Asymmetric Self-Assembly

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Double-Faced Micelles from Water-Soluble Polymers**

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Polymer technology finds much of its inspiration in nature, but it lacks the subtle input of millions of years of evolution. Conventional routes to biomimetic architectures involve elaborate syntheses and multistep preparation protocols.[1–4] Indeed, this approach has led to many new solution morphologies, including exotic geometries and multidomain structures (beyond core/shell type). Recently, a wide variety of nonspherical shapes, ranging from vesicles to nanowires,[5] from toroids[6] to hollow icosahedras,[7] as well as internally structured nanoassemblies have been reported (see, for example, literature on "layered" micelles, that is, core–shell–corona or onion-type micelles,[8,9] multicompartment micelles,[1,2] micelles with a phase-segregated corona in block-selective solvents,[4,10] and chemically cross-linked colloidal particles with a corona consisting of two different solvent-swollen polymers[3]). However, only a small percentage of these synthetic analogues to complex biological structures assemble spontaneously and reversibly from their molecular constituents. On the contrary, they are typically frozen-in architectures, dynamically arrested and thus fundamentally different from their biomacromolecular analogues. In order to preserve dynamics and responsiveness of the structure, the driving forces need to be weak and well-balanced, enforcing just the right architecture.

We set out to meet these requirements by combining associative and segregative phase separation. More specifically, electrostatic interaction (complex coacervation) is used to confine two double hydrophilic block copolymers in the same aggregate, while a subtle repulsion between unlike neutral, water-soluble blocks ensures segregation into two distinct phases on a slightly larger length scale but within the same structure. The result is the spontaneous and reversible formation of a disk-shaped micelle having a complex coacervate core and an asymmetric water-swollen corona (Figure 1) which is microphase-separated into two distinct domains or faces, that is, Janus-type.

Figure 1. Representation of a disk-shaped Janus micelle. Complex coacervate core (PAA and P2MVP): orange; coronal hemispheres: green (PEO) and blue (PAAm).

When aqueous solutions of poly(acrylic acid)-*block*-poly(acryl amide), PAA_{42}-*b*-$PAAm_{417}$, and poly(2-methylvinylpyridinium iodide)-*block*-poly(ethylene oxide), $P2MVP_{42}$-*b*-PEO_{446}, were mixed, micelles formed almost instantaneously in a narrow region around a mixing fraction $f_+ = 0.5$ ($f_+ = [P2MVP]/([PAA]+[P2MVP])$). The reversibility and responsive nature of this type of micelle, so-called complex coacervate core micelles (C3Ms),[11–13] polyion complex micelles,[14,15] block ionomer complex micelles[16,17] and interpolyelectrolyte complexes (IPEC),[18] has been extensively documented in previous work.[12,13] PAAm and PEO were chosen as corona blocks on the basis of published compatibility data.[19–21] From these reports, we estimate the Flory–Huggins interaction parameter $\chi_{PAAm,PEO}$ to be about 0.05.

In dynamic light-scattering experiments, we find a very small (linear) angular and concentration dependence for the diffusion coefficient. CONTIN analysis shows one rather narrow mode corresponding to an effective hydrodynamic radius, $R_{h,eff,c\to 0,q\to 0}$, of 18.3 ± 0.5 nm. Three independent methods (a partial Zimm analysis, a Guinier analysis, and a Debye analysis) have been used to analyze the static light-scattering data ($0.5 < C_p < 2\ g\,L^{-1}$, $0.018 < q < 0.032\ nm^{-1}$,

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where $q = 4\pi n_0/\lambda \sin(\theta/2)$, λ is the wavelength in vacuum, n_0 is the solvent refractive index, θ is the scattering angle, and C_p is the total polymer concentration) resulting in a micellar mass, $M_{micelle}$, of 860 ± 23 kg mol^{-1}, an aggregation number, P_{agg}, of 30.0 ± 0.4, and a radius of gyration, R_g, of 16.9 ± 0.25 nm. Thus we obtain a R_g/R_h value of 0.92 ± 0.04, which is rather high for spherical aggregates ($R_g/R_h = 0.775$ for hard spheres) and indicative of elongated structures, such as ellipsoids, rods, or worms. Using the P_{agg} and R_h values we can roughly estimate the volume fraction of polymer in the corona, φ_{corona}, for which we find values between 5 and 10%. Thus φ_{corona} exceeds $\varphi_{critical}$, which should induce phase separation in the corona.

Cryo-transmission electron microscopy (cryo-TEM) confirms a nonspherical morphology (Figure 2). Both core and

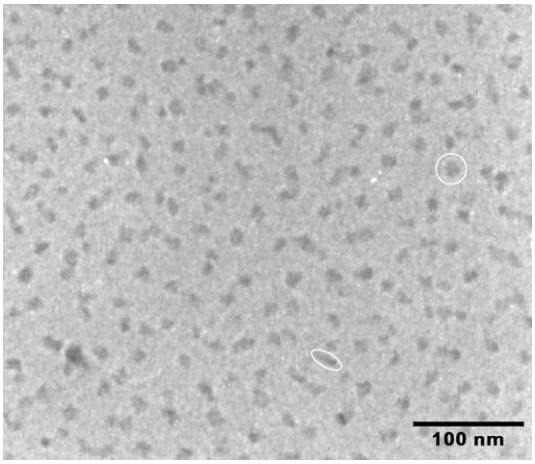

Figure 2. Cryo-TEM image of a 0.1-wt% solution of PAA_{42}-*b*-$PAAm_{417}$ and $P2MVP_{42}$-*b*-PEO_{446}.

corona are highly penetrated by solvent, resulting in a low contrast image in which only the core is visible. These low-polymer-volume fractions are typical for and directly related to the reversible character of C3Ms. A rough estimate for the core dimensions would be 20 ± 2 nm (diameter) by 7 ± 2 nm (thickness).

The small-angle neutron scattering (SANS) curves can be fitted using a form factor for monodisperse disks (Figure 3; $R = 18$ nm ± 1 nm, axial ratio $= 0.14 \pm 0.02$) but not with a monodisperse-sphere model nor with a polydisperse-sphere model, as this leads to physically unrealistically high values of polydispersity, in flagrant conflict with the DLS data and cryo-TEM images.

To the best of our knowledge, C3Ms in solution with a nonspherical morphology have never been reported before. Moreover, disk-shaped micelles are theoretically predicted as a possible morphology in the transition from spheres to lamellae,[22] but they are very rarely experimentally observed.[23] When observed, they are typically polydisperse and found as transients in the transition from (mixed) micelles to vesicles.[23] In this system, disk-shaped micelles of constant dimensions are found over a wide concentration range (0.1–1 wt%), suggesting an alternative mechanism to stabilize the disk-shaped morphology.[24,25]

We propose that this alternative mechanism is the coronal microphase separation of the PAAm and PEO blocks. To test

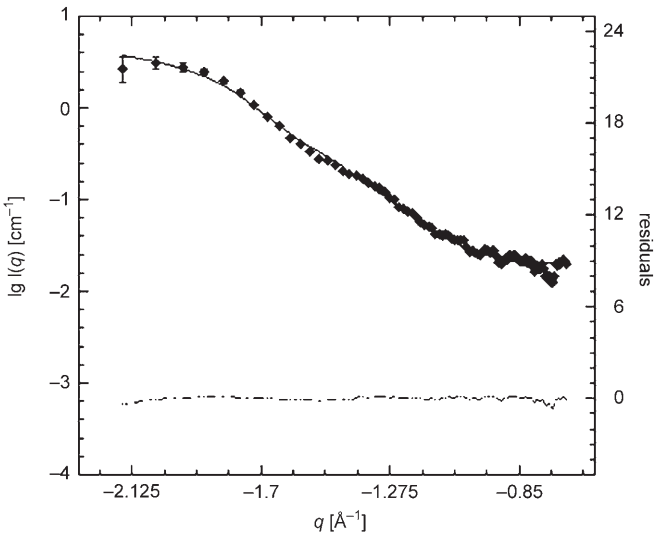

Figure 3. SANS curve of a 1-wt% aqueous solution of PAA_{42}-*b*-$PAAm_{417}$ and $P2MVP_{42}$-*b*-PEO_{446}. Experimental data (◆), form factor fit (solid line) to a uniform, monodisperse oblate ellipsoid, and residuals (dotted line). S(*q*) and core-shell structure are not included in the fit.

this hypothesis, we performed ^{1}H NMR NOESY experiments, in which the 3D spatial correlations of neighboring protons are probed. Cross peaks in the 2D ^{1}H NMR spectrum would indicate close proximity, that is, distances < 0.5 nm. Indeed, no cross peaks are observed between the ^{1}H NMR signals of PEO (3.6 ppm) and PAAm (1.65 (methylene, CH_2), 2.2 ppm (methine, CH)), while cross peaks are observed between the signals of the methylene and methine protons of PAAm and PAA (Figure 4).

As a positive control, we also present a contour plot of a ^{1}H NOESY experiment on C3Ms of $PDMAEMA_{45}$-*b*-$PGMA_{90}$ (poly(*N*,*N*-dimethylaminoethyl methacrylate)-*block*-poly(glyceryl methacrylate)) and PAA_{42}-*b*-$PAAm_{417}$. Figure 5 clearly shows cross peaks between the (fairly compatible) corona blocks PGMA and PAAm. In DLS measurements no angular dependence was found, indicating spherical morphology.

We expect that this strategy of C3Ms undergoing coronal microphase separation in combination with a systematic variation of lengths and solubility/miscibility of the corona blocks (especially towards more asymmetric ratios) will lead to a rich and exotic phase diagram in bulk, solution, and blends. More importantly, the directionality of the Janus micelle can be used in a secondary self-assembly process to produce micellar-like organization on a larger length scale.

Our current findings elegantly illustrate that highly ordered solution architectures can assemble easily and spontaneously when linear, flexible water-soluble diblock copolymers are simply mixed. This indicates a versatile and general route to hierarchical self-assembled structures on multiple length scales.

Experimental Section

Poly(2-methylvinylpyridinium iodide)-*block*-poly(ethylene oxide), $P2MVP_{42}$-*b*-PEO_{446}, and poly(acrylic acid)-*block*-poly(acryl amide),

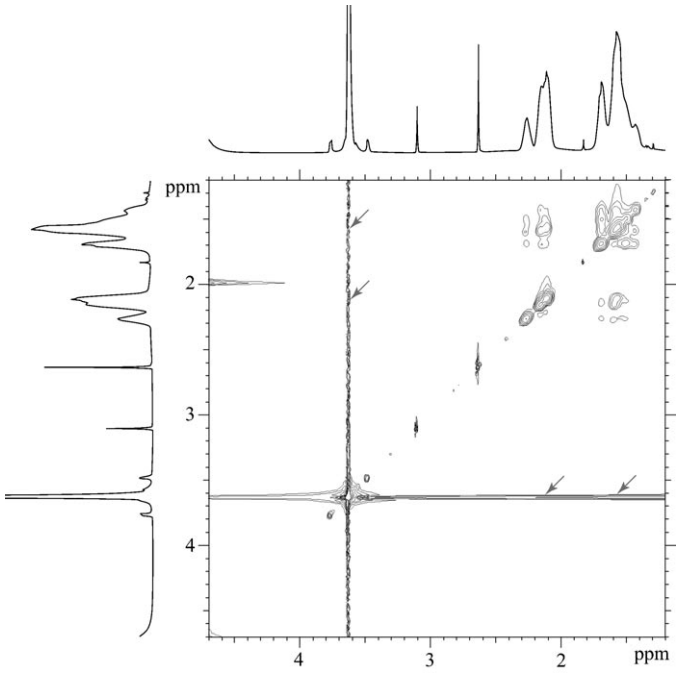

Figure 4. ^{1}H NMR 2D NOESY contour plot of a 1-wt% aqueous solution (1 mM $NaNO_3$, pH 7.73) of PAA_{42}-*b*-$PAAm_{417}$ and $P2MVP_{42}$-*b*-PEO_{446}. Arrows indicate where cross peaks between PAAm and PEO should occur in case of close proximity.

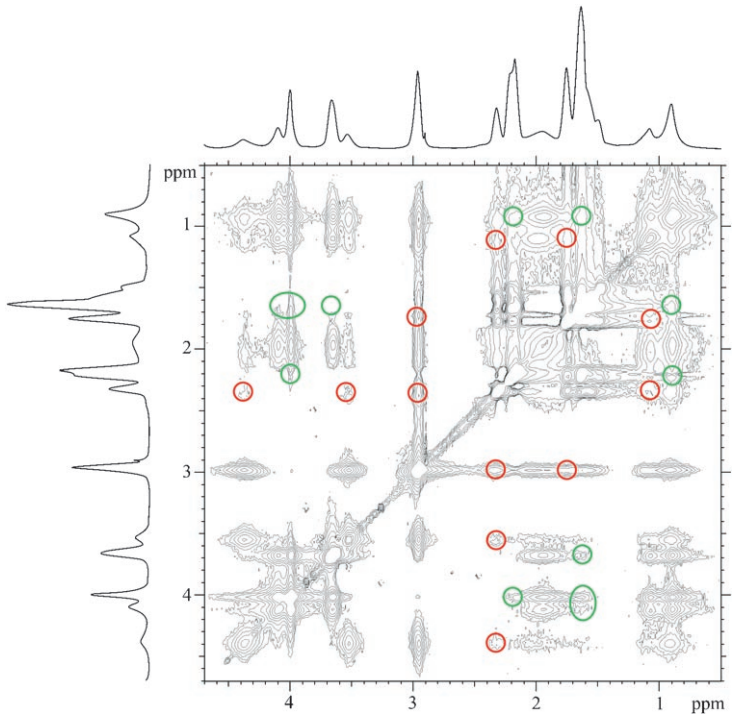

Figure 5. ^{1}H NMR 2D NOESY contour plot of a 1-wt% aqueous solution of PAA_{42}-*b*-$PAAm_{417}$ and $PDMAEMA_{45}$-*b*-$PGMA_{90}$. Circles indicate cross peaks between core (red) and corona (green) blocks. See the Supporting Information for details.

PAA_{42}-*b*-$PAAm_{417}$, were synthesized by sequential anionic polymerization[26] (followed by quaternization with methyl iodide) and the MADIX process,[27] respectively (for details see the Supporting Information). Aqueous solutions of micelles were prepared by mixing diblock copolymer stock solutions. The copolymer solutions were prepared by dissolving known amounts of copolymer into deionized water (or D_2O for SANS and ^{1}H NOESY experiments) followed by pH adjustment using NaOH and HNO_3. All experiments were performed at 1 mM $NaNO_3$, pH 7.73, and 25.0 °C.

For details on light-scattering, cryo-TEM, SANS, and ^{1}H NMR experiments, see the Supporting Information.

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[1] Z. B. Li, E. Kesselman, Y. Talmon, M. A. Hillmyer, T. P. Lodge, *Science* **2004**, *306*, 98.
[2] J. F. Lutz, A. Laschewsky, *Macromol. Chem. Phys.* **2005**, *206*, 813.
[3] R. Erhardt, A. Boker, H. Zettl, H. Kaya, W. Pyckhout-Hintzen, G. Krausch, V. Abetz, A. H. E. Mueller, *Macromolecules* **2001**, *34*, 1069.
[4] C. A. Fustin, V. Abetz, J. F. Gohy, *Eur. Phys. J. E* **2005**, *6*, 291.
[5] W. A. Lopes, H. M. Jaeger, *Nature* **2001**, *414*, 735.
[6] D. J. Pochan, Z. Y. Chen, H. G. Cui, K. Hales, K. Qi, K. L. Wooley, *Science* **2004**, *306*, 94.
[7] M. Dubois, B. Deme, T. Gulik-Krzywicki, J. C. Dedieu, C. Vautrin, S. Desert, E. Perez, T. Zemb, *Nature* **2001**, *411*, 672.
[8] E. A. Lysenko, T. K. Bronich, E. V. Slonkina, A. Eisenberg, V. A. Kabanov, A. V. Kabanov, *Macromolecules* **2002**, *35*, 6351.
[9] D. V. Pergushov, E. V. Remizova, M. Gradzielski, P. Lindner, J. Feldthusen, A. B. Zezin, A. H. E. Mueller, V. A. Kabanov, *Polymer* **2004**, *45*, 367.
[10] J. F. Gohy, E. Khousakoun, N. Willet, S. K. Varshney, R. Jerome, *Macromol. Rapid Commun.* **2004**, *25*, 1536.
[11] M. A. Cohen Stuart, N. A. M. Besseling, R. G. Fokkink, *Langmuir* **1998**, *14*, 6846.
[12] S. van der Burgh, A. de Keizer, M. A. Cohen Stuart, *Langmuir* **2004**, *20*, 1073.
[13] M. A. Cohen Stuart, B. Hofs, I. K. Voets, A. de Keizer, *Curr. Opin. Colloid Interface Sci.* **2005**, *10*, 30.
[14] A. Harada, K. Kataoka, *Macromolecules* **1995**, *28*, 5294.
[15] K. Kataoka, A. Harada, Y. Nagasaki, *Adv. Drug Delivery Rev.* **2001**, *47*, 113.
[16] A. V. Kabanov, T. K. Bronich, V. A. Kabanov, K. Yu, A. Eisenberg, *Macromolecules* **1996**, *29*, 6797.
[17] A. V. Kabanov, V. A. Kabanov, *Adv. Drug Delivery Rev.* **1998**, *30*, 49.
[18] J. F. Gohy, S. K. Varshney, R. Jerome, *Macromolecules* **2001**, *34*, 3361.
[19] M. Silva, J. C. Machado, V. Mano, G. G. Silva, *J. Polym. Sci. Part B* **2003**, *41*, 1493.
[20] R. J. Hefford, *Polymer* **1984**, *25*, 979.
[21] M. B. Perrau, I. Iliopoulos, R. Audebert, *Polymer* **1989**, *30*, 2112.
[22] J. C. Eriksson, S. Ljunggren, *Langmuir* **1990**, *6*, 895.
[23] M. Almgren, *Biochim. Biophys. Acta* **2000**, *1508*, 146.
[24] W. F. Edmonds, Z. B. Li, M. A. Hillmyer, T. P. Lodge, *Macromolecules* **2006**, *39*, 4526.
[25] T. Zemb, M. Dubois, B. Deme, T. Gulik-Krzywicki, *Science* **1999**, *283*, 816.
[26] H. Schmalz, M. G. Lanzendoerfer, V. Abetz, A. H. E. Mueller, *Macromol. Chem. Phys.* **2003**, *204*, 1056.

[27] D. Taton, A. Z. Wilczewska, M. Destarac, *Macromol. Rapid Commun.* **2001**, *22*, 1497.
[28] P. M. Frederik, D. H. W. Hubert, in *Liposomes Part E*, *Vol. 391*, Elsevier Academic, Amsterdam, **2005**, p. 431.
[29] R. K. Heenan, J. Penfold, S. M. King, *J. Appl. Crystallogr.* **1997**, *30*, 1140.
[30] R. K. Heenan in *RAL Technical Reports* **1989**.

