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Micelles of Hydrophilic−Hydrophobic Poly(sulfobetaine)-Based Block Copolymers

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Introduction

Block copolymers in selective solvents (thermodynamically good for one block and poor for the other) associate to form spherical multimolecular micelles which are, as a rule, in dynamic equilibrium with nonassociated copolymer molecules (unimers).[1] While micellization in organic solvents was studied extensively in the 1970s and 1980s, it is only relatively recently that polymer scientists have examined the micellization of hydrophilic−hydrophobic block copolymers in aqueous media.[2] Hydrophilic blocks can be anionic (e.g., poly(acrylic acid)[3] or poly(methacrylic acid)[4]), polycationic (e.g., poly(4-vinylpyridinium methyl iodide)[5]), or nonionic (e.g., poly(ethylene oxide)[6]).

Copolymers with marginally hydrophobic blocks and relatively low molar mass, e.g., poly(ethylene oxide-*block*-propylene oxide),[6] can form micelles spontaneously by direct dissolution in water. On the other hand, copolymers with strongly hydrophobic blocks (e.g., polystyrene) can form micelles only when their molar mass is lower than $\sim 20 \times 10^3$ g mol^{-1} and the mass fraction of the hydrophobic block is less than ∼0.20.[2] Micelles of the copolymers that do not meet such conditions can be prepared by direct dissolution in a mixture of water with some organic cosolvent. The cosolvent, which must be miscible with water and also a good solvent for both the micelle core and the corona, can be removed by either distillation[3] or dialysis.[2,4] While micelles prepared by direct dissolution in water or in a water−organic cosolvent mixture are in dynamic equilibrium with unimers, those transferred into water are likely to be "frozen", especially when cores are glassy.

Recently we studied[7] the micellization of poly[(2-dimethylamino)ethyl methacrylate]-*block*-poly(methyl methacrylate) (PDMAEMA-*block*-PMMA) copolymer samples prepared via group transfer polymerization (GTP). Micelle properties were studied by light scattering and sedimentation. We have shown that micelles prepared by direct dissolution in water were significantly larger than those prepared via a cosolvent route. We believe that the particles obtained by direct dissolution are nonequilibrium micellar aggregates.

Solution properties of various poly(sulfobetaine) homopolymers have been found to be sensitive to pH, ionic strength, and temprature.[8−10] There have been relatively few studies dealing with the solution properties of betaine copolymers. In one recent report,[11] statistical copolymers of (2-hydroxypropyl) methacrylamide and the acryloyl ester of *N*-(2-hydroxyethyl)piperazine-*N*′-ethanesulfonic acid of broad molar mass distribution were synthesized by conventional free-radical polymerization. Depending on the copolymer composition and solution conditions, multimolecular aggregates were formed via clustering of zwitterions.

Recently Lowe *et al.*[12] reported that near-monodisperse PMDAEMA homopolymers synthesized by GTP could be quantitatively betainized using 1,3-propanesultone under unexpectedly mild conditions to yield poly[3-[*N*-(2-methacroyloylethyl)-*N*,*N*-dimethylammonio]-propane sulfonate] (PDMAPS). As far as we are aware, this is the first example of a near-monodisperse polybetaine produced by direct synthesis rather than fractionation. Since GTP is a living polymerization, block copolymerization of DMAEMA with a wide range of methacrylate-based monomers is straightforward. Thus, betainization of PDMAEMA-*block*-poly(alkyl methacrylate) copolymers provided the first examples of betaine block copolymers.[13]

In this work we have prepared two PDMAEMA-*block*-PMMA block copolymers via GTP using both deuterated and nondeuterated methyl methacrylate as the hydrophobic comonomer. Subsequent betainization produced the corresponding PDMAPS-*block*-PMMA copolymers (see Figure 1). A preliminary study of the micellization behavior of these new hydrophilic−hydrophobic betaine-based block copolymers in aqueous solution using static/dynamic light scattering and small-angle neutron scattering is reported.

Experimental Section

Block Copolymer Synthesis. The two PDMAEMA−PMMA block copolymers were synthesized using group transfer polymerization (with an MTS initiator and a TBABB catalyst at room temperature) as described previously.[14] The DMAEMA monomer was polymerized first in each case. The first block copolymer was synthesized using normal methyl methacrylate (MMA) and the second was synthesized using deuterated MMA; the extent of deuteration was 94% by NMR spectroscopy, otherwise the conditions were identical. Betainization of both copolymers was achieved using 1,3-propanesultone in 10 mol % excess (based on DMAEMA residues) in THF at room temperature as described previously.[8]

Copolymer Characterization. The compositions of the two precursor block copolymers were determined using ^{1}H NMR spectroscopy for the normal block copolymer (DMAEMA content 80 mol %) and CHN elemental microanalysis for the deuterated block (DMAEMA content 79 mol %), respectively. Analyses of the two corresponding betainized block copolymers using ^{1}H NMR spectroscopy indicated quantitative betainization. Molar masses and molar mass distributions were determined using gel permeation chromatography (RI detector; THF; two PLgel 5 mm mixed D columns in series; flow rate of 1 mL min^{-1}). Calibration was carried out using PMMA standards ranging from about 2×10^3 to 53×10^3 g mol^{-1}. Mark−Houwink parameters were not available for the copolymers; thus all molar masses are reported as PMMA equivalents. The normal PDMAEMA−PMMA precursor block had an overall M_w of 9.8×10^3 g mol^{-1} and an M_w/M_n of 1.09. Thus, assuming 100% betainization, the M_w of the PDMAPS-*block*-PMMA copolymer should be $\sim 16 \times 10^3$ g mol^{-1}. The deuterated precursor block had an M_w of 8.9×10^3 g mol^{-1} and an M_w/M_n of 1.12. Assuming 100% betainization, the M_w of the PDMAPS-*block*-PMMA-d_8 copolymer should be $\sim 15 \times 10^3$ g mol^{-1}. To a first approximation, the molar mass, molar mass distribution, and chemical composition of both copolymers, can be considered to be identical.

Micelles. Micelles of both samples were prepared by direct dissolution in distilled water, aqueous solution of LiCl, citrate buffer (pH 2), and phosphate buffer (pH 8). Their properties

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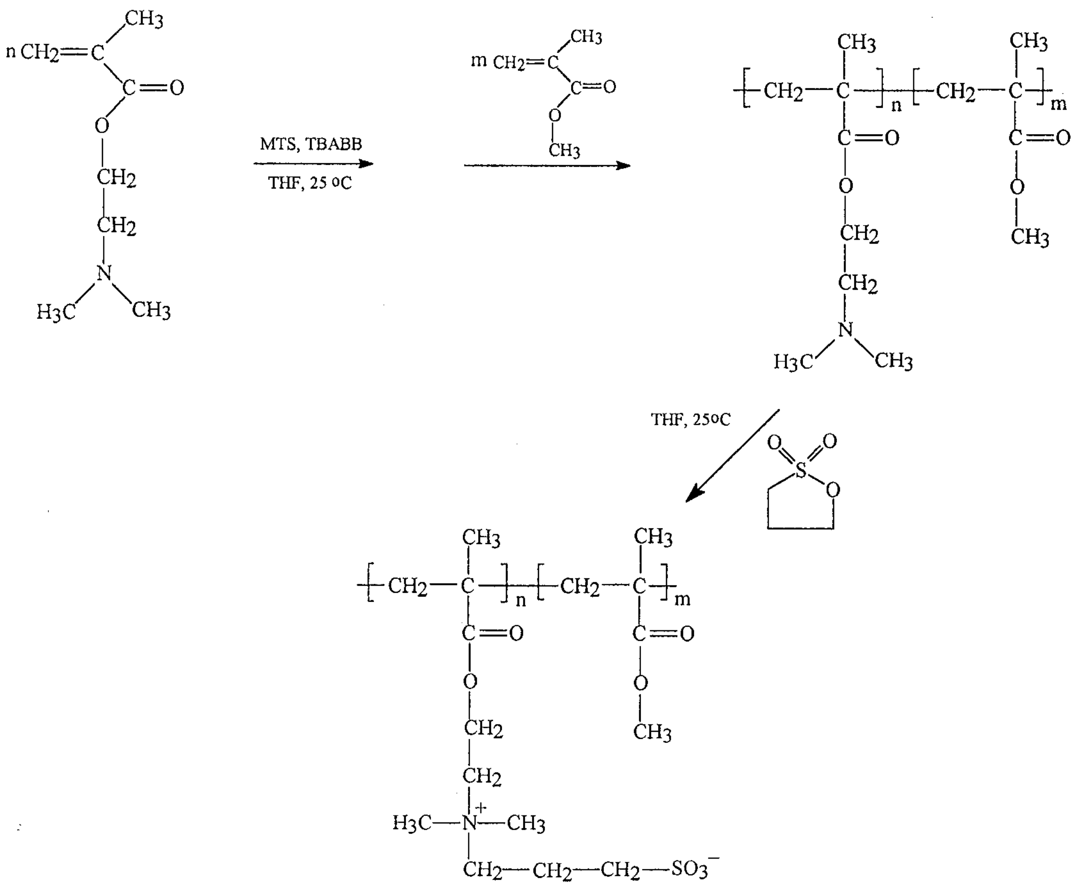

Figure 1. Outline of the synthesis of the two polysulfopropylbetaine block copolymers examined.

were studied by static and dynamic light scattering, and small-angle neutron scattering at 25 °C.

Static Light Scattering (SLS). Measurements of molar mass of micelles were performed on a Sofica instrument equipped with a He–Ne laser. Data were treated by a standard Zimm method. Refractive index increments of micelles in water were determined using a Brice-Phoenix differential refractometer. Refractive index increments in LiCl and buffer solutions were measured after dialysis to equilibrium against the corresponding solutions containing no polymer.[15]

Dynamic Light Scattering (DLS). The measurements were made using an ALV 5000, multibit, multitau autocorrelator and an argon ion laser (λ_o = 514.5 nm). Data were processed using both REPES[16] and a standard cumulant method.

Small-Angle Neutron Scattering (SANS). Solutions (1×10^2 g mL^{-1}) were prepared by dissolving PDMAPS-*block*-PMMA-d_8 directly into D_2O (isotopic purity 99 atom % D). Partial specific volumes of the betainized block copolymers were calculated from concentration dependences of the solution densities in D_2O using an Anton Paar DMA-02C vibrating densitometer. SANS measurements were performed using a time-of-flight small-angle neutron spectrometer YuMO at the IBR-2 pulse reactor in the Joint Institute for Nuclear Research, Dubna.[17] All measurements were corrected for background scattering and normalized using a vanadium standard.[18]

Results and Discussion

While the nonbetainized precursor copolymers had to be transferred into water from a good solvent for both blocks (THF) to form well-defined micelles,[7] the betainized copolymers formed micelles by direct dissolution in water, aqueous LiCl solutions, citrate buffer (pH 2), and phosphate buffer (pH 8). Since R_H values of micelles from samples with protonated and deuterated blocks were the same within experimental error (in average ±0.5 nm) for each of the solvents used, we have carried out SLS studies on the sample with the protonated block and SANS studies on the sample with the deuterated block and assumed that these systems were comparable. R_H values for micelles in D_2O solvents were typically 10% smaller than those in water.

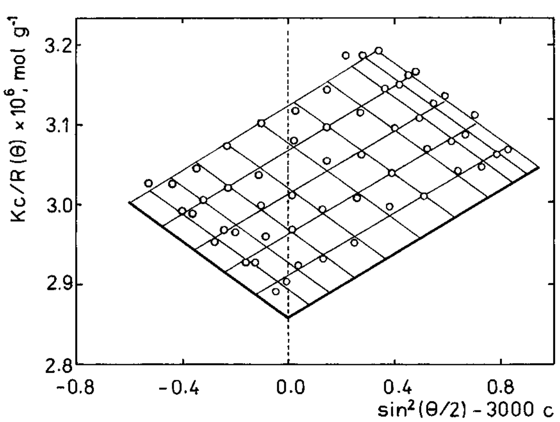

Figure 2. Zimm plot of PDMAPS-*b*-PMMA micelles in H_2O/0.1 M LiCl.

Micelle Characterization by SLS and DLS. Zimm graphs (for illustration see Figure 2) showed no anomaly, such as a shift in a unimer–micelle equilibrium.[1] Thus, in the concentration region under study (5×10^{-4}–5×10^{-3} g mL^{-1}), the molar mass, M_w, association number, n, hydrodynamic radius, R_H, and average value of the volume fraction of polymer segments in a micelle, ρ (Table 1), can be assigned to micelles only. It can be seen from Table 1 that micelles of very similar size and structure are formed in water and aqueous LiCl solution. Somewhat larger micelles with appoximately double the association number are formed in the two

Table 1. Characterization of PDMAPS-*block*-PMMA Micelles by SLS and DLS

solvent	d*n*/d*c*,[a] mL g^{-1}	$M_w \times 10^{-3}$, g mol^{-1}	*n*	R_H,[a] nm	ρ
H_2O	0.140 ± 0.002	335	22	10.3 ± 0.7	0.125
H_2O/0.1 M LiCl	0.142 ± 0.003	350	23	10.6 ± 0.8	0.120
pH 2	0.145 ± 0.002	650	43	12.1 ± 0.3	0.150
pH 8	0.144 ± 0.003	690	46	12.3 ± 0.3	0.152

[a] Average values from five measurements.

buffer solutions. The DLS data indicated that the micelle size distributions (not shown in Table 1) are rather broad (polydispersities lie in the range 0.18−0.22 by a cumulant method) in water and aqueous LiCl solution, but relatively narrow in the two buffer solutions (0.05−0.08). Although M_w and R_H in first two solvents differ from those in the two buffers, the average volume fraction of polymer segments in a micelle, ρ (defined as M_w/N_AV, where N_A is the Avogadro constant and M_w and V are the weight-average molar mass and volume of a micelle, respectively) remains essentially the same. For comparison, micelles with polystyrene cores and poly(methacrylic acid) shells[4] prepared by direct dissolution in a H_2O/dioxane mixture, where both cores and shells are swollen, had ρ values below 0.1. When the micelles transferred into water or aqueous buffers, in which the polystyrene micellar cores are glassy, the ρ values increased to almost 0.30. Our micelles with polybetaine shells have ρ values of 0.12 and 0.14, which indicate that, due to the compact PMMA cores, the shells must be very swollen.

It has been reported that, for PDMAPS homopolymers in dilute solution, an aqueous salt solution is a thermodynamically better solvent than distilled water.[8,10] The R_H values in Table 1 indicate that the presence of LiCl does not significantly influence the dimensions of the micellar shell. However, in our case, the PDMAPS chains, tethered to a spherical core/shell interface, can hardly be considered to be in the dilute regime. As far as we are aware, semidilute solutions of polysulfobetaines have not yet been studied.

Micelle Characterization by SANS. The deuterated block copolymer was used to get more detailed information regarding the micelle core−shell structure by the contrast variation technique. Unfortunately, the results from the mesurements in five D_2O/H_2O mixtures were not self-consistent. The square root of the extrapolated intensity, $I(0)^{1/2}$, varied linearly with the solvent scattering density, ρ_o, as expected. However, this dependence could not be described by any single value of micelle molar mass. Preliminary SAXS data (not presented here) revealed that an isotopic effect could be responsible for the inconsistency, since the molar mass of the micelle was significantly lower in D_2O than in H_2O. It may correspond roughly to a 10% lower R_H value from DLS. Thus, only data in D_2O are presented here.

The scattering curve (Figure 3) shows a maximum at higher *q* which may reflect micelle size. The least-squares fit of the scattering function of a homogeneous sphere to the experimental data leads to the micelle radius of 8.3 nm, a value close to the result from the Guinier analysis (9.0 nm) or from a core−shell model fit (8.2 nm). These results are in reasonably good agreement with the R_H of 9.4 nm in D_2O, obtained from DLS. Usually, such shoulders or maxima correspond to the micelle core radius.[19] In our case, the estimated radius of a deuterated PMMA core (~2 nm) would lead to a shoulder in a *q* range that is not covered under the conditions of the SANS experiments.

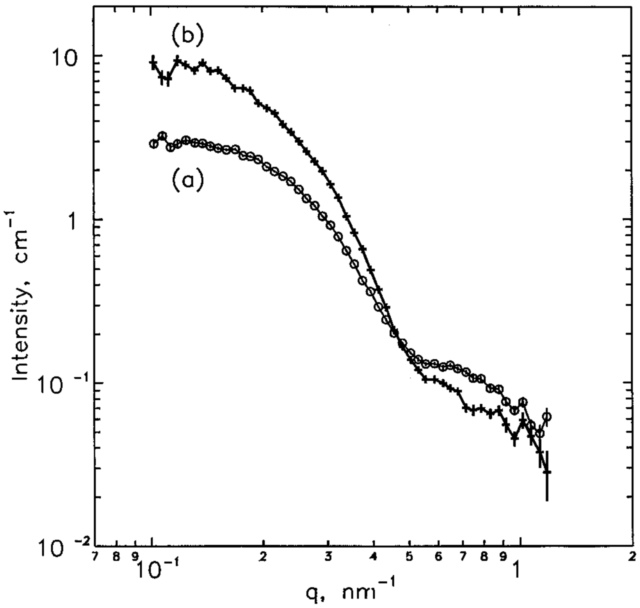

Figure 3. SANS curves of PDMAPS-*block*-PMMA-d_8 micelles ($c = 1 \times 10^{-2}$ g mL^{-1}) in (a) D_2O and (b) $D_2O/CHCl_3$.

A micelle molar mass of 190 × 10^3 g mol^{-1} was determined from the extrapolated absolute scattering intensity, *I*(0). SLS measurements in water indicated a micelle molar mass of 335 × 10^3 g mol^{-1}. This discrepancy is best explained by the isotopic effect on the micelle asssociation number.

One of the most important properties of block copolymer micelles in aqueous media is their ability to solubilize organic compounds in their hydrophobic cores.[20,21] Solubilization of chloroform by micelles comprising PMMA cores and poly(methacrylic acid) shells has been already reported.[22] For this system, SANS data indicated that up to 1.8 g of chloroform was solubilized per gram of PMMA. In the present work, the solubilization experiments were carried out as described previously;[22] i.e., an excess of chloroform was added to the PDMAPS-block-PMMA-d_8 solution in D_2O and SANS measurements were performed 24 h later. Figure 3 shows that the solubilization of chloroform results in a dramatic change in the scattering behavior of micelles. Assuming that the association number has not changed with solubilization, we estimate the number of chloroform molecules in a micelle to be 125, which corresponds to 1 g of chloroform/g of copolymer, or 11 g of chloroform/g PMMA-d_8. It is impossible to decide from the scattering curve in Figure 3 where the chloroform molecules are located, but from such a large amount, we assume that chloroform molecules are not only in the cores but in the shells also. The estimated micelle radii with solubilized chloroform are 8.7 and 10.4 nm, as judged from the position of the shoulder and from the Guinier analysis, respectively.

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