Cosolvent Effects on the Spontaneous Formation of Vesicles from 1:1 Anionic and Cationic Surfactant Mixtures

Wen-Yueh Yu, Yu-Min Yang,* and Chien-Hsiang Chang

Department of Chemical Engineering, National Cheng Kung University, Tainan, Taiwan 70101, Republic of China

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This paper aims to provide a practical catanionic vesicle-boosting method by means of cosolvent addition in water and to propose a theoretical explanation which can delineate the general trend of cosolvent effects and elucidate the possible role of cosolvent in the formation of catanionic vesicles. Effects of four homologous cosolvents (methanol, ethanol, 1-propanol, and 1-butanol) on the spontaneous formation of vesicles from eight 1:1 anionic−cationic mixed surfactant systems, sodium alkyl sulfates−alkyltrimethylammonium bromides (C_nSO_4Na−$C_mN(CH_3)_3Br$; n = 12, 14; m = 8, 10, 12, 14), at a total surfactant concentration of 10 mM were systematically studied. The experimental results revealed that varied changes in vesicle formability of different mixed surfactant systems may result from various kinds and amounts of cosolvent. Four types of cosolvent effects, however, can be classified. Among them, cosolvent effects type 2 and type 3 would serve the purpose and were exemplified by $C_{12}SO_4Na$−$C_{10}N(CH_3)_3Br$, $C_{14}SO_4Na$−$C_{10}N(CH_3)_3Br$, and $C_{12}SO_4Na$−$C_{12}N(CH_3)_3Br$ mixed surfactants. Furthermore, the effectiveness of vesicle boosting increases in the order 1-butanol > 1-propanol > ethanol > methanol. An explanation of cosolvent effects based on the medium dielectric constant was then proposed.

Introduction

Since Kaler et al.[1] gave the first example of spontaneous vesicle formation from mixed cationic and anionic single-chained surfactants using cetyltrimethylammonium tosylate and sodium dodecylbenzene sulfonate, the vesicular systems formed from mixtures of anionic and cationic surfactants in aqueous solutions have been well-documented.[2,3] The word "catanionic" vesicles is now commonly accepted to qualify such types of structures. Furthermore, the isothermal ternary phase diagrams of a few cationic surfactant−anionic surfactant−H_2O (or D_2O) systems have been constructed.[4−10] However, mixed cationic−anionic surfactant systems, especially 1:1 mixtures, usually precipitate in aqueous solutions, which greatly limits their advances in both theory and application.

Formation of self-organized assemblies in easily precipitated mixed surfactant systems sodium dodecyl sulfate (SDS)−alkylprimaryammonium chlorides ($C_{12}H_{25}SO_4Na$−$C_nH_{2n+1}NH_2\cdot HCl$; n = 8, 12) has been investigated by Zhang et al.[11] By adding 1-propanol or 2-propanol, they showed that the precipitate formed in aqueous solution was resolved and organized structures, such as bilayers or vesicles, could be observed under transmission electron
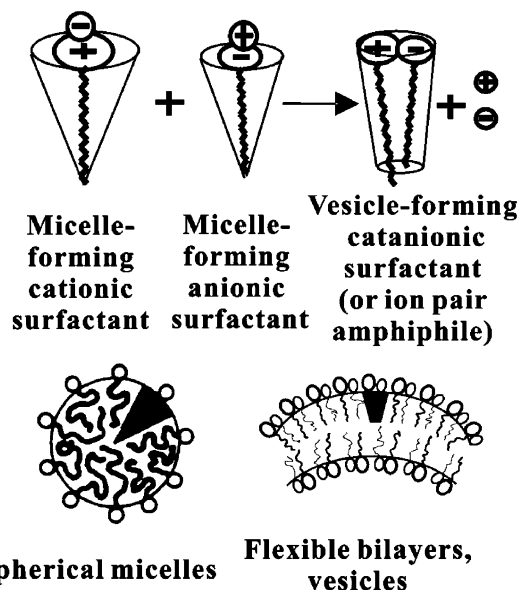

Figure 1. Formation of vesicle-forming catanionic surfactant from micelle-forming cationic and anionic surfactants.

microscopy (TEM) when the volume ratio of alcohol was appropriate. Moreover, Wang et al.[12] have investigated the formation of vesicles in two other easily precipitated mixed surfactant systems SDS−alkyltrimethylammonium bromides ($C_{12}H_{25}SO_4Na$−$C_nH_{2n+1}N(CH_3)_3Br$; n = 8, 12) and obtained the similar results by the addition of short-chained alcohols (ethanol, 1-propanol, and 1-butanol).

In fact, Huang and co-workers[11−15] have endeavored in a series of investigations to study the stability of vesicles in aqueous mixtures of anionic and cationic surfactants

* Corresponding author. Prof. Yu-Min Yang: tel., 886-6-2757575 ext-62633; fax, 886-6-2344496; e-mail, ymyang@mail.ncku.edu.tw.

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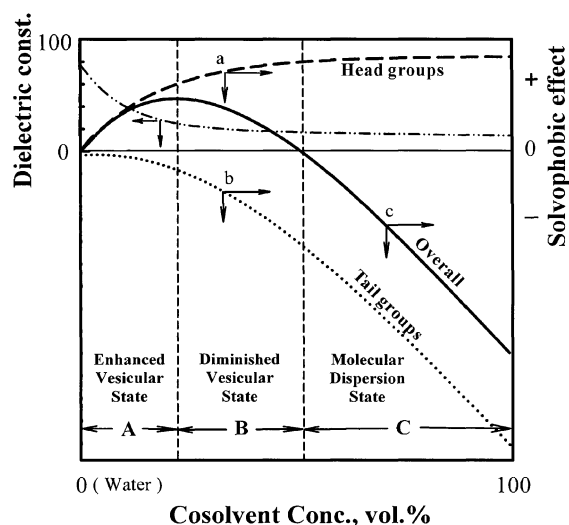
Figure 2. Schematic representation of the cosolvent effect on the formation of catanionic vesicles in water by catanionic surfactants.
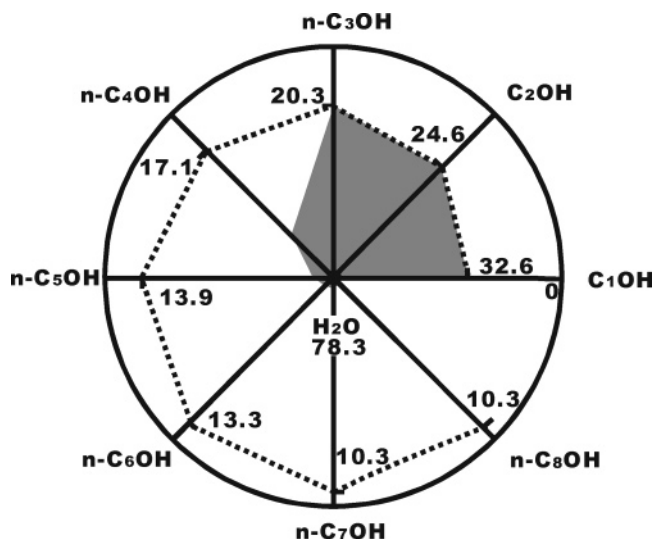

Figure 3. Dielectric plot of mixed solvents. The numerical values indicated are dielectric constants of the pure liquids, and the shaded area represents the available dielectric constants of mixed solvents. The sudden decrease in the lowering of dielectric constants in aqueous solutions of 1-butanol to 1-octanol is due to limited solubility of these alcohols in water.

with the addition of various organic solvents. In addition to vesicle formation in aqueous systems, that in non-aqueous polar solvent systems was also studied by them. For several 1:1 cationic and anionic surfactant mixtures, including SDS−alkylprimaryammonium chlorides,[11] SDS−alkyltrimethylammonium bromides,[12] and sodium alkylcarboxylates−alkyltrimethylammonium bromides,[13−15] cosolvents (or solvents) including ethanol,[12−15] 1-propanol,[11,12,15] 2-propanol,[11,12,15] dimethyl sulfoxide,[15] formamide,[15] and 1-butanol,[12] have been used and have been found to endow the surfactant mixtures with outstanding vesicle-forming capability, especially for easily precipitated surfactant systems. This may open a vista for enlarging the application scope of vesicular systems.

However, Zana and Michels[16] have argued that indeed ethanol, as well as methanol and propanol for that matter, is often used to prevent the self-organization of amphiphiles. The intuitive argument and previous findings,
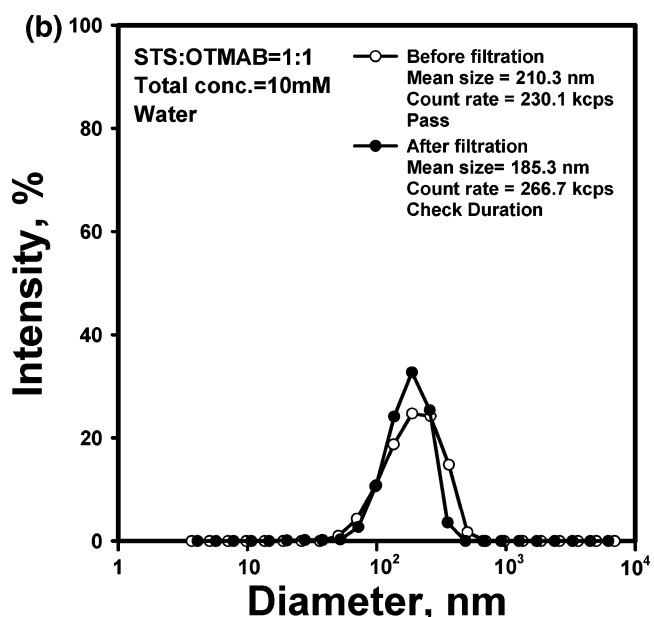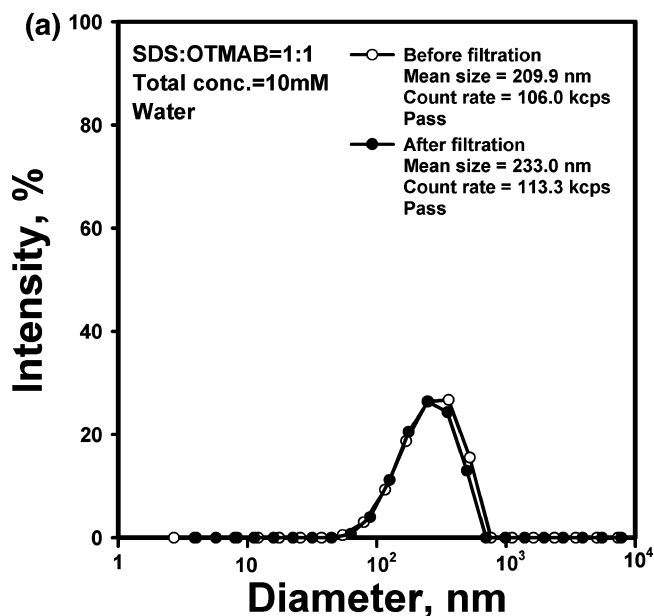
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Figure 4. Vesicle size distributions before and after filtration. (a) SDS/OTMAB and (b) STS/OTMAB.

which showed that surfactants do not self-organize in ethanol, led them to reexamine the results for a sodium dodecanoate (NaC$_{12}$)/dodecyltrimethylammonium bromide (DTMAB) equimolar mixture (EQMM) by light scattering, electrical conductivity, and DSC methods. Their results did not confirm the existence of vesicles in the EQMM of NaC$_{12}$/DTMAB in pure ethanol. At a total surfactant concentration of 6 mM, their results suggested that vesicles persist up to an ethanol content of ∼19 vol % but disappear at higher ethanol contents.

It is generally accepted that two major conditions must be fulfilled for vesicle formation in a system. The first is the requirement of energy; that is, the energy level of a system in the vesicular dispersion state should be lower than that in the molecular dispersion state. This condition ensures that the aggregation processes are spontaneous. The second is that the critical packing parameter $P_c = v/a_0 l_c$ of the amphiphiles should be in a proper range (0.5−1),[17] where v and l_c are the volume of the hydrocarbon chain or chains and the maximum effective length that chains can assume, respectively, and a_0 is the minimum

Figure 6. TEM image in the 1:1 STS−OTMAB/5% ethanol solution observed by the negative staining technique (concentration = 10 mM).
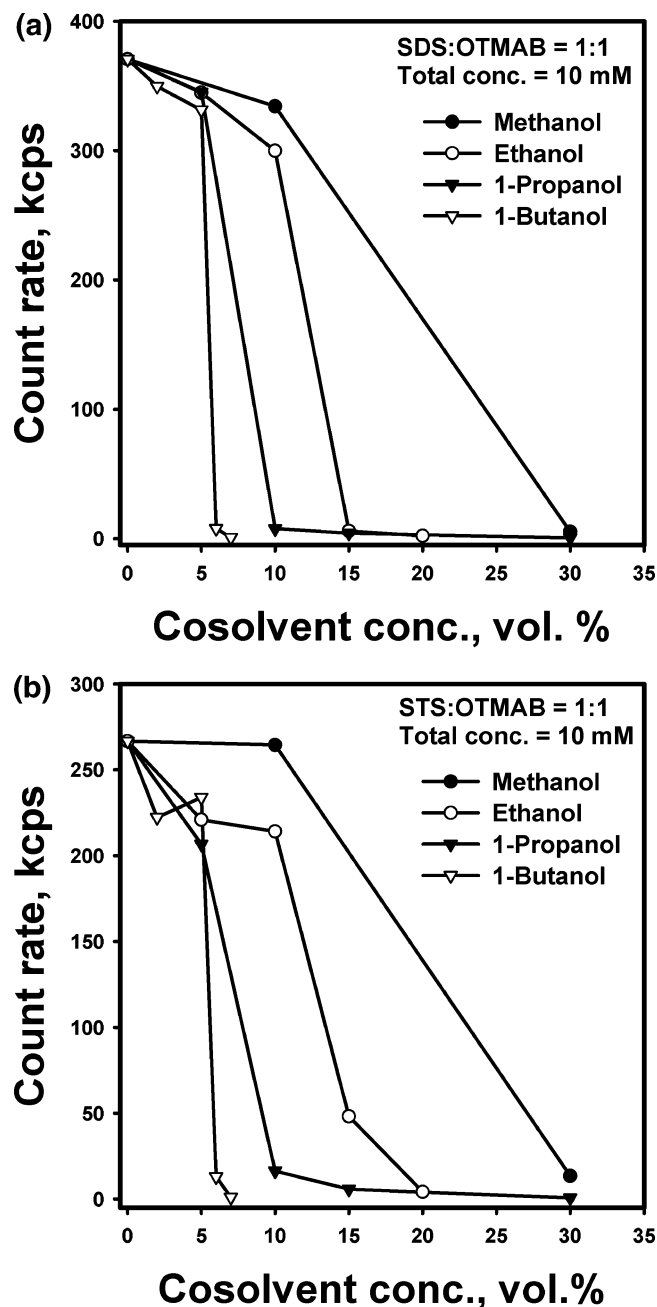
Figure 5. Cosolvent effects on the count rate of catanionic vesicles formed from (a) SDS/OTMAB = 1:1 and (b) STS/OTMAB = 1:1, total concentration = 10 mM.

interfacial area occupied by the hydrophilic groups or headgroups. This latter condition determines the form of the aggregate.

Huang et al.[14] suggested an explanation based on the medium dielectric effect that ethanol addition may affect the interaction between the hydrophobic groups and that between the hydrophilic groups of the amphiphiles. Actually, the dielectric constant of ethanol is much lower than that of water. Thus, the addition of ethanol into water will make the dielectric constant of the mixed solvent lower. Therefore, the addition of ethanol into aqueous solutions, on one hand, makes the hydrophobic effect of catanionic surfactant molecules weaker, which is a disadvantage in regards to the energy requirement for vesicle formation. Ethanol addition, on the other hand,
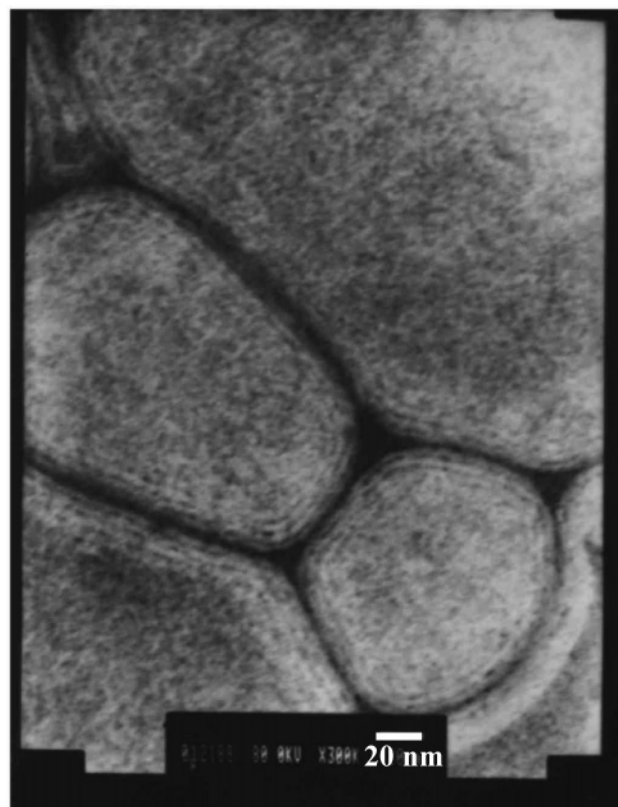
strengthens the attractive electrostatic interaction between their two oppositely charged polar groups and consequently is an advantage in regards to the energy requirement for vesicle formation. In a suitable case, it may overcome the disadvantageous influence of ethanol addition on the hydrophobic effect, resulting in a more favorable energy condition for vesicle formation. As for the second requirement regarding the critical packing parameter, some favorable effects of ethanol addition were also seen in the 1:1 cationic−anionic system studied by Huang et al. It is considered that the stronger attraction between polar groups induced by ethanol addition may result in decreasing a_0 and forcing less ethanol molecules into the polar group layer of the vesicle. Both results cannot make the critical packing parameter P_c smaller and even make it significantly larger. The spontaneous formation of vesicles rather than micelles for the $C_9COONa-C_{10}$-NMBr system in ethanol and its aqueous mixtures is, therefore, due to this reasoning.

When dealing with mixed cationic−anionic surfactant systems that precipitate easily in aqueous solutions, Zhang et al.[11] and Wang et al.[12] suggested that alcohol molecules may enter the assemblies and reside in the polar group layer, forcing surfactant molecules to pack loosely and be more soluble. The addition of 1-propanol or 2-propanol, consequently, not only improved the solubility of such a system but also increased the value of a_0, and, thus, the value of P_c may drop in the range of 0.5−1. Therefore, the formation of vesicular structure would be induced by the addition of the short-chain alcohols.

It was now well-established that phospholipids can form interdigitated structure phases under a variety of ex-

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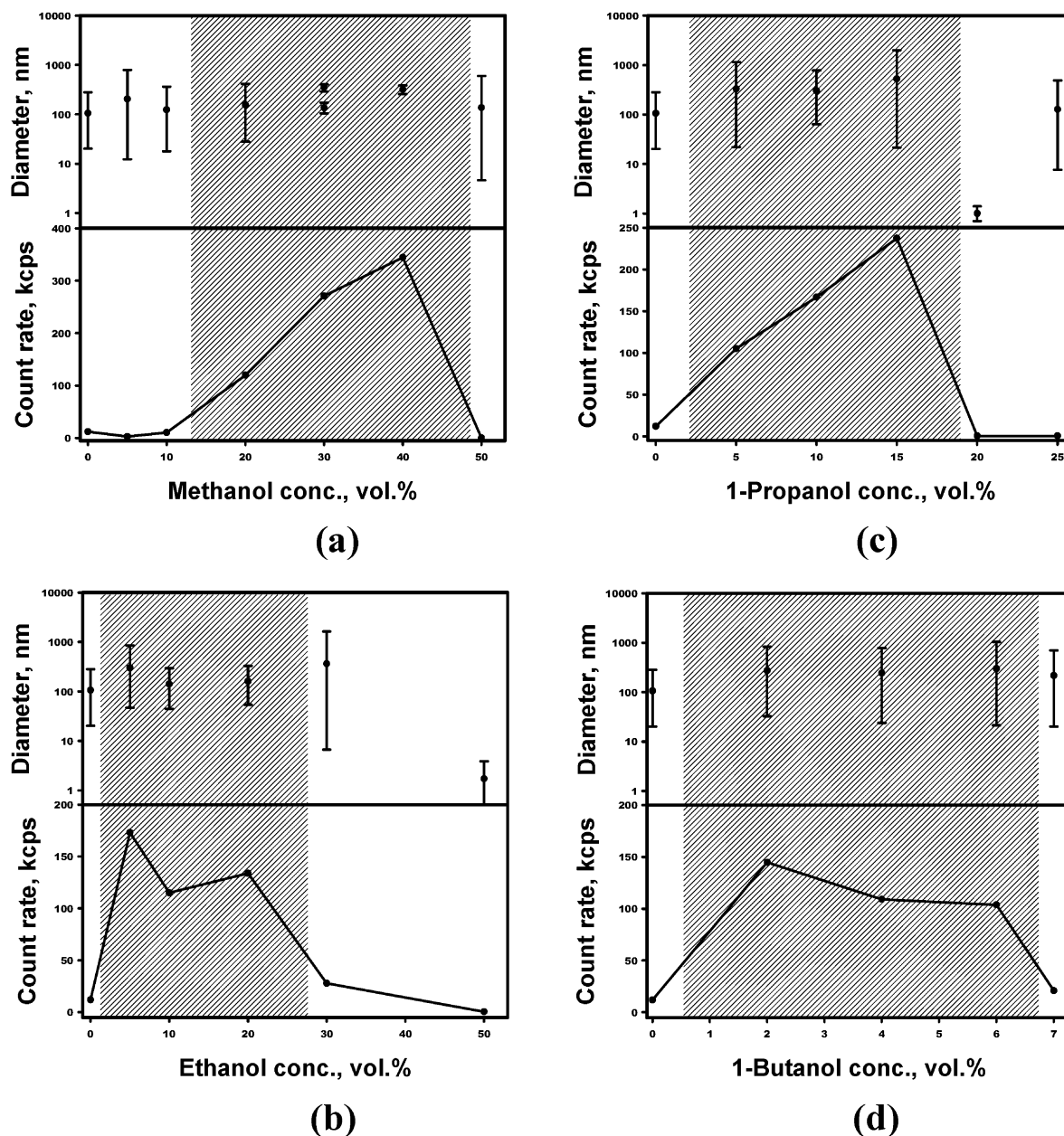
Figure 7. Cosolvent effects on the size and count rate of catanionic vesicles formed from SDS/DeTMAB = 1:1, total concentration = 10 mM. (a) Methanol, (b) ethanol, (c) 1-propanol, and (d) 1-butanol.

perimental conditions. Many small molecules cause interdigitation in lipid bilayers.[18,19] Among those molecules, alcohol is one of the best known.[20–28] It was noted that inducer molecules must be able to displace water from the interfacial region and not extend too deeply in the bilayer interior.[22] The interdigitated phase was characterized by lipid molecules from opposing monolayers interpenetrating, thereby decreasing the bilayer thickness and deteriorating the molecular order in lipid bilayers. As a result of the interdigitation effect of alcohols on the lipid bilayer, it was commonly believed that liposomes cannot coexist with a high concentration of alcohols. Currently, alcohol (ethanol) can only be found in a relatively low concentration in liposome formulations, if at all. Touitou and co-workers,[29–34] however, have discovered and have been investigating lipid vesicular systems embodying ethanol in relatively high concentrations (20–50 wt %), which they named "ethosomes" and that are efficient at enhancing the skin permeation of a

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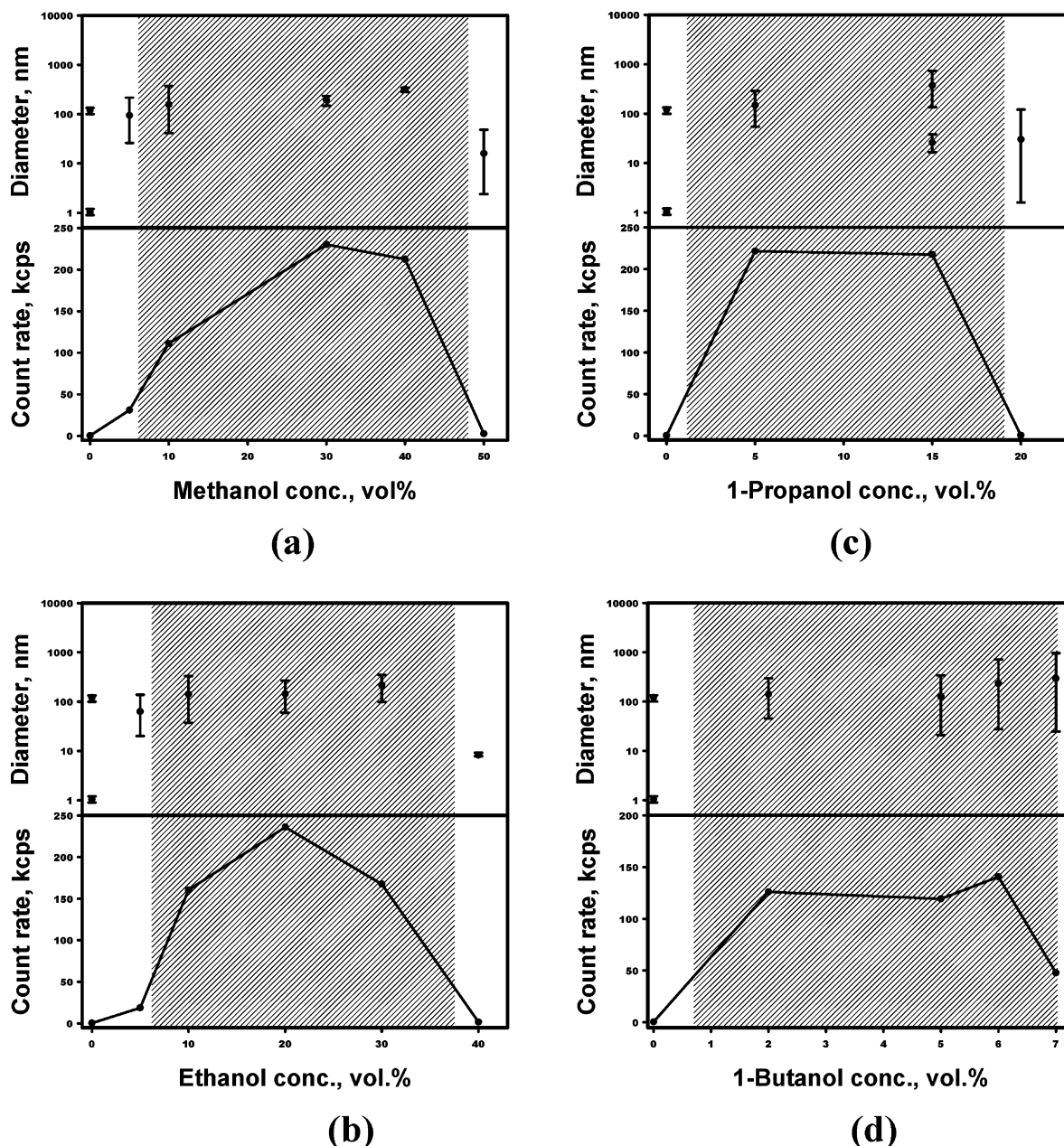(34) Dayan, N.; Touitou, E. *Biomaterials* **2000**, *21*, 1879–1885.

Figure 8. Cosolvent effects on size and count rate of catanionic vesicles formed from STS/DeTMAB = 1:1, total concentration = 10 mM. (a) Methanol, (b) ethanol, (c) 1-propanol, and (d) 1-butanol.

number of drugs. Furthermore, a few studies have been performed to demonstrate that surfactants can form bilayer or possibly vesicle structures in the presence of ethanol with high concentrations or even in pure ethanol.[35-37] Apparently, some work still need to be done in this area for more clear answers.

As mentioned above, it seems that more fundamental investigations, which can delineate the general trend of cosolvent effects and elucidate the possible role of cosolvent in the formation of catanionic vesicles, are much desirable. In this work, effects of four homologous cosolvents (methanol, ethanol, 1-propanol, and 1-butanol) on the formation of vesicles in eight 1:1 anionic−cationic mixed surfactant systems sodium alkyl sulfates−alkyltrimethyl-

ammonium bromides ($C_nSO_4Na-C_mN(CH_3)_3Br$; $n = 12$, 14; $m = 8$, 10, 12, 14) were systematically investigated. This work aims to provide a practical vesicle-boosting method by means of cosolvent addition in water and propose a general theoretical explanation, which considers the whole cosolvent concentration range. It is noteworthy that the system parameters such as number of carbon atoms in tails, asymmetry in chain length of surfactants, chain length of alcoholic cosolvents, and polarity of mixed solvents are involved.

Theoretical Considerations

The major forces that govern the self-assembly of amphiphiles into well-defined structures such as micelles and bilayers derive from the hydrophobic attraction at the hydrocarbon−water interface, which induces the molecules to associate, and the hydrophilic, ionic, or steric repulsion of the headgroups, which imposes the opposite requirement that they remain in contact with water. These two interactions compete to give rise to the idea of two

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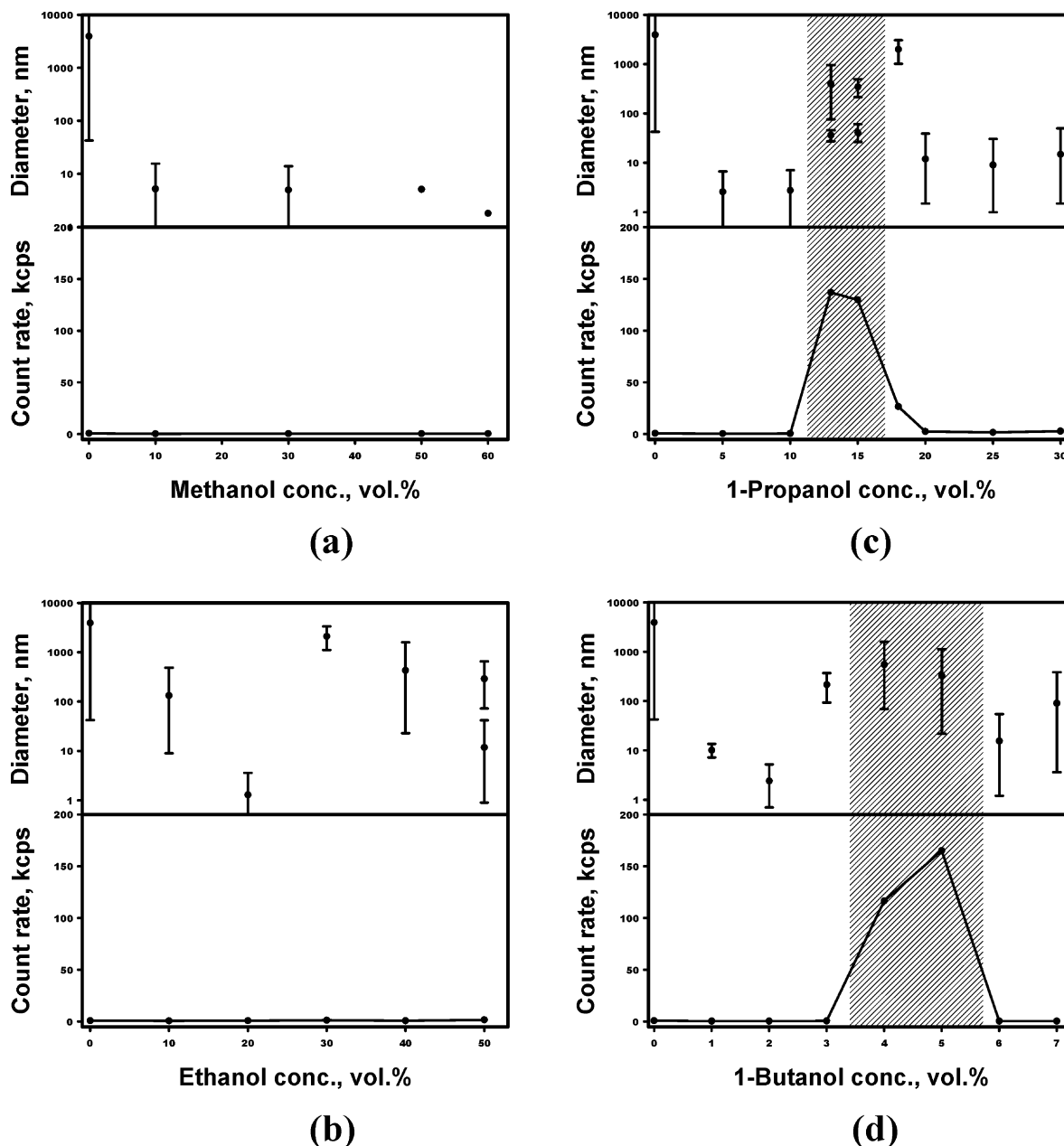
Figure 9. Cosolvent effects on the size and count rate of catanionic vesicles formed from SDS/DTMAB = 1:1, total concentration = 10 mM. (a) Methanol, (b) ethanol, (c) 1-propanol, and (d) 1-butanol.

opposing forces acting mainly in the interfacial region: the one tending to decrease and the other tending to increase the interfacial area per molecule (the effective headgroup area) exposed to the aqueous phase. The overall phenomenon is termed the hydrophobic effect or more generally the solvophobic effect.[38]

The particular size and shape of a self-assembled aggregate is the product of a fine balance between different free-energy contributions. However, a simple and common conceptual way of relating the geometric shape of an amphiphile and the preferred type of aggregation is the critical packing parameter, P_c, which has been mentioned above. On the basis of it, the formation of catanionic vesicles in the case of anionic and cationic mixed surfactants can then be reasoned that the effective interfacial headgroup area of each partner of an ion-pair amphiphile (IPA) or catanionic surfactant may be substantially

smaller than that for each individual surfactant, due to the electrostatic attraction between headgroups and a reduction in hydration. Unlike their micelle-forming parent surfactants, IPAs (catanionic surfactants) prefer to assemble into bilayer vesicles (see Figure 1).

A schematic representation of the cosolvent effect on the formation of catanionic vesicles by catanionic surfactants is shown in Figure 2. When a fraction of liquid cosolvent with a lower dielectric constant is added in water, the dielectric constant of the aqueous mixture would be lowered. As compared to that in pure water, the lower polarity of liquid may relax the unfavorable repulsion between the headgroups of catanionic surfactants and, therefore, induce a positive solvophobic effect (curve a in Figure 2) on one hand, but it may deteriorate the favorable hydrophobic attraction between the hydrocarbon chains of catanionic surfactants and, therefore, induce a negative solvophobic effect (curve b in Figure 2) on the other hand. We see, therefore, how the opposing forces lead to the

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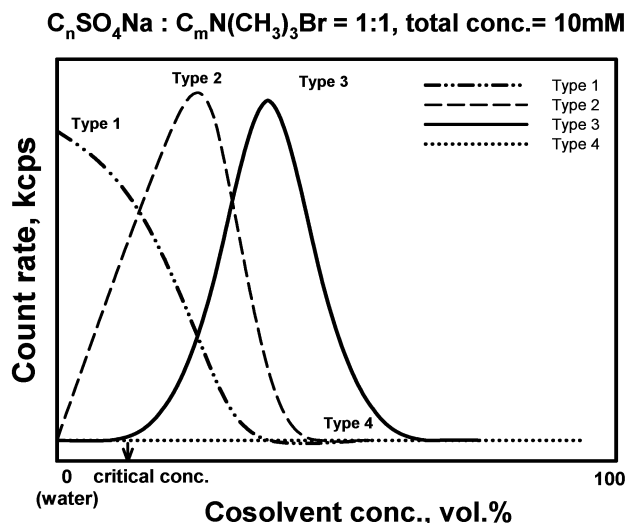
$C_nSO_4Na : C_mN(CH_3)_3Br = 1:1$, total conc.= 10mM

Figure 10. Schematic representation of the four types of cosolvent effects on the count rate and consequential formability of catanionic vesicles by anionic and cationic surfactants.

notion of an optimal liquid dielectric constant at which the overall solvophobic effect (curve c in Figure 2) on vesicle formation is a maximum. It is worthy to note that, by increasing cosolvent concentration, further lowering of the liquid dielectric constant may finally result in complete resolving of such a system. In the whole range of cosolvent concentrations, therefore, three regimes (A−C in Figure 2)—enhanced vesicular state, diminished vesicular state, and molecular dispersion state—are assumed to be observed.

As a boosting protocol for vesicle formation in water, the lowering of the liquid dielectric constant by the addition of cosolvent is, therefore, proposed. Figure 3 summarizes the dielectric constants of water and a few of aliphatic alcohols.[39] The shaded area in this figure represents the possibilities of this means by the addition of alcohols in water.

Experimental Section

Materials. The anionic surfactants used in this work were 99% SDS and sodium tetradecyl sulfate (STS) supplied by Sigma and Lancaster, respectively. The cationic surfactants octyltrimethylammonium bromide (OTMAB, 98% pure) and decyltrimethylammonium bromide (DeTMAB, 98% pure) were purchased from Fluka; DTMAB (99% pure) and tetradecyltrimethylammonium bromide (TTMAB, 99% pure) were purchased from Sigma. The cosolvents methanol (99.8% pure), ethanol (99.8% pure), 1-propanol (99.5% pure), and 1-butanol (99.5% pure) were purchased from Aldrich. All chemicals mentioned above were used as received without further purification. All experiments were conducted with pure water that was passed through a Milli-Q plus purification system (Millipore, U.S.A.) with a resistivity of 18.2 MΩ·cm.

Methods. The catanionic vesicles were prepared by gentle mixing of the cationic and anionic surfactants (1:1 molar ratio) in the solvent for 24 h at room temperature. All solutions were then let to stand at 25 °C to attain equilibrium for another 24 h before any experimental study was performed. The total concentration of the surfactants was 10 mM. The compositions of the mixed solvents were represented by the cosolvent volume percentage.

The size distribution of the vesicles was determined by dynamic light scattering using a computerized particle size analyzer (model Zetasizer 3000 HS, Malvern, U.K.). During a measurement, the count rate, that is, the sample scattering intensity, was also

provided. It is worthy to note that the count rate determined for pure water is about 0.6 kcps (kcount/s). In this work, a criterion of count rate for the existence of appreciable amounts of vesicles was set to be ≥50 kcps. It was not infrequently encountered that the systems showed a variety of multiphase regions. In these cases, the measurements were made before and after filtering the solutions through a 0.45 μm mixed cellulose esters membrane (Millex-HA, Millipore, U.S.A.) at room temperature.

A transmission electron microscope (model JEOL-TEM-200EX) was used to obtain the vesicle images with the negative-staining technique. For the sample preparation, a few drops of vesicle solutions were applied to a carbon-coated Cu grid and dried. A drop of uranyl acetate−ethanol solution was then added as the staining agent.

Results and Discussion

Size distribution and count rate were measured for all solutions following their preparations. The existence of stable vesicles was revealed by the proper measured values of size and count rate. For the process of spontaneous formation, typical vesicles with mean sizes of hundreds of nanometers are expected. The sizer used in this work, by which the lower and upper limits of accurate measurement are 3 and 3000 nm, respectively, is, therefore, suitable for measuring the size of vesicles. On the other hand, medium stable count rates are deemed to be the manifestations of the presence of vesicles in large enough numbers. Under these conditions, the liquid actually appears bluish to the eye.

Vesicle Formation in Water. First of all, the results of aggregate formation in water without cosolvent revealed that only SDS/OTMAB and STS/OTMAB form catanionic vesicles spontaneously; all the other systems, that is, SDS/DeTMAB, STS/DeTMAB, SDS/DTMAB, STS/DTMAB, SDS/TTMAB, and STS/TTMAB, form precipitates. In the former cases, proper values of size and count rate were measured both before and after filtrating the solutions prepared. Analysis of the data was, therefore, qualified for a pass. Figure 4 demonstrates the measured size distributions of vesicles for SDS/OTMAB and STS/OTMAB before and after filtration. In the latter cases, however, unusual large size values and/or low count rate values were measured either before or after the filtration. Poor quality of data analyses was, thus, indicated.

Vesicle Formation in Water with Cosolvent. By the addition of cosolvent in water, varied changes in vesicle formability of different anionic surfactant−cationic surfactant mixed systems resulted from various kinds and amounts of cosolvent. It should be noted that the experimental results of size and count rate shown hereafter were those after filtration. As shown in Figure 5 for SDS/OTMAB and STS/OTMAB mixed systems, the count rates were found to essentially decrease with the increase of cosolvent concentration for all four cosolvents. Above a critical concentration for a specific cosolvent, the count rate eventually approached a value of zero. Under these conditions, the liquid appeared clear to the eye. The effectiveness of count rate diminution, however, increases in the order $C_4OH > C_3OH > C_2OH > C_1OH$. It has been mentioned above that mixing OTMAB with SDS and STS, respectively, may form catanionic vesicles spontaneously. The addition of cosolvents, therefore, causes diminishing amounts of vesicles. For higher enough concentrations, the vesicles finally disintegrated into constituent molecules. The TEM photograph shown in Figure 6 illustrates the 1:1 STS−OTMAB surfactant vesicles formed in 5% aqueous ethanol solution.

In contrast with the cosolvent effect on vesicle formation from SDS/OTMAB and STS/OTMAB mixed surfactant systems, drastically different trends in it were found on

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Table 1. Classification of Cosolvent Effects on Vesicle Formation[a]

		solvents				
			water with cosolvents			
	systems	water (original states)	methanol	ethanol	1-propanol	1-butanol
1	SDS/OTMAB (12:8)	V	1	1	1	1
2	STS/OTMAB (14:8)	V	1	1	1	1
3	SDS/DeTMAB (12:10)	P	3	2	2	2
4	STS/DeTMAB (14:10)	P	3	3	2	2
5	SDS/DTMAB (12:12)	P	4	4	3	3
6	STS/DTMAB (14:12)	P	4	4	4	4
7	SDS/TTMAB (12:14)	P	4	4	4	4
8	STS/TTMAB (14:14)	P	4	4	4	4

[a] Total surfactant concentration = 10 mM, molar ratio of anionic surfactant/cationic surfactant = 1:1. V, vesicle; P, precipitate; 1−4, types of cosolvent effects as indicated in Figure 10.

vesicles formed from other mixed surfactant systems. It should be remembered that all mixed systems studied in this work except SDS/OTMAB and STS/OTMAB formed precipitates in water. As shown in Figure 7 for the SDS/DeTMAB mixed system, the values of size and count rate indicated that all of four cosolvents may promote the formation of vesicles significantly. Generally, vesicle formability at first increased with increasing the concentration, reached a maximum at a specific concentration, and thereafter decreased with further increasing the concentration. The vesicle formability eventually becomes negligible at concentrations higher than a specific value. It is noteworthy that the amount of cosolvent, which begins to cause noticeable vesicle formability, decreases in the

order $C_4OH < C_3OH < C_2OH < C_1OH$. This is also revealed by the concentrations at the left-hand sides of the shaded areas, which cover the cosolvent concentration ranges with count rates $\geq$ 50 kcps. Likewise, the amount of cosolvent, which ceases to cause noticeable vesicle formability, also decreases in the order $C_4OH < C_3OH < C_2OH < C_1OH$. This may be revealed also by the concentrations at the right-hand sides of the shaded area mentioned above. A subtle distinction, however, can be drawn between methanol and the other cosolvents. While considerable enhancement of vesicle formation can be found upon the addition of minute amounts of ethanol, 1-propanol, and 1-butanol, a substantial amount of methanol was required for
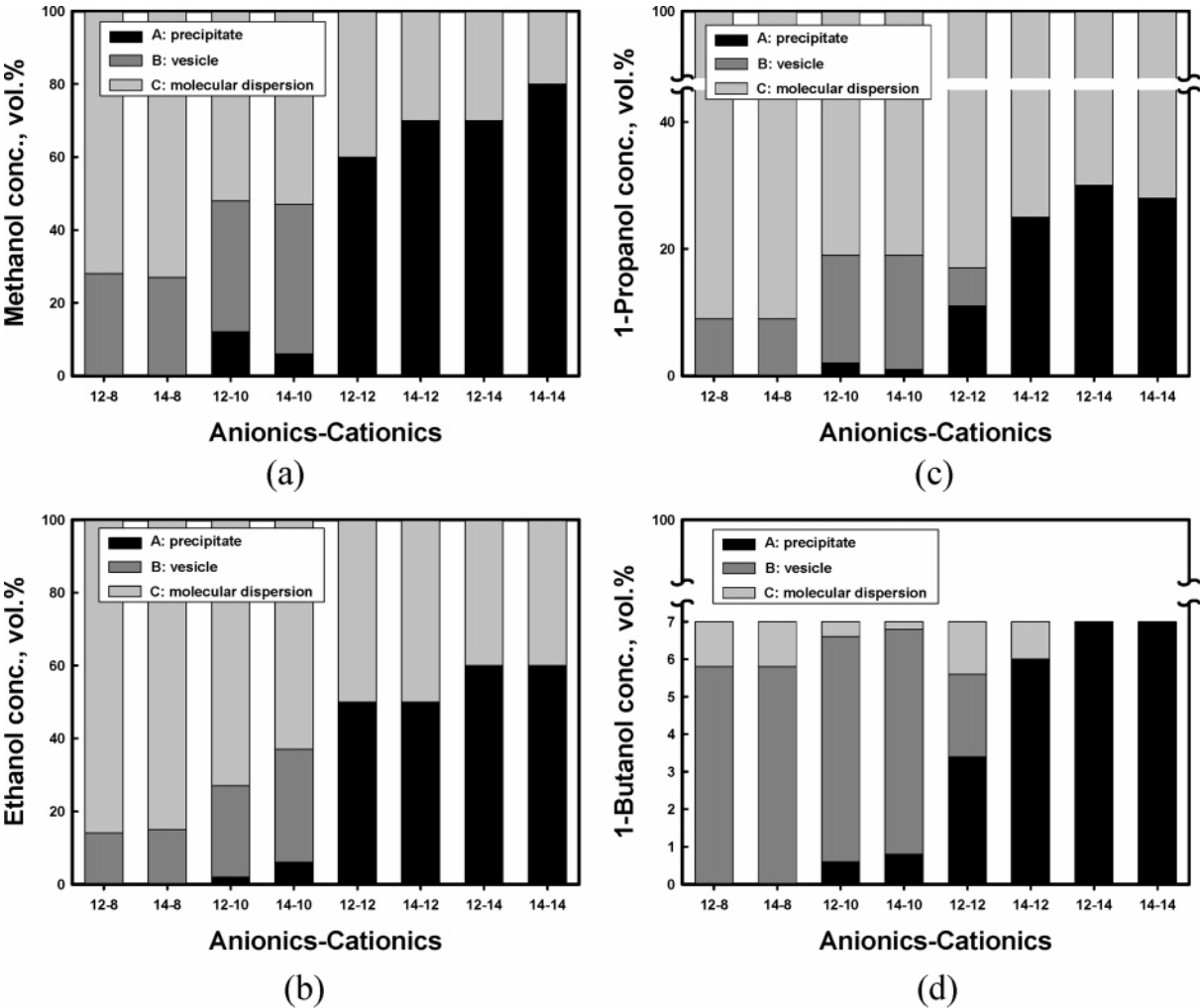

Figure 11. Possible regimes appeared for anionics−cationics by the addition of cosolvents. (a) Methanol, (b) ethanol, (c) 1-propanol, and (d) 1-butanol.

initiating the enhancement. Figure 8 shows the similar results for the STS/DeTMAB mixed system.

Another interesting and different cosolvent effect was found for the SDS/DTMAB mixed system as shown in Figure 9a,b. Precipitates rather than vesicles were usually formed in water and mixed solvents and, therefore, resulted in very low values of the measured count rate for the solutions. The precipitates, without undergoing a transition to vesicles, were found to be resolved more and more completely with the increase of cosolvent concentration. Clear solutions directly resulted from complete dissolution at higher cosolvent concentrations. This kind of cosolvent effect on vesicle formation is also true for the STS/DTMAB, SDS/TTMAB, and STS/TTMAB mixed systems.

Classification of Cosolvent Effects. As mentioned above, the cosolvent effects on the spontaneous formation of vesicles from 1:1 anionic and cationic surfactant mixtures can then be classified into four types as shown in Figure 10. Among them, cosolvent effects type 2 and type 3 indeed provide a practical vesicle-boosting method by means of cosolvent addition in water. However, it would be contended that cosolvent effect type 2 is the basic form of cosolvent effects on vesicle formation and the other types of cosolvent effects might then be regarded as the ones with transformation. Remember that Figure 2 highlights the solvophobic effect on the formation of vesicles in mixed solvents. Curve c in Figure 2, therefore, may result in cosolvent effect type 2 in Figure 10. For one extreme, the very steep curve a and very gentle curve b in Figure 2 may then result in cosolvent effect type 1 in Figure 10. For the other extreme, the very gentle curve a and very steep curve b in Figure 2 may then result in cosolvent effect type 4 in Figure 10. Moreover, cosolvent effect type 3 lies between type 2 and type 4. The general trend of cosolvent effects on the formation of vesicles from anionic—cationic mixed surfactants can then be delineated in principle.

For the eight mixed surfactant systems and four cosolvents studied in this work, Table 1 summarizes all possibilities of vesicle formation by the boosting protocol. They were exemplified by SDS/DeTMAB and STS/DeTMAB with methanol, ethanol, 1-propanol, and 1-butanol and by SDS/DTMAB with 1-propanol and 1-butanol. Furthermore, it is also important to indicate the available concentration ranges over which vesicles prevail, of

cosolvents for each mixed surfactant system. As shown in Figure 11a–d for methanol, ethanol, 1-propanol, and 1-butanol, correspondingly, three possible regimes (A–C in the figure)—precipitate, vesicle, and molecular dispersion—can then be identified. Obviously, this is consistent with the transition of regimes by considering the variation of the overall solvophobic effect with cosolvent concentration as shown in Figure 2.

Conclusions

A systematic study of cosolvent effects on the spontaneous formation of catanionic vesicles from 1:1 anionic—cationic mixed surfactants was carried out in this work. Some meaningful conclusions can be drawn from the investigation as follows.

1. The practical vesicle-boosting method by means of cosolvent addition in water becomes available for easily precipitated mixed surfactant systems. This is exemplified by SDS/DeTMAB and STS/DeTMAB with methanol, ethanol, 1-propanol, and 1-butanol and by SDS/DTMAB with 1-propanol and 1-butanol.

2. The general trend of cosolvent effects can be delineated and classified into four types. Among them, cosolvent effects type 2 and type 3 serve the purpose of boosting vesicle formation.

3. The effectiveness of vesicle boosting increases in the order 1-butanol > 1-propanol > ethanol > methanol.

4. An explanation of cosolvent effects based on the medium dielectric constant was proposed. According to this mechanism, the overall solvophobic effects and, therefore, the vesicle formability at first increase with increasing cosolvent concentration, reach a maximum at a specific concentration, and thereafter decrease with further increasing cosolvent concentration. The vesicles may finally disintegrate into constituent molecules at concentrations higher than a specific value. This constitutes the basic form of cosolvent effects and establishes the cosolvent effect type 2. Cosolvent effects type 1, type 3, and type 4 might then be regarded as the ones with transformation.