

## Solvent Responsive Micelles Based on Block and Gradient Copoly(2-oxazoline)s

Richard Hoogenboom,<sup>\*,†</sup> Hanneke M. L. Thijs,<sup>†</sup>  
Daan Wouters,<sup>†</sup> Stephanie Hoepfener,<sup>†</sup> and  
Ulrich S. Schubert<sup>\*,‡,§</sup>

Laboratory of Macromolecular Chemistry and Nanoscience,  
Eindhoven University of Technology and Dutch Polymer  
Institute (DPI), PO Box 513, 5600 MB Eindhoven, The  
Netherlands, and Laboratory of Organic and  
Macromolecular Chemistry, Friedrich-Schiller-Universität  
Jena, Humboldtstrasse 10, 07743 Jena, Germany

Received December 16, 2007

Revised Manuscript Received January 14, 2008

The aqueous self-assembly of macromolecules has been studied in detail, resulting in the formation of block copolymer micelles with various morphologies.<sup>1–4</sup> In recent years, more sophisticated self-assembled structures, including toroidal micelles<sup>5–7</sup> and discrete or wormlike multicompartiment micelles,<sup>8–10</sup> were reported based on the self-assembly of rather complex (charged) amphiphilic triblock and tetrablock copolymers.<sup>11–13</sup> Besides changing the (complex) polymer composition and/or architecture, the self-assembled structures can also be influenced by changing the solvent<sup>14–16</sup> or by using binary solvent mixtures.<sup>17–23</sup> Moreover, micellization can also be influenced by changing the block order in triblock copolymers<sup>24,25</sup> and by changing the monomer distribution.<sup>26–28</sup> However, the effects of solvent mixtures and monomer distribution were not yet studied simultaneously.

Here, we investigated the solvent responsiveness of block and gradient copoly(2-oxazoline)s in binary water–ethanol mixtures to address the effect of monomer distribution. In addition, we demonstrate the formation of complex self-assembled structures, including toroids and Y-junctions, from a simple amphiphilic statistical copolymer in binary water–ethanol solvent mixtures. The structures of the studied amphiphilic poly(2-methyl-2-oxazoline)<sub>50</sub>-block-poly(2-phenyl-2-oxazoline)<sub>50</sub> (pMeOx<sub>50</sub>-block-PhOx<sub>50</sub>) block copolymer<sup>29</sup> and the gradient poly(2-methyl-2-oxazoline)<sub>50</sub>-stat-poly(2-phenyl-2-oxazoline)<sub>50</sub> (pMeOx<sub>50</sub>-stat-PhOx<sub>50</sub>)<sup>30</sup> are depicted in Figure 1 together with the calculated monomer distribution in the polymer chains (bottom).<sup>31</sup>

The micellization of the copolymers was performed by heating a mixture of the polymer in the water–ethanol solvent mixture to 75 °C, followed by subsequent cooling to 20 °C. After two such heating cycles to facilitate the formation of hydrodynamically stable aggregates, the micellar solutions were analyzed by transmission electron microscopy (TEM). The micelles from pMeOx<sub>50</sub>-block-PhOx<sub>50</sub> in water revealed mainly wormlike micelles and some spherical micelles (Figure 2A). With 10 wt % ethanol content, the fraction of spherical micelles is higher, and with 15 wt % or more ethanol only individual micelles were observed. This shift from cylindrical to spherical micelles was previously only observed when the ratio of the blocks in block copolymers was varied.<sup>32–34</sup> The here observed morphological transition can be rationalized by the formation

of an alcohol solvation sphere around the hydrophobic part of the (polymeric) surfactants, resulting in higher interfacial curvatures and thus the formation of spherical micelles.<sup>14,35,36</sup>

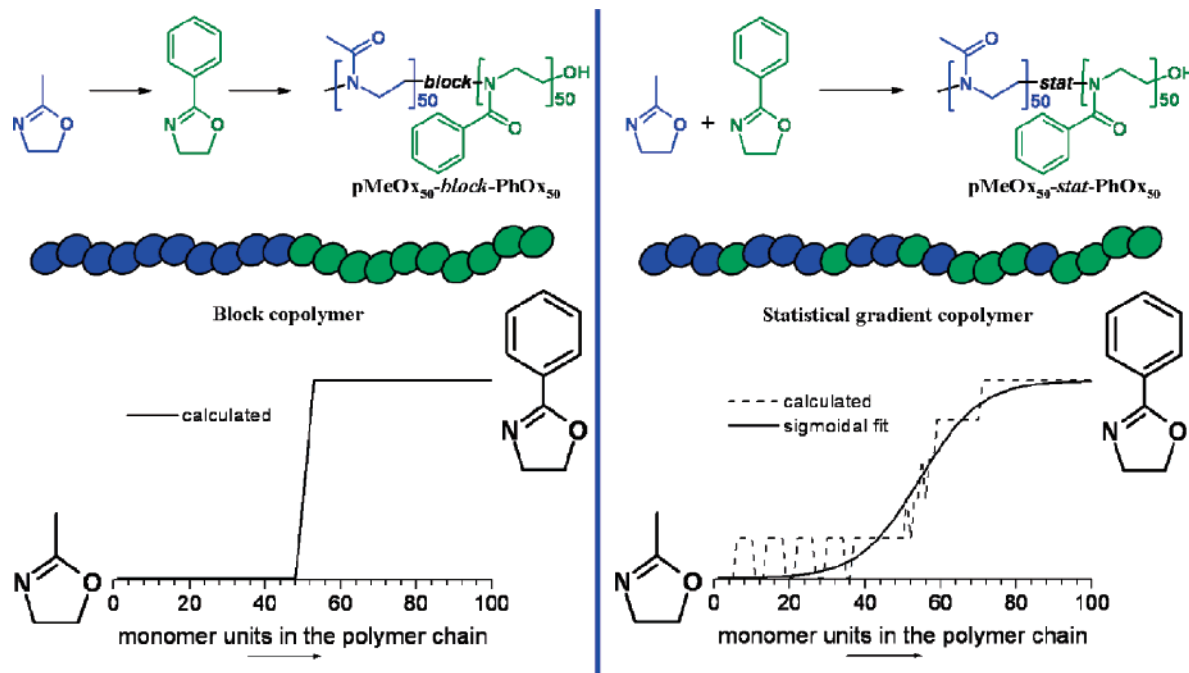
In contrast to the block copolymer, the gradient copolymer is insoluble in pure water. The lower solubility of the gradient copolymer compared to the block copolymer is due to the fact that only a small part of the polymer chain (20 monomer units) consists of pure MeOx while the rest of the chains consist of a mixture of MeOx and PhOx (Figure 1). When using binary water–ethanol solvent mixtures, micellar solutions were obtained after heating the polymer. Transmission electron microscopy (TEM), cryogenic TEM (cryoTEM), and atomic force microscopy (AFM) images of the micelles resulting from the self-assembly of pMeOx<sub>50</sub>-stat-PhOx<sub>50</sub> in solvent mixtures containing 5, 10, 15, 20, 30, and 40 wt % of ethanol in water are depicted in Figure 3 (more images are shown in the Supporting Information). The solubility of pMeOx<sub>50</sub>-stat-PhOx<sub>50</sub> with 5 wt % ethanol is regarded as a border case since partial precipitation of the sample was observed. The self-assembly of pMeOx<sub>50</sub>-stat-PhOx<sub>50</sub> with 5 and 10 wt % ethanol resulted in the formation of both spherical micelles and wormlike micelles (Figure 3A,B) while self-assembly of the copolymer in solvent mixtures with more ethanol only resulted in the formation of spherical micelles (Figure 3C–F) due to an increase in interfacial curvature as it was also observed for the block copolymer. A closer look at the self-assembled structures from the 5 and 10 wt % ethanol solutions revealed the presence of less commonly observed structures such as toroids and Y-junctions (see Figure 2A,B). Although Y-junctions have been previously observed for block copolymer cylindrical micelles,<sup>37–39</sup> they have not been reported for the self-assembly of rather simple quasi-diblock statistical copolymers. Furthermore, previous observations of the formation of toroids were based on the self-assembly of charged diblock copolymers<sup>40–42</sup> or (charged) triblock terpolymers.<sup>5–7</sup> The formation of toroids by the self-assembly of a rather simple nonionic quasi-diblock statistical copolymer is unprecedented and might be ascribed to the monomer distribution in pMeOx<sub>50</sub>-stat-PhOx<sub>50</sub>, which resembles a kind of triblock copolymer architecture with outer blocks of pMeOx and pPhOx and a middle gradient block. The cryoTEM analysis revealed that the morphologies observed for the dried samples resemble the structures present in solution, demonstrating that they are not formed by drying effects. The observed wormlike micelles appear to consist of individual spherical micelles that are merged together, indicating that this is a border case in the transition from cylindrical to spherical micelles, which is also evident from the presence of both spherical and cylindrical micelles.

The sizes of the spherical micelles (obtained from the TEM images)<sup>43</sup> that were observed in the different ethanol–water mixtures decreased linearly up to increasing the ethanol fraction to 20 wt % for both the block and the gradient copolymers due to better solvation of the insoluble part that results in increased interfacial curvatures (Figure 4). However, upon further increasing the amount of ethanol, the size of the block copolymer micelles remains constant at 18–19 nm, which correlates well to the commonly observed nonideal mixing behavior of water and ethanol that is most pronounced up to 20 wt % ethanol in water.<sup>44</sup> In contrast to these observations for the block copolymer micelles, the diameter of the gradient copolymer micelles linearly decreased from 10 to 40 wt % ethanol, which cannot be solely due to changing the solvation of the soluble

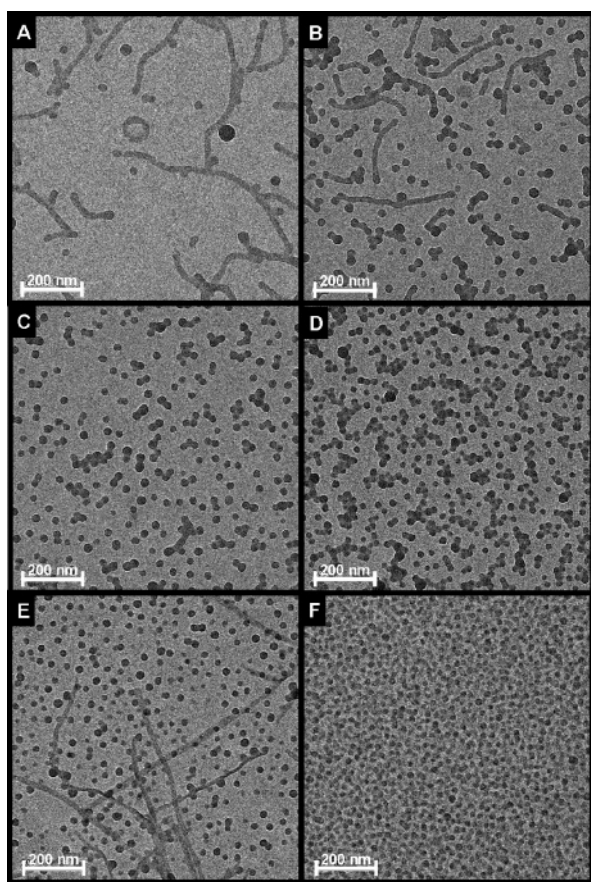
\* Corresponding authors. E-mail: u.s.schubert@tue.nl; r.hoogenboom@tue.nl.

<sup>†</sup> Eindhoven University of Technology and Dutch Polymer Institute.

<sup>‡</sup> Friedrich-Schiller-Universität Jena.

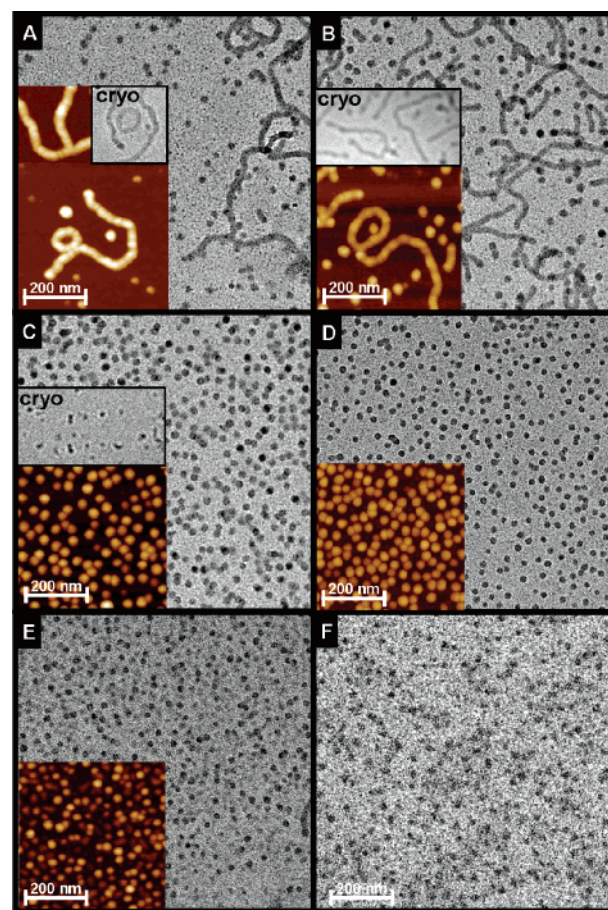


**Figure 1.** Structural representations (top) and calculated monomer distributions (bottom) of the investigated *pMeOx<sub>50</sub>-block-PhOx<sub>50</sub>* block copolymer (left) and *pMeOx<sub>50</sub>-stat-PhOx<sub>50</sub>* statistical gradient copolymer (right).



**Figure 2.** TEM images of the micellar aggregates that were obtained from *pMeOx<sub>50</sub>-block-PhOx<sub>50</sub>* in different water-ethanol mixtures: (A) H<sub>2</sub>O, (B) 5 wt % ethanol, (C) 10 wt % ethanol, (D) 20 wt % ethanol, (E) 30 wt % ethanol, and (F) 40 wt % ethanol.

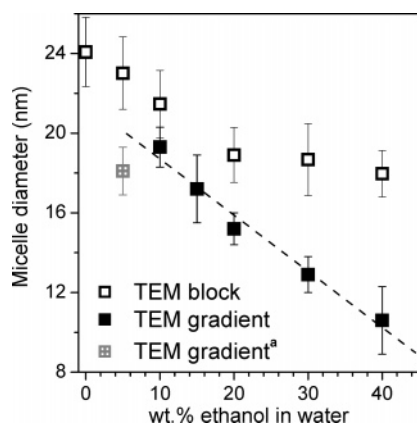
and insoluble blocks. Therefore, the observed linear decrease in gradient copolymer micelle size is ascribed to partial solvation of the gradient part of the gradient copolymer by the decrease in solvent polarity with increasing ethanol content. It is noteworthy to mention that the spherical micelles in the



**Figure 3.** TEM, AFM (insets bottom left), and cryoTEM (insets marked with cryo) images of the micellar aggregates that were obtained from *pMeOx<sub>50</sub>-stat-PhOx<sub>50</sub>* in different water-ethanol mixtures: (A) 5 wt % ethanol, (B) 10 wt % ethanol, (C) 15 wt % ethanol, (D) 20 wt % ethanol, (E) 30 wt % ethanol, and (F) 40 wt % ethanol.

5 wt % ethanol solution are smaller than the linear trend, which is thought to resemble the largest stable micellar structure with the investigated degree of polymerization (100 monomer units)





**Figure 4.** Dependence of the spherical micelle diameters of the pMeOx<sub>50</sub>-block-pPhOx<sub>50</sub> and pMeOx<sub>50</sub>-stat-PhOx<sub>50</sub> on the amount of ethanol in the water–ethanol solvent mixture. (Superscript a indicates that the pMeOx<sub>50</sub>-stat-PhOx<sub>50</sub> gradient copolymer partially precipitated in this solvent mixture.)

in combination with this monomer gradient due to a too small hydrophilic solubilizing corona. Partial precipitation was observed in this sample, which might indicate that initially some larger unstable micelles were also present.

In summary, we demonstrated that the self-assembly of block and gradient copolymers can be tuned by changing the water–ethanol solvent composition. Remarkably, the decrease of micelle diameter for the block copolymers is based on better partial solvation of the hydrophobic block resulting in increased interfacial curvature corresponding to smaller micelles. However, this effect is diminished when more than 20 wt % of ethanol is added while for the gradient copolymer the micelle diameter linearly decreased up to the addition of 40 wt % ethanol due to partial solvation of the gradient part of the polymer. As a result, future optimization and tuning of self-assembled structures could be performed by screening solvent compositions rather than polymer compositions eliminating the time-consuming process of polymer synthesis, isolation, and structural characterization. In addition, the reported use of statistical copolymers also allows simple fine-tuning of the polymer compositions by a one-step synthesis procedure. The use of water–ethanol mixtures is especially valuable for the application of polymers in pharmaceutical and personal care products due to their low toxicity. In addition, the observed gradient responsiveness might be used to prepare polymeric sensors for solvent polarity.

**Acknowledgment.** We thank the Dutch Polymer Institute, the Dutch Council of Scientific Research (NWO), and the Fonds der Chemischen Industrie for financial support. Avantium Technologies BV is thanked for the discussions during the course of the investigations. This research has been carried out with the support of the Soft Matter cryo-TEM Research Unit, Department of Chemical Engineering and Chemistry, Eindhoven University of Technology.

**Supporting Information Available:** Experimental procedures, comparison between AFM and TEM, and additional AFM and TEM images. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References and Notes

- Hamley, I. W. *The Physics of Block Copolymers*; Oxford University Press: Oxford, 1998.
- Won, Y.-Y.; Davis, H. T.; Bates, F. S. *Science* **1999**, 283, 960.
- Gohy, J.-F. *Adv. Polym. Sci.* **2005**, 190, 65.
- Discher, D. E.; Eisenberg, A. *Science* **2002**, 297, 967.
- Pochan, D. J.; Chen, Z.; Cui, H.; Hales, K.; Qi, K.; Wooley, K. L. *Science* **2004**, 306, 94.
- Ma, J. W.; Li, X.; Tang, P.; Yang, Y. J. *Phys. Chem. B* **2007**, 111, 1552.
- Reynhout, I. C.; Cornelissen, J. J. L. M.; Nolte, R. J. M. *J. Am. Chem. Soc.* **2007**, 129, 2327.
- Li, Z.; Kesselman, E.; Talmon, Y.; Hillmyer, M. A.; Lodge, T. P. *Science* **2004**, 306, 98.
- Brannan, A. K.; Bates, F. S. *Macromolecules* **2004**, 37, 8816.
- Gomze, E. D.; Rappl, T. J.; Agarwal, V.; Bose, A.; Schmutz, M.; Marques, C. M.; Balsara, N. P. *Macromolecules* **2005**, 38, 3567.
- Hadjichristidis, N.; Pitsikalis, M.; Iatrou, H. *Adv. Polym. Sci.* **2005**, 189, 1.
- Fustin, C.-A.; Abetz, V.; Gohy, J.-F. *Eur. Phys. J. E* **2005**, 16, 291.
- Lutz, J.-F.; Laschewsky, A. *Macromol. Chem. Phys.* **2005**, 206, 813.
- Loppinet, B.; Fytas, G.; Vlassopoulos, D.; Likos, C. N.; Meier, G.; Liu, G. J. *Macromol. Chem. Phys.* **2005**, 206, 163.
- Huang, H.; Hoogenboom, R.; Leenen, M. A. M.; Guillet, P.; Jonas, A. M.; Schubert, U. S.; Gohy, J.-F. *J. Am. Chem. Soc.* **2006**, 128, 3784.
- Burke, S. E.; Eisenberg, A. *Polymer* **2001**, 42, 9111.
- Armstrong, J.; Chowdhry, B.; Mitchell, J.; Beezer, A.; Leharne, S. *J. Phys. Chem.* **1996**, 100, 1738.
- Holmqvist, P.; Alexandridis, P.; Lindman, B. *Langmuir* **1997**, 13, 2471.
- Yu, Y.; Eisenberg, A. *J. Am. Chem. Soc.* **1997**, 119, 8383.
- Zhang, W.; Shi, L.; An, Y.; Gao, L.; Wu, K.; Ma, R.; Zhang, B. *Macromol. Chem. Phys.* **2004**, 205, 2017.
- Castro, E.; Taboada, P.; Mosquera, V. J. *Phys. Chem. B* **2006**, 110, 13113.
- Li, Z.; Chen, Z.; Cui, H.; Hales, K.; Wooley, K. L.; Pochan, D. J. *Langmuir* **2007**, 23, 4689.
- Cheng, G.; Böker, A.; Zhang, M.; Krausch, G.; Müller, A. H. E. *Macromolecules* **2001**, 34, 6883.
- Hoogenboom, R.; Wiesbrock, F.; Huang, H.; Leenen, M. A. M.; Thijs, H. M. L.; Van Nispen, S. F. G. M.; Van der Loop, M.; Fustin, C.-A.; Jonas, A. M.; Gohy, J.-F.; Schubert, U. S. *Macromolecules* **2006**, 39, 4719.
- Zhao, X.; Liu, W.; Chen, D.; Lin, X.; Lu, W. W. *Macromol. Chem. Phys.* **2007**, 208, 1773.
- Hodrokovos, P.; Pispas, S.; Hadjichristidis, N. *Macromolecules* **2002**, 35, 834.
- Okabe, S.; Seno, K.-I.; Kanaoka, S.; Aoshima, S.; Shibayama, M. *Macromolecules* **2006**, 39, 1592.
- Bonne, T. B.; Ludtke, K.; Jordan, R.; Papadakis, C. M. *Macromol. Chem. Phys.* **2007**, 208, 1402.
- Full details of the synthesis and characterization of the block copolymer are reported elsewhere: Wiesbrock, F.; Hoogenboom, R.; Leenen, M. A. 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.
- Full details of the synthesis and characterization of the statistical copolymer are reported elsewhere: Hoogenboom, R.; Thijs, H. M. L.; Fijten, M. W. M.; Van Lankvelt, B. M.; Schubert, U. S. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, 45, 416.
- The monomer distribution through the gradient copolymer was calculated from the copolymerization kinetics (see ref 30) by averaging the composition of each five consecutive monomers.
- Zhang, L.; Eisenberg, A. *Science* **1995**, 268, 1728.
- Yu, K.; Zhang, L.; Eisenberg, A. *Langmuir* **1996**, 12, 5980.
- Won, Y.-Y.; Brannan, A. K.; Davis, H. T.; Bates, F. S. *J. Phys. Chem. B* **2002**, 106, 3354.
- Sobisch, T.; Wüstneck, R. *Colloids Surf.* **1992**, 62, 187.
- Waghorne, W. E. *Chem. Soc. Rev.* **1993**, 22, 285.
- Jain, S.; Bates, F. S. *Science* **2003**, 300, 460.
- Dan, N.; Shimoni, K.; Pata, V.; Danino, D. *Langmuir* **2006**, 22, 9860.
- Bhargava, P.; Zheng, J. X.; Quirk, R. P.; Cheng, S. Z. D. *J. Polym. Sci., Part B: Polym. Phys.* **2006**, 44, 3605.
- Shen, H.; Zhang, L.; Eisenberg, A. *J. Am. Chem. Soc.* **1999**, 121, 2728.
- Förster, S.; Hermsdorf, N.; Leube, W.; Mühlenberg, A.; Regenbrecht, M.; Akari, S. *J. Phys. Chem. B* **1999**, 103, 6657.
- Netz, R. R. *Europhys. Lett.* **1999**, 47, 391.
- The diameter observed by TEM closely resembles the height observed by AFM (see Supporting Information), indicating that TEM shows the core diameter of the micelles.
- Noskov, S. Y.; Lamoureux, G.; Roux, B. *J. Phys. Chem. B* **2005**, 109, 6705.