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Hybridization of Block Copolymer Micelles

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Block copolymers of styrene and methacrylic acid dissolved in water/dioxane mixtures form spherical micelles with polystyrene cores and poly(methacrylic acid) shells. When two micellar solutions containing micelles made from two different copolymers are mixed, the micelles may hybridize. The hybridization was followed by the method of sedimentation velocity. The rate of hybridization was found to be a very sensitive function of the architecture of both copolymers and of the thermodynamic properties of the solvent mixture. In many instances this rate is imperceptibly slow; it may be totally frozen when the solvent is very poor with respect to the micellar core. The analysis of the hybridization of numerous micellar pairs provided new insights into the dynamics and thermodynamics of unimer/micelle equilibria.

Introduction

This study is a part of our comprehensive investigation of properties of block copolymer micelles formed by copolymers of styrene and methacrylic acid. In a previous paper[1] we have described the synthesis and molecular characteristics of these block copolymers. Preparation and characterization of the micellar solutions were described in other papers.[2-4] We have used measurements of fluorescence for studying local mobility of polymer segments within the micellar cores[5-7] and for obtaining data of uptake and release of small molecules by the micelles.[8] The present study is concerned with the mobility of the unimers, i.e., with the ability of the unimer molecules to extricate themselves from the micelles and reenter other micelles. We have found that sedimentation velocity is a very convenient method for studying this phenomenon.[9] In a supporting study, sedimentation behavior of block copolymer micelles was described.[10]

Detergent micelles and block copolymer micelles have many common features and many quite different ones. The common features are based mainly on the thermodynamics of micellization. When molecules having two dissimilar segments are dispersed in a solvent (or a mixture of solvents) that is a good solvent for one segment of the molecules but poor for the other segment (so-called selective solvents), then the insoluble segments segregate themselves in domains with low solvent content while the other segments form less concentrated domains. When the overall concentration of the copolymer or detergent is small, the thermodynamic factors lead to formation of micelles, i.e., spherical particles with a dense core of insoluble segments that is surrounded by a shell (corona) of the soluble segments. Such micelles are surrounded by solvent. In typical detergent micelles (usually dispersed in aqueous media), the core is formed by short aliphatic chains, while the shell is formed either by ionic groups (soaps and other cationic or anionic detergents) or by short hydrophilic moieties (oligo(ethylene oxides) in many nonionic detergents). At the thermodynamic equilibrium, the aggregation number (number of molecules comprising the micelle) follows from the condition that the total Gibbs free energy of the system must be at minimum. Thermodynamic analysis shows that the contribution of a single molecule (unimer) to the Gibbs energy is the determining factor: it has the lowest value in micelles that are the most frequent ones in the solution.[11] Further analysis shows that the distribution of aggregation numbers around this most stable form is quite narrow. This situation is reflected in the model of closed association, in which the unimers A are supposed to be in equilibrium with micelles A_n[12-14]

$$nA \rightleftharpoons A_n \qquad (1)$$

When n is large, this model well describes the phenomenon

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of critical micelle concentration (cmc): under this concentration no micelles are present in the solution while above it unimers remain at cmc and micelles are formed only by the excess unimers. Another feature common to detergent micelles and block copolymer micelles is solubilization of compounds insoluble in the solvent in question but soluble in the micellar cores.

The dissimilarities between the detergent and block copolymer micelles are a consequence of different dynamics of the micellar systems and of the kinetics of the equilibration phenomena. When experimental conditions (temperature, solvent composition) are changed from some conditions at which micelles are present to a different condition, for which thermodynamics requires micelles with different aggregation number, the system has a tendency to reequilibrate. Under certain changes of the conditions, micelles can be formed from molecular solution or vice versa. In the case of detergent solutions, these processes (studied by fast reaction techniques as, e.g., temperature jump) are in a submillisecond time scale.[15-18] In the case of block copolymer micelles, reequilibrization, as well as micelle formation and dissociation are necessarily much slower[19-21] due to a more complicated way in which much longer core-forming blocks are extricating from or re-entering into micelles. These processes are the subject of the present study.

As far as we know, only a few quite recent studies were devoted to it. Cantú et al.[22] mixed micelles of two different biological amphiphiles in dilute aqueous solutions of NaCl and followed the development of the system by static light scattering. The apparent molecular weight of the solution gradually increased, then leveled off after 10 h. Wang et al.[23] mixed two solutions of diblock polystyrene-*block*-poly(ethylene oxide) micelles in water. The polystyrene blocks of both copolymers they used were rather short (M_w = 4500). The polystyrene block of one copolymer was labeled by pyrene, the other one by naphthalene. The migration of unimers was followed by the changes in fluorescence. At ambient temperatures no change was observed for several days. However, when the solution was heated to 60 °C, for 3 to 97 h, fluorescence indicated that unimer transfer is occurring. The apparent rate constant was about 1.7×10^{-5} s^{-1}. Similar experiments with micelles having polystyrene cores, labeled by anthracene and carbazole, and poly(hydrogenated isoprene) shells in aliphatic solvents were performed by Procházka et al.[24] The relaxation time of the unimer exchange was on a time scale of 10^3 s. Halperin and Alexander[25] analyzed theoretically the dynamics of unimers in micellar solutions and, for several limiting cases, developed scaling relations for the unimer transfer.

In our experiments, we have used two different copolymers to prepare two micellar solutions with micelles of different size and sedimentation coefficient. We then mixed these solutions and repeatedly performed sedimentation velocity runs on aliquots of the mixture as a function of time elapsed from the mixing.

Table I. Molecular Properties of Styrene–Methacrylic Acid Block Copolymers

sample	$M_w \times 10^{-3}$ [a]	$M_{w,ps} \times 10^{-3}$ [b]	M_w/M_n	% x_{ps} [c]	% w_{ps} [d]
		Diblock Copolymers			
SA-1	40.3	24.4	1.09	56	61
SA-2	60.3	24.4	1.15	36	41
SA-5	36.3	27.8	1.05	73	77
SA-10	46.7	30.1	1.09	60	65
SA-20	39.1	20.2	1.05	47	52
SA-22	68.9	40.4	1.03	54	59
N4SA-2	48.5	21.3	1.08	45	50
N1SA-4	57.6	34.0	1.07	59	64
		Triblock Copolymers			
ASA-4	83.0	55.9	1.09	63	67
ASA-8	68.7	38.5	1.13	51	56
ASA-9	31.2	22.5	1.12	68	72
ASA-10	37.7	22.5	1.11	55	60

[a] Molecular weight of copolymer (unimer). [b] Molecular weight of polystyrene block. [c] Mole fraction of styrene units. [d] Weight fraction of polystyrene.

Experimental Section

Block Copolymers. Diblock copolymers, polystyrene-*block*-poly(methacrylic acid) (SA), and triblock copolymers, poly(methacrylic acid)-*block*-polystyrene-*block*-poly(methacrylic acid) (ASA) were synthesized by sequential anionic polymerization of styrene and *tert*-butyl methacrylate in tetrahydrofuran. Cumyl potassium was used as an initiator for the diblock copolymers; naphthalene potassium complex was used for the triblock copolymers. The *tert*-butyl groups in the side chain of the copolymers were hydrolyzed off using aqueous hydrochloric acid in dioxane. The resulting SA and ASA copolymers were precipitated in cold hexane. They were redissolved in 1,4-dioxane and freeze-dried. The degree of hydrolysis and the styrene content were calculated from NMR measurements. Molecular weights and the polydispersity index, M_w/M_n, were determined by static light scattering and by GPC, as reported in our previous paper.[1]

Micellar Solutions. The preparations of micellar solutions, as well as the dialysis procedure, were described elsewhere.[2] The concentration of the micelles was 5×10^{-3} g/mL. Micellar mixtures were prepared by mixing equal amounts of two selected micellar solutions and were immediately used for sedimentation experiments.

Ultracentrifugation. A Spinco Model E ultracentrifuge, equipped with electronic speed control and RTIC temperature control unit was used to measure sedimentation velocity at 52 000 rpm rotor speed. Double sector cells equipped with sapphire windows containing approximately equal quantities of solution and solvent in the two sectors and a schlieren optical system were used. Sedimentation coefficients were evaluated in a routine way.

Quasielastic Light Scattering. A Brookhaven BI 2030 apparatus (He–Ne laser, scattering angle 90°) was used. The autocorrelation functions were treated by the cumulant method.[5-8]

Intrinsic Viscosity. Intrinsic viscosities were measured using a Ubbelohde type viscometer with a photoelectric registration of flow times. The temperature was controlled within 25 ± 0.01 °C.

Results

The basic molecular properties of block copolymers, which were reported in our previous paper,[1] are briefly listed in Table I. Table II lists some properties of micelles prepared by direct dissolution of the individual freeze-dried samples in a mixture of 80 vol % of 1,4-dioxane and 20% water (80D/20W). These data were obtained using several hydrodynamic and light scattering techniques as described in previous paper.[2-4] We estimate the precision of the R_h and N_{ag} values as 3% and 10%, respectively. In

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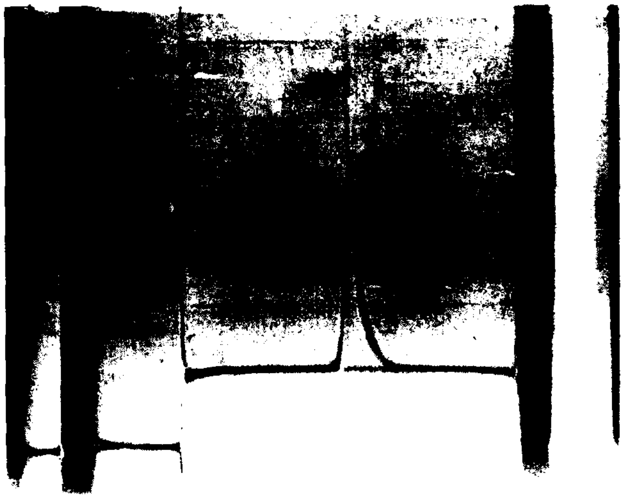

Figure 1. Sedimentation velocity experiment: diblock copolymer micelle SA-5 in 80D/20W solvent; c = 5 mg/mL; 52 000 rpm, after 30 min.

Table II. Micellar Properties of Block Copolymers in the 80D/20W Solvent

sample	$D \times 10^8$ (cm^2/s)	R_h (nm)	$[\eta]$ (mL/g)	$M_w \times 10^{-6}$	N_{ag}	$s \times 10^{13}$ (s^{-1})
		Diblock Copolymers				
SA-1	5.09	24.7	19.1	4.7	117	8.7
SA-2	4.08	30.8	43.7	4.2	70	4.7
SA-5	4.29	29.3	13.6	12.5	344	13.4
SA-10	4.42	28.5	15.1	10.4	223	12.1
SA-20	5.26	23.9	24.6	3.3	84	6.2
SA-22	2.45	51.4	29.0	30.5	443	20.2
N4SA-2	5.10	24.7	24.6	3.86	80	7.6
N1SA-4	3.85	32.7	15.5	14.2	262	15.2
		Triblock Copolymers				
ASA-4	3.26	38.6	21.6	16.7	201	11.7
ASA-8	5.26	23.9	28.6	3.01	44	5.7
ASA-9	10.1	12.5	9.6	1.27	41	2.8
ASA-10	9.11	13.8	16.5	1.00	27	2.8

sedimentation velocity experiments all micellar solutions displayed narrow sedimenting peaks (Figure 1). This behavior indicates that the micelles are quite uniform. This result was also confirmed by the quasielastic light scattering experiments. The polydispersities of hydrodynamic radii are very small.[4]

In the first series of experiments we have studied the effect of the copolymer architecture (number of blocks and their sizes) on the dynamics of the micellar hybridization under identical thermodynamic conditions, namely in the 80D/20W solvent mixture, i.e. in the same mixture in which the micelles were prepared originally. Most experiments were performed using the triblock copolymer ASA-10. This copolymer forms relatively small micelles ($s = 2.8 \times 10^{-13}$ s^{-1}; $n = 27$). It is noteworthy, that a diblock copolymer SA-20 having almost identical molecular weight and composition forms much larger micelles ($s = 6.2 \times 10^{-13}$ s^{-1}, $n = 90$). In one set of experiments, we mixed the ASA-10 micelles with diblock micelles formed by SA-2, SA-20, and N4SA-2 copolymers, respectively. All those micelles have $s < 8 \times 10^{-13}$ s^{-1}. In these three experiments, the first sedimentation run, performed about 30 min after mixing, showed the presence of only one sedimentation peak with the sedimentation coefficient in between the coefficients of the original micelles. Mixtures of ASA-10 micelles with SA-1 and SA-10 micelles (s values between 8 and 12 $\times 10^{-13}$ s^{-1}) produced two sedimenting peaks immediately after mixing. However, these two approached each other quickly and merged within 24 h. During this hybridization in the ASA-10/SA-10 mixture, the size of the slow peak (ASA-10) was gradually increasing.

Very different behavior was observed for mixtures of ASA-10 micelles with SA-5 or N1SA-4 micelles (s values 13.4 and 15.2 $\times 10^{-13}$ s^{-1}, respectively). A third peak emerged between the two original peaks and slowly grew at their expense. Finally mixtures of ASA-10 micelles with the very large SA-22 micelles ($s = 22.6 \times 10^{-13}$ s^{-1}) did not show any change in the sedimentation pattern over 20 days. Similarly, ASA-10 micelles did not show any tendency toward hybridizing (over 14 days) with larger ASA-4 micelles ($n = 242$, $s = 11.7 \times 10^{-13}$ s^{-1}).

Triblock copolymer micelles of the ASA-9 sample (which has the same central polystyrene block as the ASA-10 sample but shorter methacrylic acid blocks) hybridized with the diblock N4SA-2 micelles within the first 20 min—the same behavior as observed in the ASA-10/N4SA-2 mixture. Representative sedimentation photographs are presented in Figures 2 and 3.

In a follow-up experiment, we have mixed the fast equilibrating micelles of ASA-10 and N4SA-2 in the ratios 0/1, 1/3, 1/1, 3/1, and 1/0. In all cases, a single peak was observed already in the first run. The sedimentation coefficients were (7.6, 5.2, 4.6, 3.9, and 2.8) $\times 10^{-13}$ s^{-1}, respectively.

In the next series of experiments, we mixed the ASA-8 triblock copolymer micelles ($s = 5.7 \times 10^{-13}$ s^{-1}, $n = 44$, they are larger than the ASA-10 micelles) with diblock micelles. The SA-10 micelles that fully hybridized with ASA-10 micelles within 1 day needed at least 3 days for hybridization with ASA-8 micelles. Again the slower triblock peak grew at the expense of the larger diblock peak. Both the SA-5 micelles and N1SA-4 micelles when mixed with the ASA-8 micelles produced only two very slowly approaching peaks. In these cases, there was a change of the sedimenting pattern just perceptible after 12 days. Finally, the big SA-22 micelles did not hybridize with either the ASA-8 or ASA-10 micelles.

The shell structure plays also a significant role in the dynamic experiments. Copolymer ASA-9 has identical central polystyrene block as copolymer ASA-10, but it has shorter poly(methacrylic acid) blocks. Consequently, it forms slightly heavier micelles that, nevertheless, have a slightly smaller hydrodynamic radius. When the ASA-9 micelles are mixed with N4SA-2 micelles, they equilibrate within 20 min, similarly as ASA-10 micelles do. However, when they are mixed with N1SA-4 micelles (which formed a very slowly equilibrating three-component system with ASA-10 micelles), the hybridization process was completed within hours.

In all above described experiments, the triblock micelles had smaller sedimentation coefficients than the diblock micelles. In all cases, when the hybridization process could be observed, the small triblock micelles grew at the expense of the big diblock micelles. In our next experiment, we mixed the relatively small N4SA-2 diblock micelles with rather large ASA-4 triblock micelles. In this case, the hybridization was rather slow, but it was clear that the small diblock micelles are growing at the expense of the large triblock micelles. In other words it was the big triblock unimers that were transported primarily.

To complete our mixing picture, we mixed also the small triblock ASA-10 micelles with large triblock ASA-4 micelles. No change of sedimentation pattern was observed during 14 days. We have also mixed three pairs of diblock micelles. The smaller SA-20 micelles hybridized fully with intermediate SA-10 micelles within a week. However, mixtures of large SA-22 micelles with either SA-20 or SA-

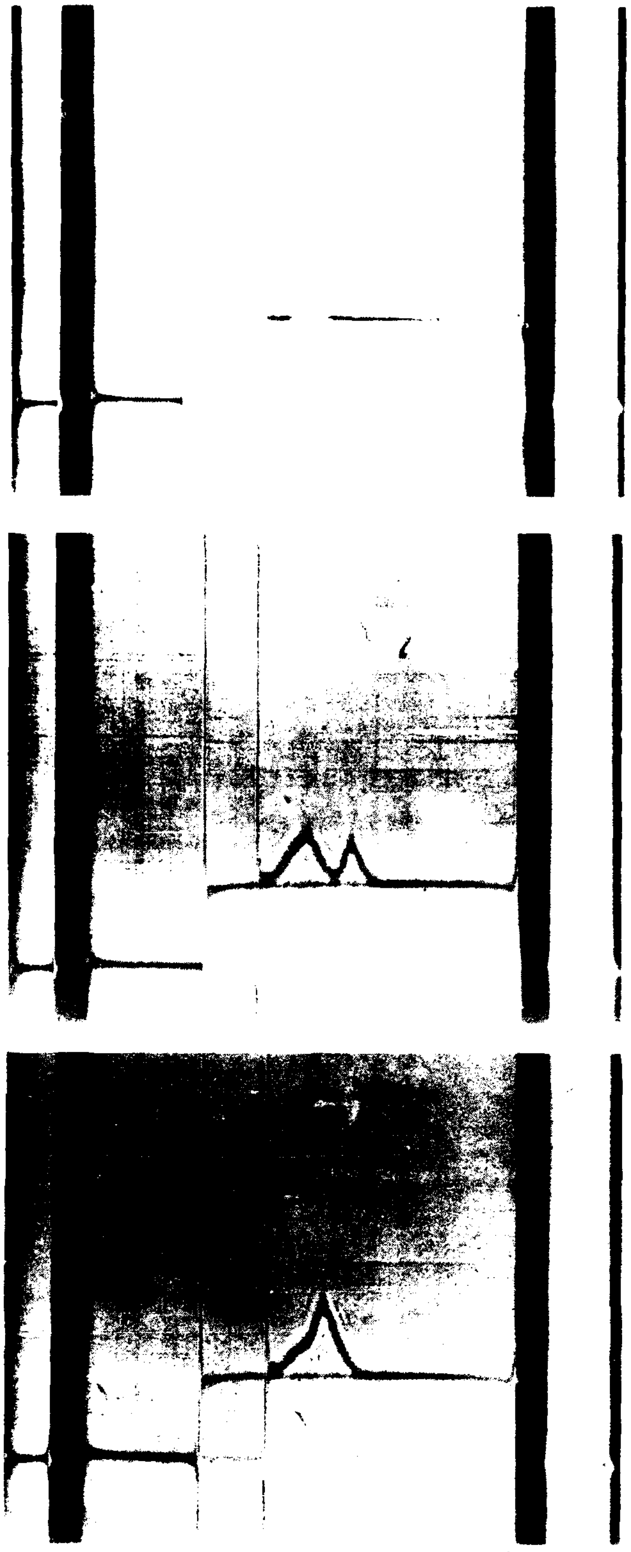

Figure 2. Sedimentation velocity experiment of mixture of micelles ASA-10/SA-1 in 80D/20W: (top) immediately after mixing; (middle) 12 h after mixing; (bottom) 25 h after mixing.

10 micelles did not show any change within 21 and 11 days, respectively.

All of the above mixing experiments are compiled in Table III. The mixtures are identified in the first column; the respective sedimentation coefficients of the two micelles in unmixed 5×10^{-3} g/mL solution are given in the second column. The third column lists the time intervals between the mixing of the solutions and start of the sedimentation run. In the fourth column, the sedimentation coefficients of the mixed solution are given. Whenever relevant, the relative peak areas are presented in parentheses.

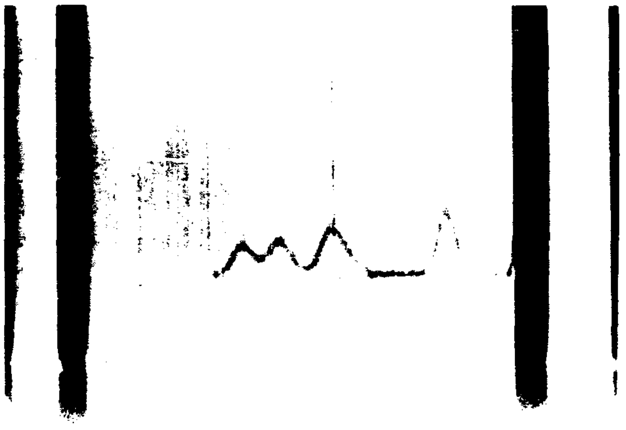

Figure 3. Sedimentation velocity experiment. In this case, a double sector cell with a long and short column was used: longer column (left triple peaks), mixture of micelles ASA-10/SA-5 in 80D/20W, 28 h after mixing; shorter column (right single peak), ASA-10 in 80D/20W.

The dynamics of micellar hybridization depends extremely strongly on the thermodynamic quality of the solvent. For example, micellar mixture of ASA-10 and SA-1 hybridizes to uniform mixed micelles within 30 min after mixing when dissolved in 80D/20W. However, when the experiment was repeated using either 70D/30W or 55D/45W solvent mixture (both copolymers are directly soluble in both of these mixtures), no change in the bimodal sedimentation pattern was observed within 18 days. We have also performed a number of mixing experiments using micelles that were transferred into aqueous buffers by stepwise dialysis. In none of these experiments did we observe any change of the sedimentation pattern with time.

While it was obvious from the above experiments that the hybridization of the micelles was in many instances slowed or prevented by kinetic reasons, there remained a possibility that in some instances the reasons were thermodynamic in nature. For several mixtures we have therefore tried to prepare the hybrid micelles by other means. In one set of experiments, we dissolved the two copolymers molecularly in wet dioxane (about 98D/2W; dry dioxane does not dissolve the poly(methacrylic acid) blocks completely), mixed the solutions, freeze-dried the mixture, redissolved the polymer in 80D/20W, and performed the sedimentation run.

We have applied the above procedure to systems containing the diblock copolymer SA-22, micelles of which are very large and did not hybridize with any other micelles. The freeze-dried mixture with diblock copolymer SA-10 (micelles of intermediate size) yielded uniform hybrid micelles with a sedimentation coefficient in between the values of the corresponding homomicelles. However, the freeze-dried mixture with diblock copolymer SA-20 (forming smaller micelles) yielded a very broad sedimentation pattern. The freeze-dried mixture with the triblock copolymer ASA-10 (small micelles) produced two narrow peaks, sedimentation coefficients of which were in between the original homomicellar values.

We have applied the freeze-drying experiment also to two mixtures that produced a three-peak pattern during our standard mixing of micelles. The ASA-10/N1SA-4 system yielded uniform micelles with sedimentation

Table III. Micellar Mixing Processes in 80D/20W Solvent

sample	s (c = 5 mg/mL)	hours	$s \times 10^{13}$ s^{-1} (peak area %)
ASA-10/SA-2	2.8/4.7	0.5	3.4
ASA-10/SA-20	2.8/6.2	0.5	4.6
ASA-10/N4SA-2	2.8/7.6	0.5	4.6
ASA-10/SA-1	2.8/8.7	0.5	5.0 (73%), 7.7 (27%)
		12	6.9
ASA-10/SA-10	2.8/12.1	0.5	3.9 (45%), 11.4 (55%)
		3.0	5.7 (54%), 11.9 (46%)
		8.0	6.1 (63%), 11.0 (37%)
		25	6.2
ASA-10/SA-5	2.8/13.4	0.5	3.3 (40%), 13.0 (60%)
		30	4.0,[a] 6.1, 13.2 (58%)
		125	3.1,[a] 7.0, 12.1 (53%)
		197	3.2,[a] 7.2, 12.2 (52%)
		436	3.5 (28%), 7.6 (30%), 12.2 (42%)
ASA-10/N1SA-4	2.8/15.2	0.5	2.5 (47%), 13.4 (53%)
		40	3.0, 12.7
		170	2.5 (20%), 7.0 (31%), 11.7 (49%)
		309	3.3 (23%), 7.1 (44%), 11.0 (33%)
		60 days	4.1,[a] 6.6, 10.0 (31%)
ASA-10/SA-22	2.8/20.2	0.5	2.9 (72%), 20.8 (28%)
		75	3.1 (68%), 23.3 (32%)
		142	2.7 (66%), 23.9 (34%)
		30 days	3.1 (67%), 23.6 (33%)
ASA-9/N4SA-2	2.8/7.6	0.5	4.3
ASA-9/N1SA-4	2.8/15.2	0.5	6.4, 8.8
		18	6.5
ASA-8/SA-10	5.7/12.1	0.5	5.9 (52%), 10.6 (48%)
		22	6.2 (64%), 9.2 (36%)
		49	6.3 (71%), 8.9 (29%)
		98	6.4
ASA-8/SA-5	5.7/13.4	0.5	6.1 (52%), 15.5 (48%)
		98	6.5 (59%), 13.5 (41%)
		144	6.8 (65%), 13.8 (35%)
		283	6.9 (63%), 13.8 (37%)
ASA-8/SA-22	5.7/22.6	0.5	5.8 (56%), 25.1 (44%)
		120	5.9 (68%), 24.5 (32%)
		283	6.0 (68%), 22.1 (32%)
ASA-8/N1SA-4	5.7/15.2	0.5	5.6 (50%), 12.9 (50%)
		25	6.0 (51%), 13.6 (49%)
		100	6.4 (51%), 13.8 (49%)
		192	6.2 (51%), 12.6 (49%)
		243	5.7 (58%), 12.0 (42%)
N4SA-2/ASA-4	7.6/11.7	0.5	7.5 (30%), 10.9 (70%)
		19	7.6 (38%), 10.5 (62%)
		69	7.8 (45%), 10.0 (55%)
		237	8.1 (43%), 10.4 (57%)
N4SA-2/N1SA-4	7.6/15.2	0.5	7.7 (43%), 14.5 (57%)
		24	9.0 (68%), 12.1 (32%)
		70	8.8
SA-20/SA-10	6.2/12.1	0.5	7.0 (48%), 12.8 (52%)
		26	7.3, 11.3
		97	7.7 (76%), 10.2 (24%)
		202	7.2
SA-10/SA-22	12.1/22.6	4.0	11.0 (61%), 24.0 (39%)
		120	10.4 (58%), 26.4 (42%)
		190	10.0, 25.2
		264	9.8 (57%), 25.0 (43%)
SA-20/SA-22	6.2/22.6	0.5	7.3 (57%), 25.8 (43%)
		22	7.1 (58%), 25.6 (42%)
		98	7.4 (58%), 24.7 (42%)
		21 days	7.6 (57%), 24.6 (43%)
ASA-10/ASA-4	2.8/11.7	0.5	3.2 (44%), 13.0 (56%)
		18	3.1 (47%), 13.1 (53%)
		75	3.3 (47%), 13.0 (53%)
		333	3.0 (44%), 12.2 (56%)

[a] Peaks are not separated well enough for obtaining the peak area.

coefficient comparable with the central peak of the three-peak experiment. However, the ASA-10/SA-5 system produced a bimodal sedimentation pattern. The slower peak sedimented similarly to pure ASA-10 micelles (or to the slowest peak in the three-peak pattern). The faster peak corresponded to the central (hybrid micelle) peak of the previous pattern, while the fast, pure SA-5 micelles were not observed.

In order to confirm these somewhat surprising results, we tried to prepare hybrid micelles for the two systems that so far resisted full hybridization attempts (the ASA-10/SA-5 and ASA-10/SA-22 systems) by still another procedure. We again prepared a mixed molecular solutions in wet dioxane and added enough 60D/40W solvent mixture to achieve the final 80D/20W composition of the solvent. The sedimentation patterns for micellar solutions prepared by this way were essentially identical with patterns of mixtures prepared by the freeze-drying procedure (Table V).

Table IV. Micellar Mixing Processes in Dioxane/Water Solvents with Different Compositions

solvent	$s \times 10^{13}$ (c = 0.5%, before mixing)	hours	$s \times 10^{13}$ s^{-1} (peak area %)
	ASA-10/SA-1		
80D/20W	2.8/8.7	0.5	5.0 (73%), 7.7 (27%)
		12.0	6.9
70D/30W		0.5	4.1 (42%), 9.6 (58%)
		70.0	4.4 (42%), 9.6 (58%)
		18 days	4.1 (43%), 9.7 (57%)
55D/45W		0.5	4.0 (61%), 9.3 (39%)
		70.0	4.4 (61%), 9.3 (39%)
		18 days	4.6 (60%), 9.2 (40%)
mixed in 98D/2W, freeze-dried, and redissolved in 55D/45W		0.5	7.0
	ASA-10/N4SA-2		
80D/20W	2.8/7.6	0.5	4.6
60D/40W[a]	3.8/7.1	0.5	4.5 (53%), 7.8 (47%)
		66.0	4.4 (57%), 7.6 (43%)
		17 days	4.3 (60%), 7.4 (40%)

[a] Homomicelles were prepared by stepwise dialysis.

Table V. Alternative Micellar Mixing Processes

sample	method of preparing	$s \times 10^{13}$ s^{-1}
ASA-10/SA-5	freeze-dried[a]	2.8, 8.0
	mixed in DOX[b]	2.8, 8.0
ASA-10/SA-22	freeze-dried[a]	4.6, 11.6
	mixed in DOX[b]	2.9, 11.1
ASA-10/N1SA-4	freeze-dried[a]	7.9
ASA-10/SA-1	freeze-dried[c]	7.0
SA-10/SA-22	freeze-dried[a]	17.2
SA-20/SA-22	freeze-dried[a]	22.3

[a] Mixed in 98D/2W solvent, freeze-dried, and redissolved in 80D/20W. [b] Mixed in 98D/2W solvent, diluted to 80D/20W by adding 60D/40W. [c] Mixed in 98D/2W solvent, freeze-dried, and redissolved in 55D/45W.

Discussion

Before proceeding to the analysis of the hybridization process, we need to mention some peculiarities of the concentration dependence of the sedimentation velocity. In our previous paper[10] we have shown that for our micellar systems the concentration dependence of the sedimentation coefficient is quite significant. Specifically, the sedimentation coefficient at 5×10^{-3} g/mL (our reference value for homomicelles) is significantly less than the one at 2.5×10^{-3} g/mL (original concentration of each micellar species in the mixture). Thus, in a mixture that is *not* hybridizing, the *slower* peak (corresponding to lower concentration than in the reference experiment) moves slightly faster than in the homomicelle experiment. For the *faster* peak, the situation is more complicated. It corresponds also to lower concentration and therefore should move faster. However, the faster component travels in the presence of a slower component and the hydrodynamic interaction slows them both. Thus, we expect that, in a mixture, the faster component will move faster than in the 5×10^{-3} g/mL solution but that this acceleration will be less pronounced than the one discussed above for the slower component. Moreover, even this acceleration will become less and less prominent as the sedimentation coefficient of the slower component approaches that of the faster component.

The Johnston–Ogston effect[26-28] also may play a role in our experiments. When a mixture of two components having a finite concentration is studied by the sedimentation velocity, the molecules of the slower component have different velocities in front and behind the faster moving boundary. As a result, the slower component piles up behind the faster boundary and the ratio of the areas of the two peaks does not represent properly the ratio of initial concentrations of the two components: the proportion of the slower component is exaggerated.

The above described phenomena, on one hand, explain why the sedimentation coefficients of presumably identical micelles vary slightly from experiment to experiment, and on the other hand, preclude a detailed quantitative analysis of the hybridization process. However, the qualitative observations, namely the uniformity of individual micellar components, the trends of changes of sedimentation coefficients with the hybridization time, and the direction of the mass transport between different micellar species, are quite unambiguous.

Let us now return to the dynamics/thermodynamics of micellar hybridization. From the thermodynamic viewpoint, in a solution of a single type of block copolymer molecules in a selective solvent at equilibrium, the entities present in the solution are micelles and unimers. The distribution of the aggregation numbers of the micelles is narrow and the average aggregation number depends on the architecture of the copolymer and on the applicable interaction coefficients. The concentration of unimers is approximately equal to the critical micelle concentration (cmc). cmc may be undetectably small in some instances. From the dynamic viewpoint, three types of molecular processes are balanced at equilibrium. 1. Assembly of new micelles from unimers and disintegration of existing micelles. 2. Fission of existing micelles into two multimolecular parts and fusion of two existing micelles. 3. Escape of individual unimers from micelles and their reentry. The same processes were described for detergent micelles.[29-31]

Kinetically, the rate of assembly of new micelles depends on a high power of the concentration of unimers.[11,14,29-31] We need to distinguish two situations. At equilibrium, the assembly rate decreases sharply with decreasing cmc. It is significant for low molecular weight detergents,[29-31] for some block copolymers in marginally selective solvents,[32] and for copolymers of similar blocks as poly(propylene oxide)-*block*-poly(ethylene oxide) in water.[33-37] The assembly rate in our systems is probably quite negligible due to their undetectably low cmc.

The assembly/disintegration process may become significant-to-dominant in some nonequilibrium situations, for example when the concentration of the unimers is inappropriately high. This may happen after a sudden jump in temperature or in the composition of the mixed solvent. The micellization then becomes a nucleation process driven by the supersaturation of the unimers in the solution. Once the supersaturation is relieved, the assembly of new micelles may be stopped for all practical purposes.

As Halperin and Alexander[25] pointed out, the free energy penalty of fission or fusion of large micelles would often be too high and this process may be kinetically hindered or fully frozen. This leaves the escape and reentry of single unimers from and into the micelles as the main dynamically functional equilibration process. It should be mentioned that in experiments in which the escape/reentry process is the only operative one, the number of micelles must remain constant even when the distribution of aggregation numbers is changing. The number of micelles could be changed only by the assembly/disintegration mechanism or by the fission/fusion mechanism.

What factors influence the rate of unimer escape from the micelle? In order to escape, the insoluble block of the unimer first has to extricate itself from the central part of the core and locate itself at the core boundary. This extrication will be slower, the larger the core, the longer the insoluble block, and the tighter the core. The tightness of the core depends on the degree of its swelling and on the glass transition temperature (T_g) of the core material. We expect the rate of extrication from glassy cores to be negligibly small for all unimers. Once the unimer is at the core boundary, it has to separate itself from the core. This separation causes contact energy penalty that also increases with increasing size of the insoluble block. The separated unimer then has to negotiate its passage through the shell, which is occupied by a relatively high concentration of the soluble chain. The longer the passage lasts, the higher the probability that the unimer will be recaptured by the core. Thus, longer soluble blocks also reduce the rate of the unimer escape. In summary, the rate of unimer escape is a very sensitive function of the copolymer architecture, of the nature of the insoluble blocks, and of the thermodynamic interactions between the two blocks and among these blocks and the solvent. The degree of core swelling plays a major role. It is thus not surprising that seemingly minor changes in the above factors may mean a difference between a fast escape and an essentially frozen situation.

We will now turn attention to the dynamics/thermodynamics of a solution of two different block copolymers. If the two copolymers are rather similar to each other, then general thermodynamic considerations predict that the system with the lowest Gibbs energy is the one with fully hybridized uniform micelles. However, as the dissimilarity (in our case the differences between block sizes of the two unimers) increases, the molecules of the two types may find it increasingly difficult to be accommodated within the same micelles. The situation is similar to mixtures of two liquids. When their interaction becomes more and more unfavorable, they separate into two phases. However, these two phases are not pure components; both phases are mixtures and the difference of their composition depends on the details of the appropriate change in Gibbs energy of mixing, ΔG_{mix}. By analogy, we expect that, at equilibrium, the mixture of two dissimilar block copolymers in a selective solvent will produce two types of hybridized micelles. The difference in their compositions,

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their sizes, and their sedimentation coefficients will increase with the dissimilarity of the copolymers. If the dissimilarity is sufficiently small, micelles of one uniform type will result.

In our experiments, we are starting with systems in which the two types of unimers are segregated in two different micellar types. Hence, the situation is far from equilibrium and we must carefully reexamine the dynamics of the hybridization.

We will assume that the hybridization process is fully controlled by the escape/reentry of single unimers. We will consider the situation at the very beginning of the hybridization. In this case, the escape of the unimers and their reentry into their own micelles is governed by the same factors as in the equilibrium situation; this process does not contribute to the changes in the system. What is important is the reentry of the unimers into the micelles of the other type.

What changes in Gibbs energy accompany such a reentry? The enthalpy change is always favorable for reentry: the reentry reduces the number of solvent-insoluble polymer contacts. The entropy change of reentry is unfavorable. The reentry disturbs the distribution of end-to-end distances for individual chains (blocks) and thus decreases entropy. For reentry into their own micelles (an equilibrium process) the entropy change exactly balances the enthalpy change.

Is the reentry into the other type of micelle accompanied by a more or less favorable change of entropy? Such a reentry always represents mixing of components and contributes the favorable combinatory entropy. This increase of the combinatory entropy is the driving force for hybridization of micelles made from similar unimers. However, in the case of rather different unimers, the reentry of the dissimilar unimer causes different changes in the distribution of end-to-end distances. When a unimer with a short insoluble block enters a micelle, the core of which is made from long blocks, it increases the volume and radius of the core and forces the resident chains to stretch more to reach to the central region of the core. However, the short newcomer cannot reach the center and cannot contribute to the filling process. The situation is exacerbated if the entering unimer is a triblock copolymer (for which both ends of the central block need to be located at the core boundary) that enters a micelle made from diblock unimers. In such a case, the entropy penalty may be such as to preclude this type of entry. Thus, this hybridization pathway is blocked thermodynamically. It should be noted, that this conclusion does not contradict the previously reached expectation that at equilibrium hybridized micelles (of one or two types) will exist. Such equilibrium hybrid micelles would be composed from a smaller number of the long insoluble blocks than is the number of such blocks in the original homomicelle.

Let us now consider reentry of a unimer with a large insoluble block into a micelle, the core of which is made by short chains. No extra stretching of the resident blocks is needed as the long entering block may nicely accommodate itself in the core interior. Thus, such an entry may be thermodynamically favored.

We will now list the major experimental observations from this study and interpret them in terms of the above discussion.

1. Under comparable conditions (in the same solvent mixture) the rate of hybridization of various micellar pairs varies in broad limits (Table III). Generally, the rate decreases when the size of either block of either copolymer increases. The rate controlling process is apparently the rate of escape of the unimers from the micelles that is slowed down both by increasing size of the insoluble block extricating itself from the core and by increasing width of the shell complicating the passage from the micelle.

2. Increasing content of water—an extremely poor solvent for polystyrene—strongly suppresses the hybridization (Table IV). In fact, the hybridization for any given pair of micelles occurs only in a rather narrow range of solvent compositions. This effect is apparently caused (a) by decreasing swelling of the core by dioxane that substantially increases the friction forces acting on the polystyrene block on its way to the core boundary and (b) by increasing incompatibility of the polystyrene block with the mixed solvent. In the limiting case of a micellar solution from which all the dioxane was removed by dialysis, the core apparently becomes glassy and the escape of unimers is totally frozen.

3. In all hybridization processes that occurred on a convenient time scale, transfer of unimers from the large micelles to the small ones clearly dominated the transfer in the opposite direction irrespective of the diblock or triblock nature of the participants. Now, escape of smaller unimers is faster than escape of the larger ones. Consequently, we would expect a dominant transport from small micelles to the large ones, contrary to the experimental evidence. Apparently, the small unimers that are moving more quickly distribute themselves in a type of quasiequilibrium way; they cannot enter the large micelles appreciably, because this would destabilize both the large and the small micelles (as long as their numbers remain constant). The rate limiting factor for the changes must clearly be the movement of the large unimers and, more precisely, their escape from the large micelles.

4. Some copolymer pairs, that would not hybridize in our standard experiment in 80D/20W solvent (e.g., SA-22/SA-10), readily form uniform hybrid micelles when mixed in a molecular solution, freeze-dried, and redissolved. Apparently, the uniform hybrid micelles are preferred thermodynamically, but hybridization from the homomicelles is prevented kinetically.

5. Other copolymer pairs, that would not hybridize from micellar solutions (e.g., SA-22/ASA-10), when subjected to the freeze-drying procedure, produced a solution containing simultaneously two types of uniform micelles, both of them apparently being hybrid micelles. This type of mixture contains copolymers with rather large differences in sizes of insoluble blocks. We believe that these hybrid micelles are equilibrium micelles of the "two-phase" model discussed above.

6. In two hybridization experiments, a third peak (apparently hybrid micelles) emerged between the original peaks and grew at their expense. Such behavior is difficult to explain within the unimer transfer model. In our opinion, the hybrid micelles in these systems are strongly preferred thermodynamically, while the direct transport of the unimers to the other micelles may be hindered entropically as explained above. In such a situation, the solvent phase, that is saturated by both unimers with respect to their homomicelles, may become supersaturated with respect to the hybrid micelles and their nucleation may occur. We have applied the freeze-drying hybridization procedure to both these systems and obtained different results. The ASA-10/N1SA-4 mixture produced uniform hybrid micelles defining them as the equilibrium ones. However, the ASA-10/SA-5 mixture produced micelles corresponding to the hybrid middle peak of the routine experiment plus another peak very similar to that of the original ASA-10 homomicelles. A similar pattern

was obtained when the mixture was hybridized by changing the solvent composition. In this case, probably two thermodynamic effects were operating simultaneously: the supersaturation with respect to the equilibrium hybrid micelles and the requirement of lowest Gibbs energy that led to the "two-phase" micellar system.

At the end of this discussion we would like to stress that the dominance of the single unimer transfer mechanism implies that the number of micelles does not change during the hybridization. Thus, even if the resulting hybrid micelles are uniform, they may not be the equilibrium ones having an inappropriate aggregation number. However, the existence of the nucleation mechanism may lead to a true equilibrium situation. Ironically, mixtures of micelles that are very dissimilar may have the nucleation as the only feasible equilibration mechanism and may eventually equilibrate fully, while mixtures of similar micelles that may lower their Gibbs energy faster by the unimer transfer mechanism may end up in a nonequilibrium state.

Conclusions

Experiments, in which two different micellar solutions are mixed and their hybridization is followed by sedimentation velocity measurements, provide a wealth of information about the kinetics and mechanism of the hybridization. We have performed a large number of such experiments using micelles formed by diblock and triblock copolymers of styrene and methacrylic acid. Analysis of the results yielded the following conclusions: 1. The escape rate of unimers from the micelles is a very sensitive function of the sizes of both the hydrophilic and hydrophobic blocks as well as of the composition of the mixed solvent. 2. The reentry of small unimers into large micelles may be hindered thermodynamically, while the reentry of large unimers into small micelles is more feasible. 3. Hybridization of copolymers with very different insoluble blocks may lead to a mixture of two different types of hybrid micelles. 4. When the direct transfer of unimers among micelles of different types is hindered thermodynamically, nucleation of hybrid micelles may become the dominant hybridization process.

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