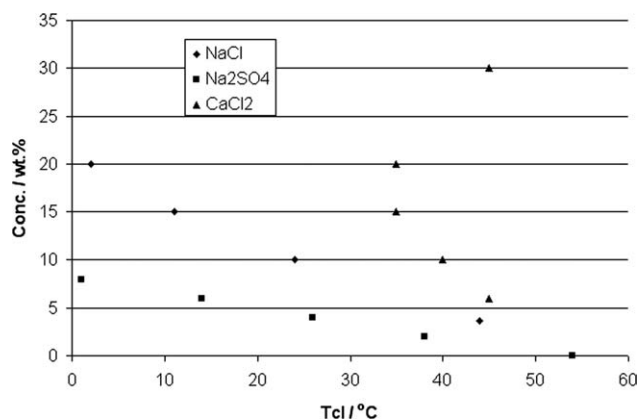


Figure 7 Cloud points of 10 mg/mL of poly(ester amide) PEA03 at pH 7 in three different salt solutions at varying salt concentrations.

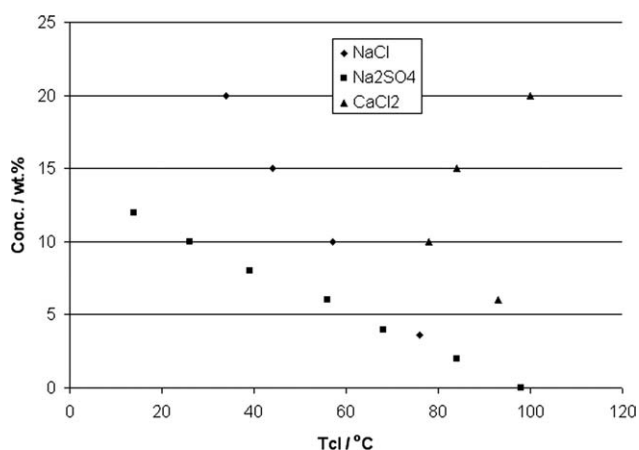


Figure 8 Cloud points of 10 mg/mL of poly(ester amide) PEA10 at pH 9 in three different salt solutions at varying salt concentrations.

CONCLUSIONS

We have demonstrated that hyperbranched poly-(ester amide)s based on diisopropanolamine can be tuned in several ways to obtain thermoresponsive polymers with LCSTs near physiological temperatures. For example, the size of the hydrophobic groups on succinic anhydride can be varied or the peripheral groups on the polymer can be adjusted. Conversion of peripheral tertiary amine groups into amine oxide or quaternary ammonium groups can drastically increase the polymer cloud point making it possible to use this class of hyperbranched poly(ester amide)s as KHIs in high salinity fluids.

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References

1. Choi, C.; Young Chae, S.; Nah, J.-W. *Polymer* 2006, 47, 4571.
2. Hoffman, A. S.; Stayton, P. S. *Macromol Symp* 2004, 207, 139.
3. Schmaljohann, D. *Adv Drug Delivery Rev* 2006, 58, 1655.
4. Haraguchi, K.; Li, H. J. *Angew Chem Int Ed Engl* 2005, 44, 2.
5. Yu Galaev, I.; Mattiasson, B. *Enzyme Microb Technol* 1993, 15, 354.
6. Zhu, P. W. *J Mater Sci: Mater Med* 2004, 15, 567.
7. Lokuge, I.; Wang, X.; Bohn, P. W. *Langmuir* 2007, 23, 305.
8. Wu, G.; Li, Y.; Han, M.; Liu, X. *J Membr Sci* 2006, 283, 13.
9. Hamamoto, H.; Suzuki, Y.; Yamada, Y. M. A.; Tabata, H.; Takashi, H.; Ikegami, S. *Angew Chem Int Ed Engl* 2005, 44, 4536.
10. Ebara, M.; Hoffman, J. M.; Hoffman, A. S.; Stayton, P. S. *Lab Chip* 2006, 6, 843.
11. Hoffman, A. S. *J Controlled Release* 1987, 6, 297.
12. Alarcon, C. D. H.; Pennadam, S.; Alexander, C. *Chem Soc Rev* 2005, 34, 276.
13. Ono, Y.; Shikata, T. *J Am Chem Soc* 2006, 128, 10030.
14. Okada, Y.; Takada, F. *Macromolecules* 2005, 38, 4465.
15. Schild, H. G. *Prog Polym Sci* 1992, 17, 163.
16. Xue, W.; Huglin, M. B.; Jones, T. G. J. *Macromol Chem Phys* 2003, 16, 1956.
17. Kirsh, Y. E.; Yanul, N. A.; Popkov, Y. M. *Eur Polym J* 2002, 38, 403.
18. Schmitz, S.; Ritter, H. *Macromol Rapid Commun* 2007, 28, 2080.
19. Kelland, M. A.; Svartaas, T. M.; Øvsthus, J.; Namba, T. In *3rd International Conference on Gas Hydrates; Annals of the New York Academy of Science: New York, 2000; Vol. 912, p 281.*
20. Kirsh, Y. E.; Yanul, N. A.; Kalninh, K. K. *Eur Polym J* 1999, 35, 305.
21. Wiesbrock, F.; Hoogenboom, R.; Leenen, M.; van Nispen, S. F. G. M.; van der Loop, M.; Abeln, C. H.; van den Berg, A. M. J.; Schubert, U. S. *Macromolecules* 2005, 38, 7957.
22. Park, J.-S.; Kataoka, K. *Macromolecules* 2007, 40, 3599.
23. Malmsten, M.; Lindman, B. *Macromolecules* 1992, 25, 5440.
24. Aoshima, S.; Sugihara, S. *J Polym Sci Part A: Polym Chem* 2000, 38, 3962.
25. Sugihara, S.; Kanaoka, S.; Aoshima, S. *Macromolecules* 2005, 38, 1919.
26. Jana, S.; Rannard, S. P.; Cooper, A. I. *Chem Commun* 2007, 2962.
27. Jia, Z.; Chen, H.; Zhu, X.; Yan, D. *J Am Chem Soc* 2006, 128, 8144.
28. Boyer, C.; Whittaker, M. R.; Luzon, M.; Davis, T. P. *Macromolecules* 2009, 42, 6917.

29. Lutz, J.-F.; Akdemir, Ö.; Hoth, A. *J Am Chem Soc* 2006, 128, 13046.
30. Jiang, X.; Smith, M. R., III; Baker, G. L. *Macromolecules* 2008, 41, 318.
31. Seiler, M. *Fluid Phase Equilib* 2006, 241, 155.
32. Mishra, M. K.; Kobayashi, S. *Star and Hyperbranched Polymers*; Marcel Dekker: New York, 1999.
33. Newkome, G. R.; Moorefield, C. N.; Vogtle, F. *Dendrimers and Dendrons*; Wiley-VCH: Weinheim, 2001.
34. Frechet, J. M. J.; Tomalia, D. A. *Dendrimers and Other Dendritic Polymers*; Wiley: New York, 2001.
35. Kim, Y. H. *J Polym Sci Part A: Polym Chem* 1998, 36, 1685.
36. Voit, B. *J Polym Sci Part A: Polym Chem* 2000, 38, 2505.
37. Jikei, M.; Kakimoto, M. *Prog Polym Sci* 2001, 26, 1233.
38. Jikei, M.; Kakimoto, M. *J Polym Sci Part A: Polym Chem* 2004, 42, 1293.
39. Voit, B. *J Polym Sci Part A: Polym Chem* 2005, 43, 2679.
40. Yates, C. R.; Hayes, W. *Eur Polym J* 2004, 40, 257.
41. Jiang, G.; Chen, W.; Xei, W. *Des Monomers Polym* 2008, 11, 105.
42. Haxton, K. J.; Burt, H. M. *Dalton Trans* 2008, 5872.
43. Kaanumalle, L. S.; Nithyanandhan, J.; Pattabiraman, M.; Jayaraman, N.; Ramamurthy, V. *J Am Chem Soc* 2004, 126, 8999.
44. Haba, Y.; Kojima, C.; Harada, A.; Kono, K. *Angew Chem Int Ed Engl* 2007, 46, 234.
45. Swarts, J. C. *Angew Makromol Chem* 1993, 207, 123.
46. Machado, M.; de, L. *Angew Makromol Chem* 1992, 195, 35.
47. Garamus, V. M.; Maksimova, T.; Richtering, W.; Aymonier, C.; Thomann, R.; Antonietti, L.; Mecking, S. *Macromolecules* 2004, 37, 7893.
48. Chen, H.; Jia, Z. F.; Yan, D. Y. *Acta Polym Sin* 2007, 11, 1097.
49. Malmström, E.; Hult, A. *Macromolecules* 1996, 29, 1222.
50. Malmström, E.; Johansson, M.; Hult, A. *Macromolecules* 1995, 28, 1698.
51. Liu, Y.; Chen, Y.; Shen, Z. *J Polym Sci Part A: Polym Chem* 2007, 4, 1177.
52. Li, X.; Zhan, J.; Li, Y. *J Am Chem Soc* 2004, 37, 7584.
53. Bonacucina, G.; Ponchel, G.; Ringard, C.; Palmieri, G. F.; Gros-siord, J.-L. *J Drug Delivery Sci Technol* 2006, 16, 59.
54. Li, W.; Zhang, A.; Chen, Y.; Feldman, K.; Wu, H.; Schlüter, A. *D. Chem Commun* 2008, 5948.
55. Luzon, M.; Boyer, C.; Peinado, C.; Corrales, T.; Whittaker, M.; Tao, L.; Davis, T. P. *J Polym Sci A: Polym Chem* 2010, 48, 2783.
56. Froehling, P. E. *J Polym Sci Part A: Polym Chem* 2004, 42, 3110.
57. Muscat, D.; Van Benthem, R. A. T. M. *Top Curr Chem* 2001, 212, 41.
58. Van Benthem, R. A. T. M.; Meijerink, N.; Geladé, E.; de Koster, C. G.; Muscat, D.; Froehling, P. E.; Hendriks, P. H. M.; Vermeulen, J. A. A.; Zwartkruis, T. J. G. *Macromolecules* 2001, 34, 3559.
59. Van Benthem, R. A. T. M. *Prog Org Coat* 2000, 40, 203.
60. Stanssens, D.; Hermanns, R.; Worries, H. *Prog Org Coat* 1993, 22, 379.
61. Klomp, U. C. U.S. Pat. 6,905,605 (2005).
62. Kelland, M. A. *Energy Fuels* 2006, 20, 825.
63. Tian, J.; Rivers, G.; Trenery, J. B. *Int. Pat. Appl. WO/2008/017,018* (2008).
64. Kelland, M.; Del Villano, L. *Chem Eng Sci* 2009, 64, 3197.
65. Porter, J. R.; Millican, T. A.; Morphy, J. R.; Beeley, N. R. A. U.S. Pat. 5,889,058 (1999).
66. Kendall, M.; Wells, R. J. *Aust J Chem* 1974, 27, 2293.
67. Van Benthem, R. A. T. M. *Int. Pat. Appl. WO/2000/056,804* (2000).
68. Bergbreiter, D. E.; Fu, H. *J Polym Sci Part A: Polym Chem* 2008, 46, 186.
69. Kjøniksen, A.-L.; Laukkanen, A.; Galant, C.; Knudsen, K. D.; Tenhu, H.; Nyström, B. *Macromolecules* 2005, 38, 948.
70. Boutris, C.; Chatzi, E. G.; Kiparissides, C. *Polymer* 1997, 38, 2567.
71. Madea, Y.; Sakamoto, J.; Wang, S.-Y.; Mizuno, Y. *J Phys Chem B* 2009, 113, 12456.
72. Geladé, E.; Goderis, B.; De Coster, C. G.; Meijerink, N.; Van Benthem, R. A. T. M.; Fokkens, R.; Nibbering, N. M. M.; Mortensen, K. *Macromolecules* 2001, 34, 3552.
73. You, Y. Z.; Zhou, Q.-H.; Manickam, D. S.; Wan, L.; Mao, G.-Z.; Oupicky, D. *Macromolecules* 2007, 40, 8617.
74. Hofmeister, F. *Arch Exp Pathol Pharmacol* 1888, 24, 247.
75. Ninham, B. W.; Yaminsky, V. *Langmuir* 1997, 13, 2097.
76. Kunz, W.; Lo Nostro, P.; Ninham, B. W. *Curr Opin Colloid Interface Sci* 2004, 9, 1.
77. Kunz, W.; Henle, J.; Ninham, B. W. *Curr Opin Colloid Interface Sci* 2004, 9, 19.
78. Okamura, H.; Morihara, Y.; Masuda, S.; Minagawa, K.; Mori, T.; Tanaka, M. *J Polym Sci Part A: Polym Chem* 2002, 40, 1945.
79. Ataman, M. *Colloid Polym Sci* 1987, 265, 19.
80. Napper, D. H. *J Colloid Interfac Sci* 1970, 33, 384.
81. Kelland, M. A., *Chem. Eng. Sci.*, manuscript in preparation.
82. Power, D.; Slater, K.; Aldea, C.; Lattanzi, S. In *AADE National Technology Conference, AADE-03-NTCE-48*, Houston, TX, April 1–3, 2003.
83. Dzialowski, A.; Patel, A.; Nordbo, K. In *Proceedings of the Offshore Mediterranean Conference and Exhibition, Ravenna, Italy, March 28–30, 2001*.
84. Kelland, M. A.; Mønig, K.; Iversen, J. E.; Lekvam, K. *Energy Fuels* 2008, 22, 2405.