Novel Associative Polymer Networks Based on Cyclodextrin Inclusion Compounds

Xuhong Guo,[†] Ahmed A. Abdala,[†,||] Bruce L. May,[‡] Stephen F. Lincoln,[‡] Saad A. Khan,[§] and Robert K. Prud'homme*[,†]

Department of Chemical Engineering, Princeton University, Princeton, New Jersey 08544; Departmant of Chemistry, University of Adelaide, Adelaide, SA 5005, Australia; and Department of Chemical Engineering, North Carolina State University, Raleigh, North Carolina 27695-7905

Received January 12, 2005

Introduction

There has been considerable interest in exploiting specific interactions to drive macromolecular self-assembly. DNA complementarity[1] and polypeptide helix formation[2,3] have been used to produce three-dimensional structures and biomaterials. Polysaccharides have also been employed to create tailored supramolecular structures.[4−7] For example, polysaccharide interactions are the basis for many applications in foods,[8−11] and biomolecular recognition often involves polysaccharide−protein interactions.[11,12] Supramolecular assemblies based on polysaccharides have recently attracted considerable attention.[13−15] Cyclodextrins (CDs) are one example of materials that have been used to create novel supramolecular structures.[4−7]

Cyclodextrins are ringed structures with 6, 7, or 8 dextrose units (α-, *β*-, and *γ*-CD, respectively). The central cavity is hydrophobic and can specifically bind hydrophobic species to form "inclusion compounds".[4,5] The inclusion interactions of CDs with hydrophobic guest molecules have been widely studied.[4−7,16,17] However, if cyclodextrins and hydrophobic groups are incorporated onto two different polymer chains and mixed, polymer networks will be formed due to inclusion interactions that involve only binary interactions.[18−21]

The first studies of rheology modification and self-assembly between CD bearing chains and hydrophobically modified chains appear to be that of Gosselet,[21] who looked at association between a side-chain hydrophobically modified dimethylacrylamide (DMA)/hydroxyethyl methacrylate (HEMA) copolymer and a copolymer of CD and epichlorhydrin (EP). They observed specific viscosity enhancement of 10-fold and for some ratios uncontrolled gelation. The weight fraction of CD in the CD/EP polymers were on the order of 50%, and the hydrophobic substitution levels on the hm-DMA/HEMA were 0.6−5%. The results are encouraging, but the mismatches in molecular weights of the polymers and the mismatches in CD/HM ratios make it difficult to understand the stoichiometry of assembly or to develop a theory of association.

Associative thickeners based on water-soluble polymers with terminal hydrophobes or multiple hydrophobes pendant along the backbone have made substantial inroads in the coatings, cosmetics, and pharmaceutical industries.[22−26] They provide fluids with tunable viscosities, diffusion characteristics, and relaxation times without undesirable effects associated with elongational thickening.[27−29] The theory of associative polymers has also developed significantly over the past decade. While the theories capture the qualitative features of the systems, a quantitative comparison between theory and experiment has not been possible because tractable theories have had to incorporate only binary associative interactions.[30−34] But fluorescence measurements indicate the hydrophobic associative groups form clusters with 10−30 groups per junction (see Figure 1a), and the number of groups in the junction changes with the overall polymer concentration.[25,35,36]

In this paper we present a new associative polymer system based on inclusion interactions between hydrophobes and cyclodextrins (Figure 1b) that not only produces tunable rheology and higher viscosities than purely hydophobically modified polymers but also provides a model network for quantitative comparisons with theory. We describe the synthesis of a novel associative polymer system based on mixtures of CD-modified and hydrophobically-modified (HM) water-soluble polymer chains. The cyclodextrin inclusion is strictly binary, and its strength can be tuned by the choice of CD and hydrophobic species. The inclusion interactions lead to stronger associations and higher solution viscosities than purely hydrophobic interactions at the same polymer concentration. The disruption of the association between hydrophobically modified poly(acrylic acid) by free cyclodextrin occurs at approximately a stoichiometric ratio of cyclodextrin to hydrophobe. This and the fact that the viscosity maximum for the mixed CD-polymer:HM-polymer occurs at a stoichiometric ratio of cyclodextrin-to-hydrophobe indicates that the network involves binary associations. The ability to mask the hydrophobe interactions with cyclodextrins and to "unmask" them by enzymatic removal of the cyclodextrins may provide novel routes to fluids with triggered rheological responses. The binary nature of the interactions also makes the system ideally suited to test the predictions of theories for the statics and dynamics of associative fluids.

Experimental Section

Materials. Poly(acrylic acid) (PAA) (M_w = 250 kg/mol, $M_w/M_n \approx 2$) was purchased from Aldrich. Octadecylamine (97%, Aldrich), *N*-methylpyrrolidone (NMP) (99.5%, Aldrich), dicyclohexylcarbodiimide (99%, Aldrich), sodium hydroxide (97%, EM Science, NJ), methanol (99.5%, Aldrich), and α- and *β*-cyclodextrin (Wacker Biochem. Corp.) were used without further purification. The 6-amino-α-deoxy-α- and *β*-cyclodextrins were synthesized and characterized as reported previously.[37] The modified cyclodextrins were characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry that gave results identical to those published.

Modification of Poly(acrylic acid)s with Cyclodextrin Side Groups. Poly(acrylic acid)s with α- or *β*-cyclodextrin side groups (α- and *β*-CDMPAA) were obtained by the reaction of monoamino cyclodextrin with the carboxyl group of PAA in an aprotic solvent in the presence of dicyclohexylcarbodiimide (DCC). The selective acylation of the amino group in the

† Princeton University.
‡ University of Adelaide.
§ North Carolina State University.
|| Present address: Department of Chemical Engineering and Petroleum Refining, Faculty of Petroleum and Mining Engineering, Suez Canal University, Suez, Egypt.
* To whom correspondence should be addressed. E-mail: prudhomm@princeton.edu.

10.1021/ma050071o CCC: $30.25
Published on Web 03/08/2005

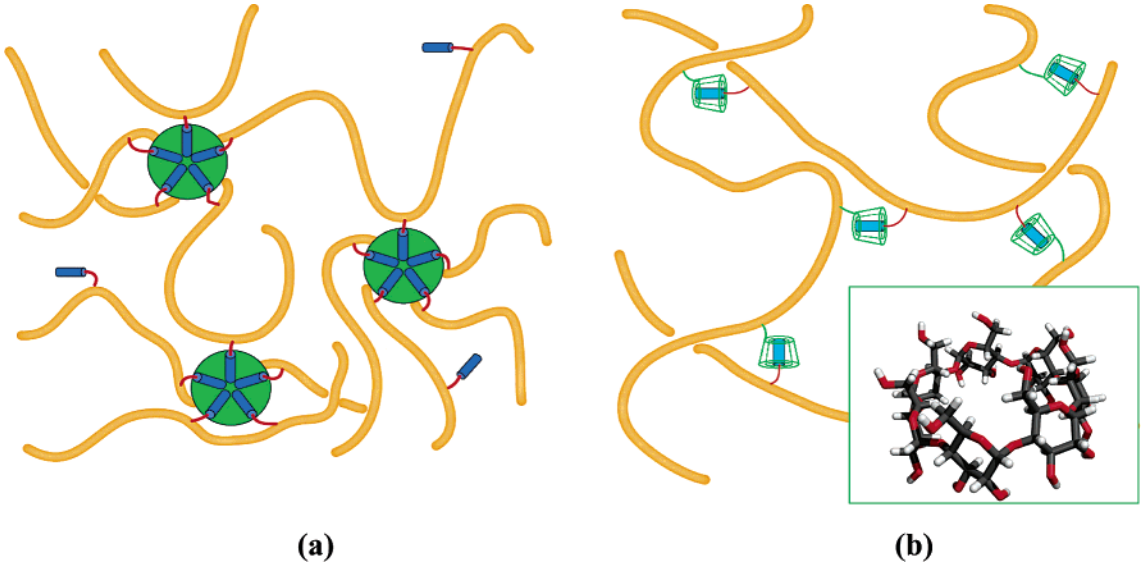

Figure 1. Schematic structures of polymer associations: (a) pure hydrophobic association; (b) polymer network generated by encapsulation (inclusion) of the hydrophobes of one polymer within the annuli of the cyclodextrins contained in another polymer. Inset shows chemical structure of β-cyclodextrin.

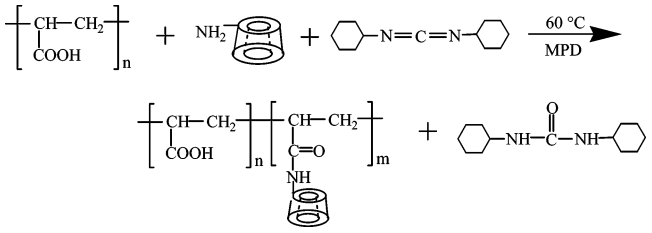

Figure 2. Synthesis of modified PAA bearing α- or β-cyclodextrin side groups.

presence of the cyclodextrin hydroxyl groups occurs because of the much greater reactivity of the primary amine under the experimental conditions (Figure 2).

In a typical run, 0.90 g (12.5 mmol of −COOH groups) of PAA of 250K was dissolved in 30 mL of NMP at 60 °C for 24 h. Then, 0.43 g (0.37 mmol) of monoamino-β-cyclodextrin (dissolved in 3.0 g of NMP) and 0.10 g (0.48 mmol) of DCC (dissolved in 2.0 g of NMP) were introduced into the PAA solution under vigorous stirring. After a reaction for 48 h at 60 °C, the system was cooled to room temperature, followed by addition of 35 mL of 40 wt % NaOH aqueous solution to precipitate the polymer. The precipitate was washed twice with 15 mL of hot NMP (60 °C) and then with 20 mL of methanol at room temperature. After filtration under vacuum, the solid product was dissolved in 12.5 mL of DI water and precipitated in 100 mL of methanol (twice).

Finally, the product was dissolved into 20 mL of DI water and dialyzed (Spectra/Por 3 tubing, molecular weight cutoff 3500 g/mol) against DI water until the conductivity of water outside the tube remained constant. The final dry product was obtained by freeze-drying after concentrating the solution to 10 wt % by evaporation.

Synthesis of Hydrophobic Modified Poly(acrylic acid). Hydrophobically modified poly(acrylic acid) (HMPAA) was synthesized following the procedure developed by Iliopoulos et al.[38−40] *n*-Octadecylamine grafting onto precursor poly(acrylic acid) is conducted using dicyclohexylcarbodiimide (DCC) in *N*-methylpyrrolidinone (NMP) as solvent. Throughout this note we will denote the modified polymer HMPAA*x*%*y*C*z*, where *x* is the mol % hydrophobic substitution, *y* is the PAA molecular weight in daltons, and *z* is the number of carbon atoms in the alkyl side group. For example, HMPAA3%250KC18 means 3 mol % carboxyl groups in PAA with molecular weight of 250K Da are substituted by *n*-octadecylamine.

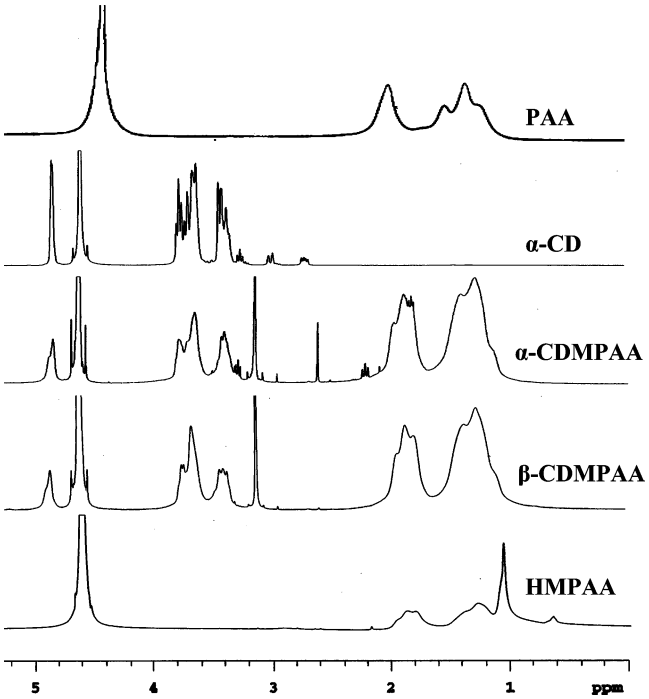

Figure 3. ^{1}H NMR spectra of PAA, cyclodextrin, and modified polymers in D_2O.

Characterization. ^{1}H NMR spectra were recorded on a Varian Inova-400 NMR spectrometer operating at 400 MHz for protons at room temperature (Figure 3). Samples were dissolved in D_2O at ca. 2 wt %. The degree of substitution for the carboxyl groups in PAA by α- or β-cyclodextrin side groups was determined according to eq 1:

$$\text{substitution (mol \%)} = \frac{\frac{A_1}{n}}{\frac{A_2}{2}} \times 100 \qquad (1)$$

where n is the number of dextrose units in cyclodextrin; A_1 and A_2 denote the peak areas of cyclodextrin at 4.85 ppm and the CH_2 peak at 1.30 ppm in ^{1}H NMR spectra (Figure 3). The

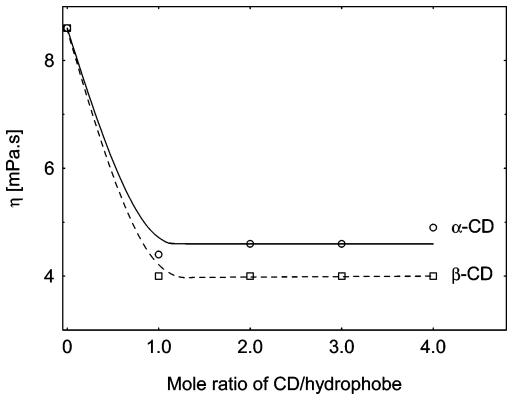

Figure 4. Viscosity as a function of molar ratio of α-CD (○) and β-CD (□) to C18 group in 0.5 wt % hydrophobically modified polymer HMPAA3%250KC18 (in 0.1 M NaCl, pH = 7) at a shear rate of 20 s^{-1}.

calculated substitution degree for α-CDMPAA and β-CDMPAA are 2.5% and 2.1%, respectively.

The hydrophobic substitution level for HMPAA3%250KC18 was determined as 3.0% from the peak areas of CH_3 group (A_3) from *n*-octadecyl side group at 0.63 ppm and CH_2 groups (A_2) from both PAA backbone (1.30 ppm) and *n*-octasdecyl side group (1.08 ppm) (Figure 3)[38] according to eq 2:

$$\text{substitution (mol \%)} = \frac{A_3}{A_2 - \frac{2mA_3}{3}} \times 100 \qquad (2)$$

where m denotes the number of CH_2 in a hydrophobic side chain, e.g., $m = 17$ for *n*-octadecyl side chain.

The steady and dynamic rheological measurements were performed on a Rheometrics DSR stress-controlled rheometer with 25 mm cone and plate geometry. The temperature was controlled to 25 ± 0.1 °C by a Peltier plate. Samples for the rheological measurements were prepared as follows: the polymer was dissolved in 0.1 M NaCl aqueous solution in order to screen the electrostatic interactions, and the pH was adjusted to 7.0 ± 0.2 using 0.2 M NaOH. The effect of pH and ionic strength on the rheology of hydrophobically modified PAA has been studied by Wang et al.[40] They observed that a viscosity maximum occurs as a function of ionic strength (η_{max} at 0.17 M NaCl) and pH (η_{max} at pH = 5). These maxima have been explained in terms of the competition between hydrophobic association and electrostatic repulsions. For this study we have chosen a fully substituted PAA-Na at a pH of 7.0 and an ionic strength of 0.1 M NaCl.

Results and Discussion

Disruption of Hydrophobically Modified Poly(acrylic acid) (HMPAA) Association by Free Cyclodextrin. Addition of α- or β-cyclodextrin to the aqueous solution of HMPAA leads to significant reduction in the solution viscosity and dynamic moduli as the free cyclodextrin sequesters hydrophobic association sites.[16,17]

Figure 4 shows the effect of adding different amounts of α- or β-cyclodextrin to 0.5 wt % HMPAA aqueous solution on the solution shear viscosity obtained at a shear rate of $\dot{\gamma} = 20\ s^{-1}$. The viscosity of precursor PAA at this shear rate is 3.9 mPa·s, and the addition of α- or β-cyclodextrin leads to 2-fold decrease in the solution viscosity (Figure 4). The viscosity reduction is due to the removal of the hydrophobic aggregation as the hydrophobic groups form inclusion compounds with cyclodextrins (cf. Figure 1b).

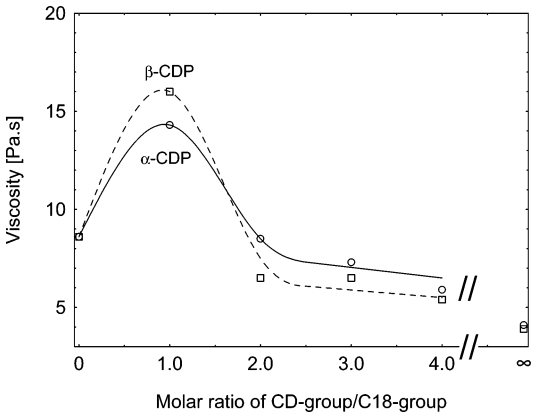

Figure 5. Viscosity as a function of molar ratio of α-CD (○) or β-CD (□) groups in 0.5 wt % modified PAA aqueous solutions to C18 group in 0.5 wt % hydrophobically modified polymer (in 0.1 M NaCl, pH = 7) at a shear rate of 20 s^{-1}.

The viscosity drops to a plateau, implying complete suppression of the hydrophobic interactions, when the molar ratio of α- or β-cyclodextrin to hydrophobic side groups reaches one. There are no other direct studies of the relative ability of α- vs β-cyclodextrin to disrupt hydrophobically modified polymer associations. Abdala et al.[17] quantified precipitates formed by α- and β-cyclodextrin interacting with hydrophobic "macromonomers" that were not part of a polymer chain. α-Cyclodextrin was found to precipitate a greater amount of macromonomers from solution, but there is no direct link between this precipitation and solution viscosity. Karlson et al. studied the effects of α-methylcyclodextrin, β-cyclodextrin, and β-methylcyclodextrin on the viscosity of hydrophobically modified hydroxylethylcellulose solutions and showed a reduction in viscosity with added cyclodextrin.[16]

Binary Macromolecular Association between Cyclodextrin-Modified Poly(acrylic acid) (CDMPAA) and HMPAA. When the cyclodextrin is a component of the polymer chain, rather than free in solution, then key-in-lock structures are formed. A synergetic effect is observed upon addition of 0.5 wt % α- or β-CDMPAA to 0.5 wt % HMPAA solution (Figure 5). Note that the viscosities of 0.5 wt % α- and β-CDMPAA are 4.1 and 3.9 mPa·s, respectively. The viscosity increases upon mixing resulting from the association of the two polymers types by inclusion of hydrophobic alkyl side groups (C18) into α- or β-cyclodextrin cavities (Figure 1b).

Figure 4 shows a maximum in the shear viscosity at a molar ratio of cyclodextrin to alkyl groups (C18:CD) of 1:1. At this ratio, the majority of hydrophobic groups on HMPAA are involved in a 1-to-1 association with α- or β-cyclodextrin group on CDMPAA. The decrease in the solution viscosity at CDMPAA/HMPAA ratio higher than 1 is due to the fact that the viscosity of the nonassociating CDMPAA is less than one-half of the viscosity of HMPAA, which has some minor level of interchain hydrophobic association. The one-to-one complex has a viscosity 2 times the viscosity of the pure HMPAA3%250KC18 polymer and 4 times the viscosity of CDMPAA solution.

The specificity of the cyclodextrin inclusion interaction thus provides a new way to produce association fluids with variable structure. The addition of excess cyclodextrin, or enzymatic removal of cyclodextrin, provides

a new means for controlling structure. And the 1:1 stoichiometry of the association will allow quantitative tests of associating network theories.

Conclusions

A new routine to synthesize α- and β-cyclodextrin-modified PAA and a novel associative polymer networks based on mixtures of CD-modified and hydrophobically-modified (HM) PAAs were described. The inclusion interactions between CD and hydrophobe grafts in PAAs lead to stronger associations and solution viscosities than purely hydrophobic interactions at the same polymer concentration. The screening of the association between hydrophobically modified poly(acrylic acid)s by free α- or β-cyclodextrins occurs at approximately a stoichiometric ratio of cyclodextrin to hydrophobe. And the maximum of solution viscosity for the mixed CDMPAA and HMPAA also occurs at a stoichiometric ratio of cyclodextrin-to-hydrophobe. This indicates that the network involves binary associations driven by cyclodextrin inclusion. These novel associative polymer networks with unique binary interactions should be ideal model systems to test the theoretical predictions for the statics and dynamics of associative fluids.

Acknowledgment. R.K.P. and S.A.K. gratefully acknowledge NSF for partial support of this work.

References and Notes

(1) Shih, W. M.; Quispe, J. D.; Joyce, G. F. *Nature (London)* **2004**, *427*, 618.
(2) Nowak, A. P.; Breedveld, V.; Pakstis, L.; Ozbas, B.; Pine, D. J.; Pochan, D.; Deming, T. J. *Nature (London)* **2002**, *417*, 424.
(3) Breedveld, V.; et al. *Macromolecules* **2004**, *37*, 3943.
(4) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743.
(5) Easton, C. J.; Lincoln, S. F. *Modified Cyclodextrins: Scaffolds and Templates for Supramolecular Chemistry*; Imperial College Press: London, 1999.
(6) Huang, L.; Tonelli, A. E. *J. Macromol. Sci., Rev. Macromol. Chem. Phys.* **1998**, *C38*, 781.
(7) Harada, A. *Adv. Polym. Sci.* **1997**, *133*, 141.
(8) Ross-Murphy, S. B.; Wang, Q.; Ellis, P. R. *Macromol. Symp.* **1998**, *127*, 13.
(9) Dea, I. C. In *Industrial Gums, Polysaccharides and Their Derivatives*, 3rd ed.; Whistler, R. L., BeMiller, J. N., Eds.; Academic Press: New York, 1993; p 21.
(10) Kesavan, S.; Prud'homme, R. K. *Macromolecules* **1992**, *25*, 2026.
(11) Benichou, A.; Aserin, S.; Garti, N. *J. Dispersion Sci. Technol.* **2002**, *23*, 93.
(12) Chen, T.; Small, D. A.; Wu, L.; Rubloff, G. W.; Ghodssi, R.; Vazquez-Duhalt, R.; Bentley, W. E.; Payne, G. F. *Langmuir* **2003**, *19*, 9382.
(13) Nishikawa, T.; Akiyoshi, K.; Sunamoto, J. *Macromolecules* **1994**, *27*, 7654.
(14) Akiyoshi, K.; Sunamoto, J. *Supramol. Sci.* **1996**, *3*, 157.
(15) Klemm, D.; Einfeldt, L. *Macromol. Symp.* **2001**, *163*, 35.
(16) Karlson, L.; Thuresson, K.; Lindman, B. *Carbohydr. Polym.* **2002**, *50*, 219.
(17) Abdala, A. A.; Tonelli, A. E.; Khan, S. A. *Macromolecules* **2003**, *36*, 7833.
(18) Weickenmeier, M.; Wenz, G.; Huff. J. *Macromol. Rapid Commun.* **1997**, *18*, 1117.
(19) Gosselet, N. M.; Borie, C.; Amiel, C.; Sebille, B. *J. Dispersion Sci. Technol.* **1998**, *19*, 805.
(20) Morine, L.; Cammas, S.; Amiel, C.; Renard, E.; Sebille, B.; Guerin, P. *Macromol. Symp.* **1998**, *130*, 45−52.
(21) Gosselet, M. N.; Beucler, F.; Renard, E.; Amiel, C.; Sebille, B. *Colloids Surf., A* **1999**, *155*, 177.
(22) Rubinstein, M.; Dobrynin, A. V. *Trends Polym. Sci.* **1997**, *6*, 181.
(23) Serero, Y.; Porte, A. R.; Berret, J. F.; Calvet, D.; Collet, A.; Viguier, M. *Phys. Rev. Lett.* **1998**, *81*, 5584.
(24) Glass, J. E. *J. Coat. Technol.* **2001**, *73*, 79.
(25) Horiuchi, K.; Rharbi, Y.; Spiro, J. G.; Yekta, A.; Winnik, M. A.; Jenkins, R. D.; Bassett, D. R. *Langmuir* **1999**, *15*, 1644.
(26) Berret, J.-F.; Serero, Y.; Winkelman, B.; Calvet, D.; Collet, A.; Viguier, M. *J. Rheol.* **2001**, *45*, 477.
(27) Lundberg, D. J.; Glass, J. E.; Eley, R. R. *J. Rheol.* **1991**, *35*, 1255.
(28) Tae, G.; Kornfield, J. A.; Hubbell, J. A.; Johannsmann, D.; Hogen-Esch, T. E. *Macromolecules* **2001**, *34*, 6409.
(29) Anna, S. L.; McKinley, G. H.; Nguyen, D. A.; Sridhar, T.; Muller, S. J.; Huang, J.; James, D. F. *J. Rheol.* **2001**, *45*, 83.
(30) Tanaka, F.; Edwards, S. G. *Macromolecules* **1992**, *25*, 1516.
(31) Rubinstein, M.; Semenov, A. N. *Macromolecules* **2001**, *34*, 1058.
(32) Semenov, A. N.; Rubinstein. M. *Macromolecules* **1998**, *31*, 1373.
(33) Rubinstein, M.; Semenov, A. N. *Macromolecules* **1998**, *31*, 1386.
(34) Rubinstein, M. D.; Dobrynin, A. V. *Curr. Opin. Colloid Interface Sci.* **1999**, *4*, 83.
(35) Yekta, A.; Duhamel, J.; Brochard, P.; Adiwidjaja, H.; Winnik, M. A. *Macromolecules* **1993**, *26*, 1829.
(36) Yekta, A.; Xu, B.; Duhamel, J.; Adiwidjaja, H.; Winnik, M. A. *Macromolecules* **1995**, *28*, 956.
(37) Brown, S. E.; Coates, J. H.; Coghlan, D. R.; Easton, C. J.; van Eyk, S. J.; Janowski, W.; Lepore, A.; Lincoln, S. E.; Luo, Y.; May, B. L.; Schiesser, D. S.; Wang, P.; Williams, M. L. *Aust. J. Chem.* **1993**, *46*, 953.
(38) Wang, K. T.; Iliopoulos, I.; Audebert, R. *Polym. Bull. (Berlin)* **1988**, *20*, 577.
(39) Yang, B. S.; Lal, J.; Richetti, P.; Marques, C. M.; Russel, W. B.; Prud'homme, R. K. *Langmuir* **2001**, *19*, 5834.
(40) Wang, K. T.; Iliopoulos, I.; Audebert, R. *ACS Symp. Ser.* **1991**, *467*, 218.

MA050071O