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SHORT COMMUNICATION

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Surfactant effect on the lower critical solution temperature of poly(organophosphazenes) with methoxy-poly(ethylene glycol) and amino acid esters as side groups

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Abstract The surfactant effect on the lower critical solution temperature (LCST) of thermosensitive poly(organophosphazenes) with methoxy-poly(ethylene glycol) and amino acid esters as side groups was examined in terms of molecular interactions between the polyphosphazenes and surfactants including various anionic, cationic, and nonionic surfactants in aqueous solution. Most of the anionic and cationic surfactants increased the LCST of the polymers: the LCST increased more sharply with increasing length and hydrophobicity of the hydrophobic part of the surfactant molecule. The ΔLCSTs ($T_{0.03M} - T_{0M}$), the change in the LCST by addition of 0 and 0.03 M sodium dodecyl sulfate (SDS), were found to be 7.0 and 14.5 °C for the polymers bearing ethyl esters of glycine and aspartic acid, respectively. The LCST increase of poly(organophosphazene) having a more hydrophobic aspartic acid ethyl ester was 2 times larger compared with that of the polymer having glycine ethyl ester as a side group. The binding behavior of SDS to the polymer bearing glycine ethyl ester as a hydrophobic group was explained from the results of titration of the polymer solutions containing SDS with tetrapropylammonium bromide. Graphic models for the molecular interactions of polymer/surfactant and polymer/surfactant/salt in aqueous solutions were proposed.

Key words Polyphosphazene · Thermosensitivity · Lower critical solution temperature · Surfactant effect

Introduction

Recently much attention has been focused on interactions of water-soluble polymers with additives in aqueous solution [1–5]. Their solution properties have been studied by various methods, such as osmotic pressure, solubilization, magnetic resonance, surface tension, clouding, conductivity, self-diffusion, and so on. In particular, the solution behavior of thermosensitive polymers is easy to study since they show a lower critical solution temperature (LCST) which can be measured by a simple method using a melting-point apparatus. Four well-known organic polymers with LCSTs are poly(ethylene glycol) [6], poly(propylene glycol) [7], poly(*N*-isopropylacrylamide) [8], and poly(vinylpyrrolidone) [9]. The effects of additives such as salts [10], saccharides [11], surfactants [12], and solvents [13] on the LCST of these organic polymers have been extensively investigated because of their potential biomedical applications.

Among the additives, surfactants have been employed as a third component in order to investigate the solution behavior of biologically useful polymers such as thermosensitive polymers and their hydrogels. The surfactant is usually composed of hydrophobic and hydrophilic groups, which gather at (or are adsorbed to) the interface of mutually repelling materials, such as oil and water, to reduce interface tension. Because of such

amphiphilic characteristics, surfactants have been used for the study of the solution behavior of amphiphilic polymers.

Most thermosensitive organic polymers are homo- or copolymers with both hydrophobic and hydrophilic segments. Since the physicochemical properties of polyphosphazenes are largely dependent on the side groups composed of organic, organometallic, or inorganic components attached to the flexible inorganic backbone and the composition of the side groups can be varied from a single substituent to mixed substituents, poly(organophosphazenes) are a good example to study the solution behavior resulting from the interaction of the polymers with additives in aqueous solutions. Recently, we reported that poly(organophosphazenes) bearing methoxy-poly(ethylene glycol)(MPEG) and amino acid esters as side groups exhibited a wide variety of LCSTs depending on the compositions and kinds of side groups [14], and their hydrolytic degradability and salt effect [15] were examined in aqueous solution. The thermosensitivity and biodegradability of these poly(organophosphazenes) may offer a wide range of potential applications as biomaterial.

In this study, the surfactant effect on the LCST of poly(organophosphazenes) was investigated in relation to the structures of anionic, cationic, and nonionic surfactants, and binding models for their molecular interactions were proposed.

Experimental

Polymers

Among the poly(organophosphazenes) with MPEG and amino acid esters as side groups previously synthesized [14], the following copolymers were used: $[NP(MPEG350)_{1.42}(GlyEt)_{0.58}]_n$ (**1**), $[NP(MPEG350)_{0.99}(GlyEt)_{1.01}]_n$ (**2**), $[NP(MPEG350)_{0.58}(GlyEt)_{1.42}]_n$ (**3**), $[NP(MPEG350)_{1.03}(GlyMe)_{0.97}]_n$ (**4**), $[NP(MPEG350)_{1.00}(GlyBz)_{1.00}]_n$ (**5**), $[NP(MPEG750)_{1.09}(GlyEt)_{0.91}]_n$ (**6**), $[NP(MPEG350)_{1.00}(AlaEt)_{1.00}]_n$ (**7**), and $[NP(MPEG350)_{1.01}(AspEt_2)_{0.99}]_n$ (**8**). In addition, a new polymer, $[NP(MPEG350)_{1.03}(\beta\text{-AlaEt})_{0.97}]_n$ (**9**), was synthesized and characterized using the same method as previously [14]: MPEG350(17.26 mmol) and β-alanine ethyl ester(34.52 mmol) were used. Yield: 68%. ^{31}P NMR(acetone-d_6), δ(ppm): 24.01. ^1H NMR(D_2O), δ(ppm): 1.2–1.4(m, 3H), 2.6–2.7(m, 2H), 3.2–3.3(m, 2H), 3.4(s, 3H), 3.6–3.9(b, 26H), 4.0–4.4(b, 4H). Elementary analysis (%) calculated: C, 46.84; H, 8.11; N, 5.36; P, 6.07. Found: C, 47.06; H, 8.23; N, 5.42; P, 6.11.

Surfactants

Guaranteed reagent grade sodium dodecyl sulfate (SDS), sodium tetradecyl sulfate (STS), sodium dodecylbenzene sulfonate (SDBS), dodecyltrimethylammonium chloride (DTAC), dodecyltrimethylammonium bromide (DTAB), tetradecyltrimethylammonium bromide (TTAB), and hexadecyltrimethylammonium bromide (HTAB) were used as received from Acros. Nonaoxyethylene dodecyl ether (NODE), Triton X-100, and tetrapropylammonium bromide (TPAB) were used as received from Aldrich.

Measurement of the LCST

The phase transition of the polymer solution (5 wt%) containing different kinds and concentrations of surfactants (0.005–0.1 M) was detected visually in a closed glass tube immersed in an oil bath. The LCST was identified as the temperature at which the solution became turbid. In the two-surfactants system, the second surfactant was added to the polymer solution containing SDS and the dependence of the LCST on SDS concentration was examined.

Results and discussion

The effect of each surfactant on the LCST of poly(organophosphazenes) was studied as a function of the polymer structure and surfactant concentration. In this study, both ionic properties (anionic, cationic, or nonionic groups) and structural aspects of surfactants, including lengths of hydrophobic alkyl chains (decyl, dodecyl, tetradecyl, or hexadecyl groups), the existence of a benzene ring in the hydrophobic alkyl chain, and chain lengths of the ethylene oxide unit in the nonionic surfactants, were considered in relation to the behavior of aqueous polymer/surfactant solutions. Various thermosensitive poly(organophosphazenes) with MPEG and amino acid esters as side groups were employed in this study and their characteristics are listed in Table 1.

Polymers **2** and **8** have nearly the same composition of MPEG and amino acid ester (1:1), which induces the N-P-O repeating unit of the polymer backbone; however,

Table 1 Characteristics of poly(organophosphazenes)

Polymer	Formula	LCST (°C)[a]	M_w ($\times 10^{-4}$)	ΔLCST (°C) ($T_{0.03M} - T_{0M}$)[b]
1	$[NP(MPEG350)_{1.42}(GlyEt)_{0.58}]_n$	93.2	4.73	1.5
2	$[NP(MPEG350)_{0.99}(GlyEt)_{1.01}]_n$	77.5	3.84	7.0
3	$[NP(MPEG350)_{0.58}(GlyEt)_{1.42}]_n$	64.5	1.77	18.0
4	$[NP(MPEG350)_{1.03}(GlyMe)_{0.97}]_n$	88.5	3.08	2.7
5	$[NP(MPEG350)_{1.00}(GlyBz)_{1.00}]_n$	49.5	2.13	8.0
6	$[NP(MPEG750)_{1.09}(GlyEt)_{0.91}]_n$	98.5	4.14	2.0
7	$[NP(MPEG350)_{1.00}(AlaEt)_{1.00}]_n$	67.0	3.58	12.0
8	$[NP(MPEG350)_{1.01}(AspEt_2)_{0.99}]_n$	60.2	4.40	14.5
9	$[NP(MPEG350)_{1.03}(\beta\text{-AlaEt})_{0.97}]_n$	70.3	2.18	7.0

[a] Data from Ref. [14]
[b] The change in the LCST by addition of 0.03M SDS

polymers **2** and **8** have different amino acid esters: glycine ethyl ester and L-aspartic acid ethyl ester as hydrophobic groups, respectively. The former is a monocarboxylate and the latter a dicarboxylate. The changes in the LCST depending on the different surfactants and their concentrations for polymers **2** and **8** are shown in Fig. 1. In aqueous solution containing one of the anionic (STS, SDBS, DTAC) or cationic (DTAB, TTAB, HTAB) surfactants, the LCST of the polymers increased to over 100 °C at low surfactant concentrations; however, nonionic NODE 400, NODE 600, and Triton-X 100 did not exhibit any observable effect on the LCST of the polymer solutions. The anionic SDS surfactant brought about an initial increase in the LCST up to a certain concentration, but a further increase in the concentration of these surfactants gave rise to a slight decreasing effect on the LCST.

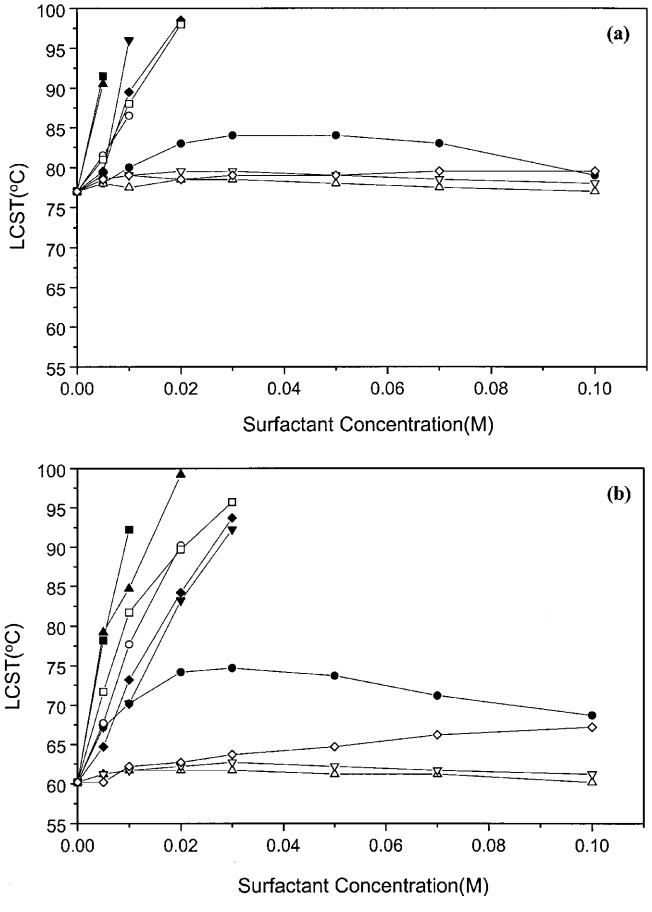

Fig. 1 Change in the lower critical solution temperature (*LCST*) of **a** polymer **2** and **b** polymer **8** solutions by addition of surfactants: sodium dodecyl sulfate (*SDS*) (●); sodium tetradecyl sulfate (■); sodium dodecylbenezene sulfonate (▲); dodecyltrimethylammonium chloride (▼); dodecyltrimethylammonium bromide (◆); tetradecyltrimethylammonium bromide (○); hexadecyltrimethylammonium bromide (□); nonaoxyethylene dodecyl ether (*NODE*)400 (△); NODE600 (▽); Triton X-100 (◇)

SDS and STS have 11 and 13 methylene units in their hydrophobic segments, respectively. The solutions of polymers **2** and **8** showed a stronger "salting-in effect" on addition of STS compared with SDS, which indicates that the surfactant with a longer chain, i.e., more hydrophobic alkyl group, has a better binding ability to the polymers through hydrophobic interactions. Although SDS, SDBS, DTAC, and DTAB have the same 11 methylene units in their alkyl chains, SDBS, DTAC, and DTAB exhibit a stronger salting-in effect than SDS, probably because SDBS has a benzene ring between the alkyl chain and the sulfonate group and DTAC and DTAB have a trimethyl group on the nitrogen between the alkyl chain and the counterion. The benzene ring and the trimethyl group seem to enhance the salting-in effect of the polymer/surfactant solution. Furthermore, it is known that anionic surfactants exhibit significantly stronger interactions than cationic ones with a similar chain length [16].

The surfactant effect on the LCST of thermosensitive polyphosphazenes can be readily understood by assuming that the side group of poly(organophosphazene) is ionized upon binding of the surfactant molecules to the polymer network: it is reasonable to consider that the surfactant molecules bind to the polymer network through hydrophobic interactions, subsequently converting an otherwise neutral polyphosphazene into a polyelectrolyte. These acquired polymer charges should be associated with counterions. Such phenomena were widely observed in polymer/surfactant solutions composed of STS, SDBS, DTAC, TTAB, and HTAB [17–21].

Interestingly, the increase in the LCST of polymer **8** bearing aspartic acid ethyl ester was much greater than that of polymer **2** bearing glycine ethyl ester as a side group. The degree of increase of the LCST was dependent on the kind of hydrophobic groups attached to the polymer. The ΔLCSTs ($T_{0.03M} - T_{0M}$), the change in the LCST by addition of 0 and 0.03 M SDS for polymers **2** and **8**, were found to be 7.0 and 14.5 °C, respectively. A graphic model of the interaction between SDS and hydrophobic parts of the polymers is shown in Fig. 2. Ethyl esters of glycine and aspartic acid have one and two ethyl groups as a hydrophobic group, respectively, and the amount of SDS binding to polymer **8** is 2 times larger than to polymer **2**. This assumption is supported by the results shown in Table 1: the ΔLCSTs ($T_{0.03M} - T_{0M}$) by SDS were found to increase with increasing content of glycine ethyl ester, the hydrophobic part, in polymers **1**, **2**, and **3**.

However, nonionic NODE 400, NODE 600, and Triton X-100 did not induce a significant increase in the LCST for polymers **2** and **8**. It is known that the interaction between an uncharged water-soluble polymer and an uncharged surfactant is generally weak. Such results have also been observed for the effect of

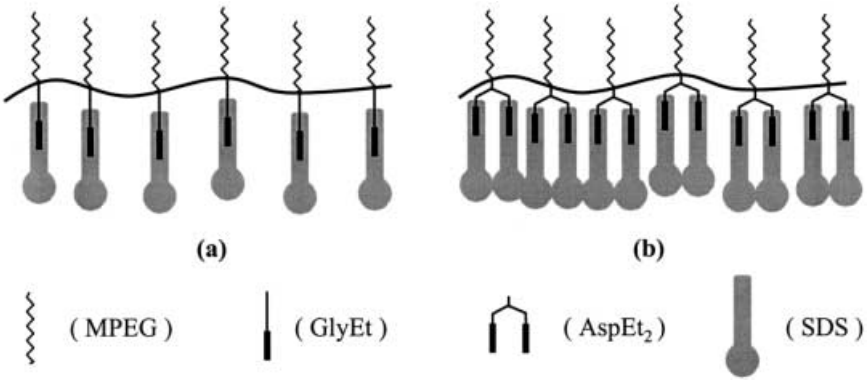

Fig. 2 Graphic models for interactions of **a** polymer **2** and **b** polymer **8** with SDS in aqueous solution. The heads and tails of SDS indicate its hydrophilic and hydrophobic parts, respectively

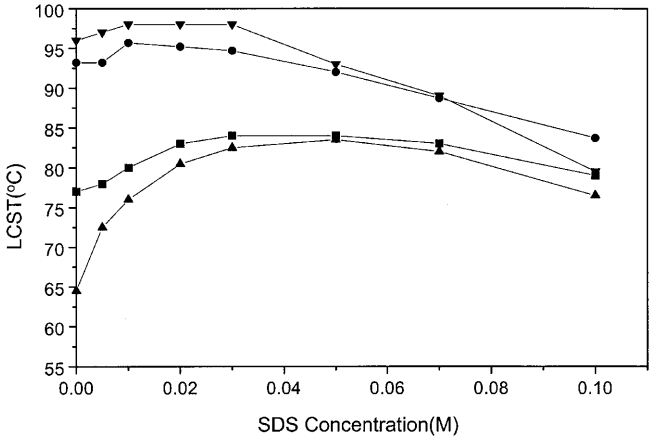

Fig. 3 Change in the LCST of polymer **1** (●), polymer **2** (■), polymer **3** (▲), and polymer **6** (▼) solutions by addition of SDS

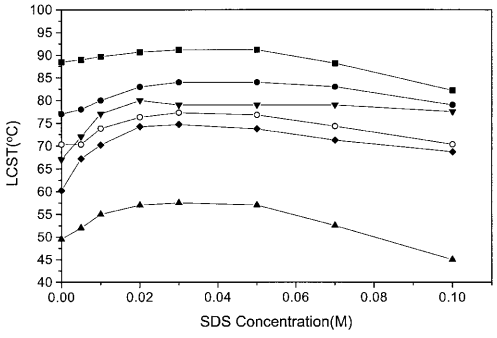

Fig. 4 Change in the LCST of polymer **2** (●), polymer **4** (■), polymer **5** (▲), polymer **7** (▼), polymer **8** (◆), and polymer **9** (○) solutions by addition of SDS

surfactants on the LCST of poly(*N*-isopropylacrylamide) and poly(ethylene oxide) [5, 22].

LCSTs are plotted against the concentration of SDS for polymers with different compositions of side groups, MPEG350 and amino acid esters, and different lengths of MPEG in Fig. 3. The LCST increased with increasing concentration of SDS up to 0.03 M, but beyond this concentration the LCST decreased with increasing concentration of SDS. The ΔLCSTs ($T_{0.03M} - T_{0M}$) of polymers **1, 2, 3,** and **6** are 1.5, 7.0, 18.0, and 2.0 °C, respectively. When the polymers have more hydrophobic character, the LCST of the polymers shows more drastic change depending on the surfactant concentration. This result may be due to the relatively high content of hydrophobic groups, glycine ethyl ester in the polymer backbone leading to a high hydrophobic interaction with the surfactant. The LCSTs of polymers **1, 2, 3,** and **6** at 0.1 M SDS concentration are 83.7, 79.5, 76.5, and 79.5, respectively, which shows that all the LCST curves converge to approximately 80 °C at about 0.1 M SDS concentration. Such a result provides indirect evidence for the optimal formation of polymer/surfactant aggregates at this SDS concentration. These aggregates seem to be similarly made in aqueous solutions of polymers **1, 2, 3,** and **6** bearing the same amino acid as a side group.

The effect of SDS on the LCST of polymers with different amino acid esters is shown in Fig. 4. The ΔLCSTs ($T_{0.03M} - T_{0M}$) of the polymers by addition of SDS are shown in Table 1. The more hydrophobic amino acids afforded larger ΔLCSTs ($T_{0.03M} - T_{0M}$). The ΔLCSTs ($T_{0.03M} - T_{0M}$) of polymers **2, 7,** and **8** are 7.0, 12.0, and 14.5 °C, respectively. A similar trend was observed for polymers **2, 4,** and **5** composed of the same amino acid but different ester groups. The more hydrophobic ester groups afforded larger ΔLCSTs ($T_{0.03M} - T_{0M}$): the ΔLCST of polymers with methyl (**4**), ethyl (**2**), and benzyl (**5**) esters are 2.7, 7.0, and 8.0 °C, respectively.

In order to examine the interaction between the polymer and surfactant molecules, we studied how the LCST of poly(organophosphazenes) in a constant concentration of SDS is changed when salts such as TPAB and NaCl are added. Generally, TPAB and NaCl are representative salts affording strong "salting-in" (LCST increase) and "salting-out" (LCST decrease) effects in aqueous solutions of thermosensitive polymers, respectively [13]. The LCST of polymer **2** is plotted against the concentration of TPAB at different SDS

concentrations in Fig. 5. Interestingly, the LCST of the polymer solution decreased with increasing concentration of TPAB in the lower concentration range in spite of the strong salting-in effect of TPAB, but beyond this concentration the polymer solution showed an increasing LCST corresponding to a normal salting-in effect of TPAB in the higher concentration range.

Such a result is assumed to be due to hydrophobic interactions among the polymer, surfactant, and TPAB. A tentative model for the interaction is presented in Fig. 6. The SDS molecules in the polymer solution are likely to bind to the hydrophobic part of the polymer through hydrophobic interactions. If TPAB is added to the polymer solution containing SDS and its concentration is lower than that of SDS, TPAB molecules seem to interact with SDS bound to the polymer as shown in Fig. 6a, resulting in the production of two kinds of salts, i.e., tetrapropylammonium dodecyl sulfate and NaBr. The first salt may increase the hydrophobicity of the polymer because the tetrapropylammonium cation makes the hydrophilic part of SDS hydrophobic, and NaBr decreases the LCST of the polymer because of the salting-out effect; therefore, the LCST of the polymer solution decreased with increasing TPAB concentration up to that of SDS. On the other hand, when the TPAB concentration is higher that that of SDS, TPAB molecules may interact both with the tetrapropylammonium and dodecyl sulfate ions, resulting in ionization of the hydrophobic part of the polymer, as shown in Fig. 6b; therefore, the LCST of the polymer increases with increasing TPAB concentration.

In contrast, in the case of NaCl, the LCST decreased in the full range of NaCl concentration owing to its strong salting-out effect. The effect of NaCl on the LCST of polymers **2** and **8** in 0.03 M SDS solution is shown in Fig. 7. The ΔLCSTs ($T_{1.0M} - T_{0M}$) of polymers **2** and **8** by NaCl at a constant SDS concentration are −32.5 and −31.5 °C, respectively, but in the absence of SDS [15] the values are −19.2 and −16.5 °C, respectively. The SDS-mediated effect of NaCl on the LCST of the polymers has been shown to be influenced drastically by the larger area of the polymers/SDS aggregates to be bound by NaCl.

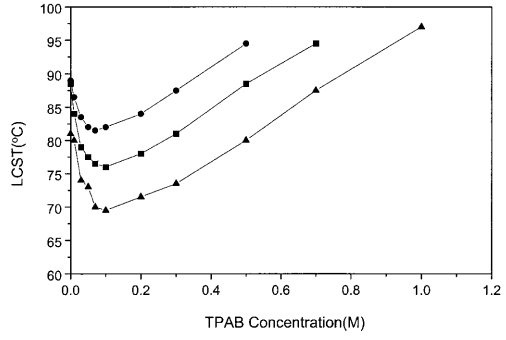

Fig. 5 Change in the LCST of polymer **2** in 0.03M SDS (●), 0.1M SDS (■), and 0.17M SDS (▲) by addition of tetrapropylammonium bromide (*TPAB*)

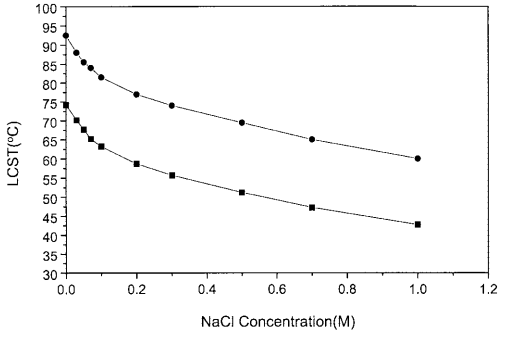

Fig. 7 Change in the LCST of polymer **2** (●) and polymer **8** (■) in 0.03M SDS by addition of NaCl

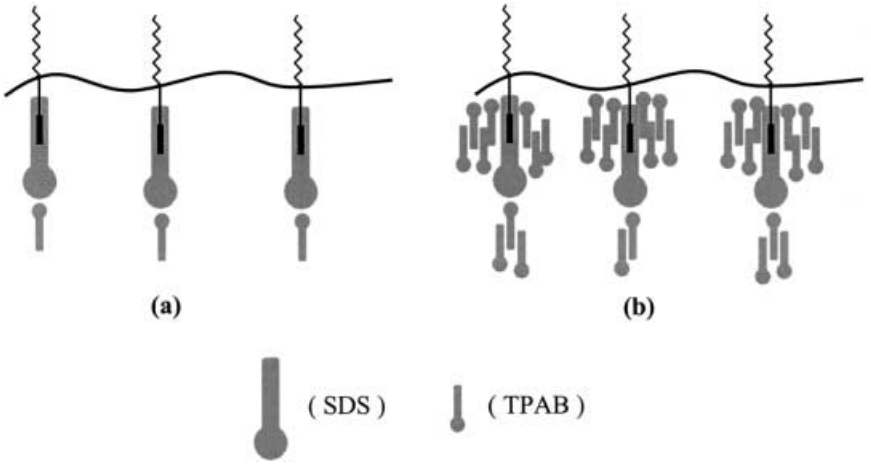

Fig. 6 Graphic models for interactions among polymer **2**, SDS, and TPAB. The concentration of TPAB is **a** lower or **b** higher than that of SDS, and the heads and tails of the surfactants indicate their hydrophilic and hydrophobic parts, respectively

Conclusion

Addition of a small amount of a surfactant to an aqueous solution of the present poly(organophosphazenes) gave rise to a significant increase in their LCST. The LCST increase of these thermosensitive poly(organophosphazenes) was found to be affected by the kinds of surfactants as well as by the composition of the substituents, the structure of the amino acid ester groups, and the chain length of the MPEG of the polyphosphazenes. Most of the ionic surfactants increased the LCST: when the surfactants have more hydrophobic character, the LCST of the polymers increases more drastically depending on the surfactant concentration. This result may be interpreted as binding of surfactant molecules to the polymer network. In contrast, NODE 400, NODE 600, and Triton-X 100, which are nonionic surfactants, did not exhibit any remarkable increase in the LCST of the polymer solutions, which is probably due to very weak hydrophobic interactions between the surfactant and polymer molecules. The strong hydrophobic interactions between the present polymer and surfactant molecules could be explained from the results obtained on addition of ionic salts with salting-out or salting-in effects to an aqueous solution of the polymer and surfactant. It is presumed from the results that SDS binds to the amino acid esters through its hydrophobic alkyl chain as shown in the graphic model.

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