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Polymeric Surfactants for the New Millennium: A pH-Responsive, Zwitterionic, Schizophrenic Diblock Copolymer**

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Recently, we have demonstrated that certain hydrophilic AB diblock copolymers can self-assemble in aqueous media to form both conventional micelles (with the A block forming the micelle core) and reverse micelles (with the B block forming the micelle core),[1–3] and we have described these diblock copolymers as having "schizophrenic" character.[3] To date, only two well-documented examples of schizophrenic diblock copolymers have been reported. The first "proof-of-concept" example was reported by Bütün et al. who polymerized 2-(*N*-morpholino)ethyl methacrylate (MEMA), followed by 2-(diethylamino)ethyl methacrylate (DEA) using group-transfer polymerization (GTP).[1, 2] The two micellar transitions of this polymer were induced by changes in solution pH and ionic strength, respectively. In both cases micellization occurred at around 20 °C, but the addition of large quantities of electrolyte (1.0 M Na_2SO_4) to produce MEMA-core micelles was somewhat artificial. The second example involved using a poly(propylene oxide)-based (PPO) macro-initiator for the polymerization of DEA by atom-transfer radical polymerization (ATRP) in alcoholic media at 55 °C. The resulting PPO–DEA diblock copolymer dissolved in cold water at pH 6.5. DEA-core micelles were formed at 5 °C in mildly alkaline solution (pH 8.5) and PPO-core micelles were obtained at pH 6.5 at elevated temperatures (40–70 °C). Thus, neither micellar state was stable at ambient temperature; this is rather inconvenient for characterization purposes and, more importantly, for industrial applications of this particular polymeric surfactant.

Herein we describe a new zwitterionic AB diblock copolymer that undergoes spontaneous self-assembly in aqueous solution at ambient temperature to form both micelles and reverse micelles, simply by switching the solution pH (Figure 1). This remarkable diblock copolymer is poly(4-vinyl benzoic acid-*block*-2-(diethylamino)ethyl methacrylate) (VBA-*b*-DEA), which was synthesized by ATRP using protecting group chemistry, followed by hydrolysis; the degrees of polymerization of the VBA and DEA blocks are 60 and 66, respectively (for experimental details, see Supporting Information).

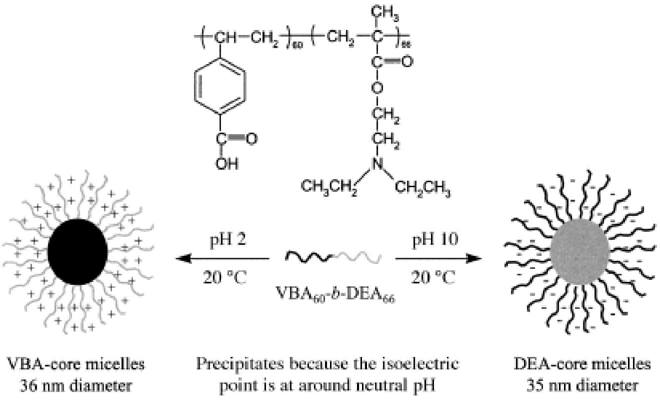

Figure 1. Chemical structure of VBA_{60}-*b*-DEA_{66} diblock copolymer and its pH-induced "schizophrenic" micellization behavior in aqueous solution.

It is known that DEA homopolymer is a weak polybase with a pK_a of approximately 7.3.[4] DEA homopoplymer dissolves in acid as a cationic polyelectrolyte, by protonation of its amine groups, but becomes insoluble above pH 7.1. VBA homopolymer has a pK_a of around 7.1 (determined by hydrogen ion titration); it is insoluble at low pH but becomes soluble as an anionic polyelectrolyte above pH 6.2, by ionization of its carboxylic acid groups. Hence, the VBA-*b*-DEA diblock copolymer is a more hydrophobic analogue of

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the extensively reported poly(2-(dimethylamino)ethyl methacrylate)-*block*-(methacrylic acid)) zwitterionic diblock copolymer.[5–15] Depending on its block composition, and on the ionic strength and pH of the aqueous solution, the latter diblock copolymer is either soluble,[5, 12–13] insoluble, or forms large, nonmicellar aggregates of 400 – 500 nm diameter.[11] In contrast, the VBA-*b*-DEA diblock copolymer reported herein was expected to form compact, well-defined VBA-core micelles at low pH and DEA-core micelles at high pH (Figure 1). Dynamic and static light scattering, ^{1}H NMR spectroscopy, aqueous electrophoresis, transmission electron microscopy, surface tensiometry, and fluorescence techniques were used to characterize the aqueous-solution properties of this unique zwitterionic diblock copolymer.

Figure 2 shows the ^{1}H NMR spectra of the protected diblock copolymer before hydrolysis (spectrum a) and after hydrolysis (spectrum b). In its deprotected, zwitterionic form there are very few organic solvents for the VBA-*b*-DEA diblock copolymer. Fortunately, it proved to be sufficiently soluble in [D$_5$]pyridine. In this basic solvent, the DEA block is in its neutral form and the VBA block is ionized (carboxylate salt form). The poly(*tert*-butyl 4-vinylbenzoate) block is efficiently hydrolyzed to form poly(4-vinylbenzoic acid). Moreover, before and after hydrolysis, the DEA content of the diblock remains constant within experimental error, which indicates that no unwanted hydrolysis of the DEA residues occurred during removal of the *tert*-butyl protecting groups.

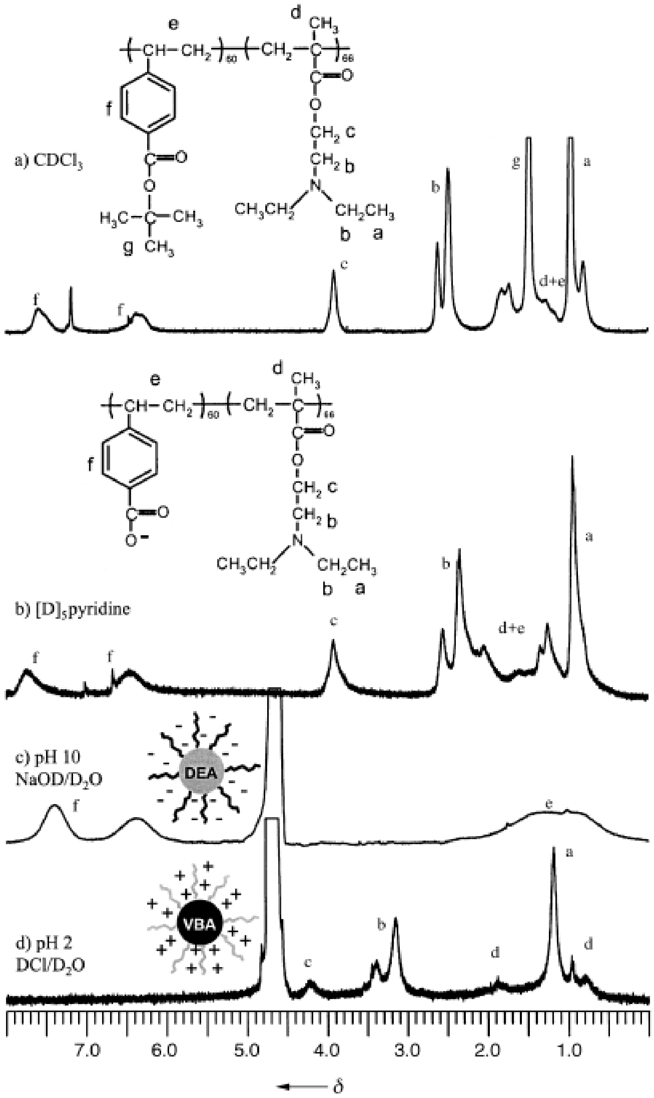

Figure 2. ^{1}H NMR spectra obtained for a) the *t*BuVBA$_{60}$-*b*-DEA$_{66}$ precursor diblock copolymer in CDCl$_3$; b) after hydrolysis in [D$_5$]pyridine (note the disappearance of the signal at 1.5 ppm, caused by the removal of the *t*Bu protecting groups); c) DEA-core micelles formed at pH 10; d) VBA-core micelles formed at pH 2.

The deprotected VBA$_{60}$-*b*-DEA$_{66}$ diblock copolymer dissolves in either dilute acidic or dilute alkaline solution. After initial dissolution at high or low pH, a 1.0 g L^{-1} solution of this copolymer precipitated between pH 6.6 – 8.3. In principle, such precipitation should be confined to a discrete, well-defined pH value known as the isoelectric point (IEP), at which the cationic charge on the DEA block just balances the anionic charge on the VBA block.[5–15] In practice, a pH range is usually observed rather than a single value; this maybe because of polydispersity effects. Below pH 6 or above pH 9, the zwitterionic diblock copolymer redissolved to form a bluish or transparent micellar solution. Because the calculated IEP[5] is 7.25, this pH-dependent solubility is in good agreement with the respective pK_a and pK_b values of the VBA and DEA blocks; it is also consistent with the observations of several research groups who have studied related zwitterionic diblock copolymers.[5–15]

In Figure 2, spectrum c, aromatic signals corresponding to the VBA block are evident at $\delta = 6.3 - 7.8$, but there are no signals corresponding to the DEA residues, which indicates that DEA-core micelles with anionic VBA coronas are formed at pH 10, as expected. However, in spectrum d, all of the characteristic signals arising from the DEA residues are visible but there are no signals corresponding to the aromatic VBA block; this indicates that VBA-core micelles with cationic DEA coronas are formed at pH 2.

Figure 3 a shows the variation of averaged hydrodynamic diameter ($\langle D_h \rangle$) on adjusting the pH of a 1.0 g L^{-1} VBA$_{60}$-DEA$_{66}$ diblock-copolymer aqueous solution. At pH 2, well-defined VBA-core micelles are formed with a $\langle D_h \rangle$ of 36 nm and a polydispersity of 0.15. As the pH is increased, the micelle diameter increased monotonically because of the concomitant decrease in degree of protonation of the DEA block and increasing degree of ionization of the VBA block. Thus, as the solubility of the VBA block increases and the DEA block becomes less hydrophilic, the overall hydrophilic – hydrophobic balance of the diblock copolymer changes and larger, nonmicellar aggregates[11, 16–20] are formed at around pH 6 with a $\langle D_h \rangle$ of about 120 nm. A further increase in pH leads to precipitation, indicated by the dramatic increase in turbidity (see shaded region, Figure 3). Above pH 8.5, the solution becomes transparent again. At pH 9.2, colloidal aggregates are formed with a $\langle D_h \rangle$ of around 66 nm. Well-defined, compact DEA-core micelles with a mean diameter of 35 nm are formed at pH 10. The polydispersities of micelles formed in alkaline media ranged from 0.1 – 0.2.

Aqueous electrophoresis studies (Figure 3 b) indicate that the net charge on the particles is close to zero at pH 7.5; this IEP is very close to the midpoint of the precipitation region,

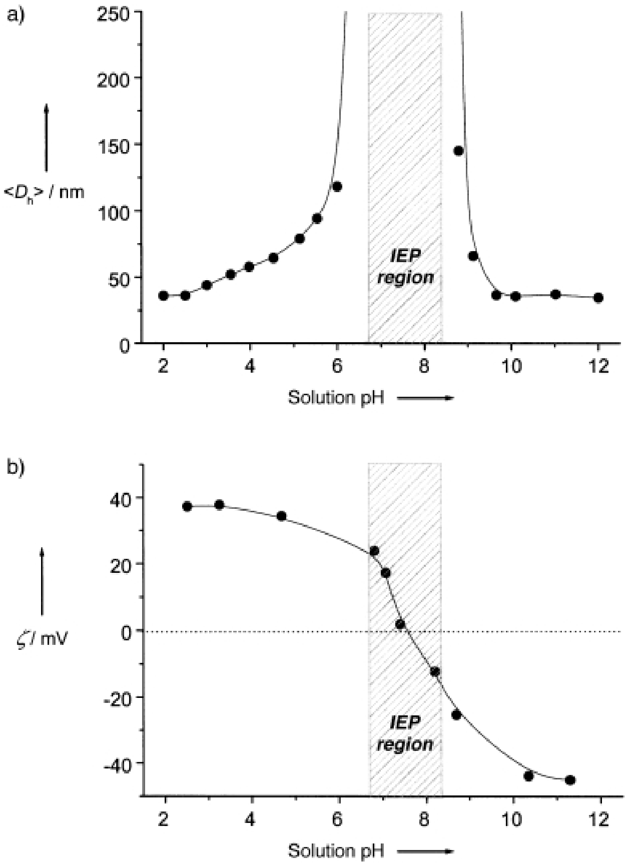

Figure 3. a) The variation of hydrodynamic micelle diameter as a function of solution pH for a dilute aqueous solution (1.0 $\mathrm{g\,L^{-1}}$) of the $\mathrm{VBA_{60}}$-*b*-$\mathrm{DEA_{66}}$ diblock copolymer at 20 °C. b) The variation of zeta potential as a function of pH for a 1.0 $\mathrm{g\,L^{-1}}$ aqueous solution of the $\mathrm{VBA_{60}}$-*b*-$\mathrm{DEA_{66}}$ zwitterionic diblock copolymer at 20 °C.

as determined by visual inspection (pH 7.4). Either side of this IEP, the micelles had either positive zeta potentials because of cationic DEA coronas (at low pH) or negative zeta potentials because of anionic VBA coronas (at high pH).

Static light-scattering studies (Zimm analysis) for VBA-core micelles and DEA-core micelles, formed at pH 2 and pH 10, respectively, yielded weight-average micelle masses of approximately 1.45×10^6 and $2.25 \times 10^6\ \mathrm{g\,mol^{-1}}$. The corresponding micelle aggregation numbers (N_{agg}) were estimated to be 46 and 72, respectively (see Table 1). By use of $\langle\rho\rangle = M_w/(4\pi\langle R_h\rangle^3/3)$, where R_h is the hydrodynamic radius, the average densities $\langle\rho\rangle$ of the VBA-core and DEA-core micelles were estimated to be 0.11 and 0.15 $\mathrm{g\,cm^{-3}}$, respectively. Thus, the average density of the VBA-core micelles is somewhat higher than that of the DEA-core micelles. The $\langle R_g\rangle/\langle R_h\rangle$ ratio, where R_g is the radius of gyration, follows a similar trend, with the value of 0.82 obtained for the VBA-core micelles lying closer to the theoretical value of 0.774 for a hard sphere. However, these average micelle densities are much lower than the solid-state density of 1.28 $\mathrm{g\,cm^{-3}}$, determined for the $\mathrm{VBA_{60}}$-*b*-$\mathrm{DEA_{66}}$ diblock copolymer by helium pycnometry. This result indicates that both types of micelles are appreciably swollen, which suggests significant stretching of the polyelectrolyte chains in the micelle corona.

Table 1. Static and dynamic light-scattering data obtained for the two types of micelles formed by the "schizophrenic" $\mathrm{VBA_{60}}$-*b*-$\mathrm{DEA_{66}}$ diblock copolymer in water at 20 °C.

Conditions	DEA-core micelles at pH 10	VBA-core micelles at pH 2
$M_{w,\mathrm{micelles}}$	1.45×10^6	2.25×10^6
$\langle R_g\rangle$ [nm]	16.5	14.7
$\langle R_h\rangle$ [nm]	17.5	18
$\langle R_g\rangle/\langle R_h\rangle$	0.94	0.82
N_{agg}	46	72
$\langle\rho\rangle$ [$\mathrm{g\,cm^{-3}}$]	0.11	0.15

Transmission electron microscopy (TEM) studies of both types of micelles (Figure 4) indicated spherical morphologies, with mean number-average diameters of about 25 nm and 40 nm for DEA-core and VBA-core micelles, respectively. The DEA-core micelles have a fairly uniform size-distribution and, taking into account both the degree of hydration and polydispersity effects, the mean diameter determined by TEM compares reasonably well to that from dynamic light scattering (DLS). TEM studies of the VBA-core micelles indicated that these micelles are somewhat more polydisperse, with diameters ranging from 20–70 nm; these values should be compared to the $\langle D_h\rangle$ of 36 nm obtained by DLS. This discrepency may indicate some degree of spreading of these micelles on the surface of the TEM grid; such "flattening" has recently been observed for similar micelles with cationic coronas adsorbed at a planar mica surface.[21].

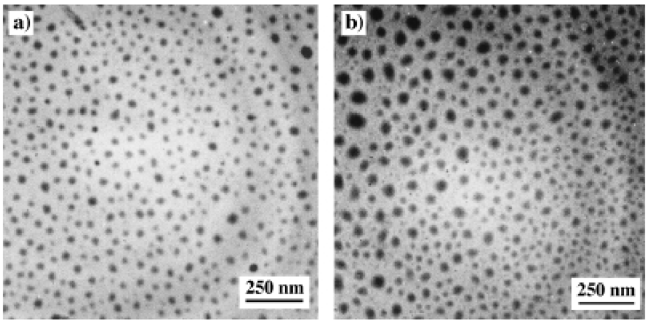

Figure 4. Typical TEM micrographs of a) DEA-core micelles at pH 10 and b) VBA-core micelles at pH 2, prepared using the $\mathrm{VBA_{60}}$-*b*-$\mathrm{DEA_{66}}$ schizophrenic diblock copolymer. The micelles were stained with $\mathrm{RuO_4}$ vapor to enhance contrast.

Such micellar self-assembly is fully reversible for many cycles, provided that the additional background salt formed during pH adjustment does not cause salting out (which typically occurs at around 0.8 M NaCl). However, the mean micelle diameter increases gradually at higher salt concentrations, because the insoluble block becomes more hydrophobic and the soluble block less hydrophilic. Surface tension and fluorescence studies of the block copolymer micelles are summarized in the Supporting Information.

In summary, a new zwitterionic diblock copolymer has been synthesized by ATRP, which exhibits a rich phase behavior in aqueous solution at 20 °C. Depending solely on the solution pH, this "schizophrenic" copolymer can exist in two different micellar states and also exhibits an isoelectric point at around neutral pH. This novel zwitterionic diblock copolymer may have potential applications as a pigment dispersant,[10, 22, 23] or in the separation and purification of proteins.[7, 24]

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[16] At intermediate pH values either side of the IEP, the electrostatic interaction of the oppositely charged blocks can lead to the formation of aggregates (soluble polyelectrolyte complexes), which are stabilized by uncompensated cationic charge on the DEA block (below the IEP) or anionic charge on the VBA block (above the IEP). In contrast, at pH 2 (or pH 10) the VBA block (or DEA block) is uncharged; thus hydrophobic interactions of this neutral block should produce compact, well-defined micelles.

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A Selective Chromogenic Reagent for Nitrate**

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The selective sensing of anions by natural and synthetic receptors is an important area of supramolecular chemistry.[1] Anions play significant roles in biological and environmental processes, therefore the development of new chemosensors for anions is an important topic. Anion-sensing receptors incorporate into their structures groups that are capable of interaction with anions, and sensing subunits in which spectroscopic[2] or electrochemical[3] features change upon anion binding. Chemosensors with changes in their spectroscopic behavior have either fluorogenic[4] or chromogenic[5] signalling subunits. Chromogenic reagents are especially attractive because the anion determination can be carried out by the naked eye, without the use of expensive equipment. Chromogenic reagents for the selective detection of inorganic and organic anions have been reported.[6] However, it is still a challenge to find chromogenic receptors for the selective sensing of poorly coordinating anions such as nitrate. As far as we know, the only example of nitrate sensing by color change, by use of receptors coupled to dyes, was reported recently, and it involved a competitive assay between nitrate and methyl red or resorufin in binding a polyamide cage, in dichloromethane:methanol 50:50 v/v. The system, however, is not specific and addition of bromide or perchlorate also produced color changes, although to a lesser extent.[7] We now report a new and specific chromogenic reagent for nitrate using a *p*-nitrophenylazobenzene group as a dye and a mercuric complex as an anion-binding site. The system shows a selective change of color in acetonitrile but can also be applied to the selective determination of nitrate in water.

The aza-oxa-thia macrocycle (see Scheme 1) was obtained by the cyclization of 3,6-dioxa-1,8-octanedithiol and dimesilated *N*,*N*-diethanolphenylamine in acetonitrile/K_2CO_3 at reflux,[8] under high dilution conditions. The macrocycle was obtained in a 40 % yield. The macrocycle was coupled with the azonium salt of *p*-nitroaniline in HCl to obtain **L^1** as a red-orange powder (80 % yield). ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis are consistent with the proposed formulation.

The visible spectrum of the ligand **L^1** in acetonitrile is characterized by an intense band centered at 490 nm ($\varepsilon = 26\,000\,\mathrm{M}^{-1}\,\mathrm{cm}^{-1}$), which is responsible for the orange color of the solutions and is caused by a charge transfer from the

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