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Gel Filtration of Solubilized Systems. V.[1] Effects of Sodium Chloride on Micellar Sodium Lauryl Sulfate Solutions Solubilizing Alkylparabens[2]

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The present investigation was undertaken to examine the effects of added sodium chloride on solubilized systems of sodium lauryl sulfate (SLS) micellar solutions solubilizing alkylparabens by gel filtration. The results showed that the addition of sodium chloride decreased the distribution coefficients of alkylparabens between the SLS micellar and aqueous phases. The factors causing the decrease of distribution coefficients were investigated. Activity coefficients of SLS and alkylparabens in mixed micelles were estimated on the basis of ideal solution theory. The activity coefficients suggested that the addition of sodium chloride hardly changed the SLS-alkylparaben interaction in the mixed micelles. The decrease in the surface area per SLS molecule in the micelles on addition of sodium chloride seems to be an important factor.

Keywords——solubilization; alkylparabens; sodium lauryl sulfate; sodium chloride; gel filtration; distribution coefficient; activity coefficient; solubility method; surface area; ideal solution theory

The effects of added electrolytes on solubilized systems have important consequences of interest not only in colloid chemistry but also in connection with pharmaceutical applications. However, little work has yet been reported concerning the effects of added electrolytes on solubilized systems,[4–6] though several studies have been made on the effects of added electrolytes on the Critical Micelle Concentration (CMC) and micellar size of ionic surfactants.

The effects of added electrolytes on solubilized systems were investigated by the solubility method[4–7] but this can deal only with the effects of added NaCl on the solubility limits of solubilizates in micellar solutions.

In studying the effects of added electrolytes on solubilized systems, it is more important to investigate the effects of added electrolytes on the distribution of a solubilizate between the micellar and aqueous phases rather than on the solubility limits of solubilizates in micellar solution. However, few studies on the effects of added electrolytes on the distribution have been reported.

Solubilized systems of sodium lauryl sulfate (SLS) micellar solutions solubilizing alkylparabens have been investigated by gel filtration.[8–10] The present investigation was under-

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1) Part IV: A. Goto and F. Endo, *J. Colloid Interface Sci.*, **68**, 163 (1979).

2) This work was presented at the 31st Symposium on Colloid and Surface Chemistry of Japan, Toyama, autumn 1978.

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taken to examine the effects of addition of sodium chloride on solubilized systems of SLS micellar solutions solubilizing alkylparabens by gel filtration.

Experimental

Materials——SLS (sodium lauryl sulfate) was purified as described previously.[8] Methyl-, ethyl-, and butylparabens were reagent-grade commercial products, as was sodium chloride. The sample solutions were prepared by dissolving alkylparabens in 40 mM SLS containing 10 or 50 mM NaCl.

Gel Filtration——Bio-Gel P-4 was placed in a jacketed column (1.6 × 40 cm, Pharmacia, Sweden) maintained at 27.0 ± 0.2°. The total volume and the void volume of the gel bed were 43.0 and 18.3 ml, respectively. Tail analysis[9,10] on Bio-Gel P-4 was carried out as follows: The sample was eluted with 10 or 50 mM NaCl on a gel column preequilibrated with 120 ml of a solubilized solution containing 10 or 50 mM NaCl. Tail analysis on Sephadex G-75 was carried out in the same way. The total volume and the void volume of the gel bed were 58.0 and 23.3 ml, respectively.

Analytical Methods——Concentrations of alkylparabens and SLS were determined by the methods described previously.[9,10]

Measurement of the Solubility of Alkylparaben in SLS Solution——Excess of alkylparabens was placed in glass-stoppered flasks containing 10 ml of SLS solution at various concentrations. The concentration of added NaCl was 50 mM. The flasks were then shaken at 27.0 ± 0.1° in an incubator (Taiyo type M-1) to attain equilibrium. A given volume of the supernatant was diluted appropriately with water, and the concentration of alkylparaben was determined.

Results

Effects of NaCl on the Solubilities of Alkylparabens in Aqueous SLS Solutions

Figure 1 shows solubility curves of alkylparabens in aqueous SLS solutions in the presence of 50 mM NaCl and in the absence of NaCl. The addition of NaCl apparently increased the solubilities of alkylparabens in low concentrations of SLS. Table I shows the effects of 50 mM NaCl on the solubilities of alkylparabens in 40 mM SLS at 27°; solubility data for alkylparabens in 40 mM SLS without NaCl are also shown for comparison. It should not be concluded that the addition of NaCl resulted in an increase in the solubilities of alkylparabens in high concentrations of SLS, however.

Gel Filtration of the Solubilized Solution on Bio-Gel P-4 in the Presence of NaCl

Figure 2 shows the tail analysis of the elution curves on Bio-Gel P-4 for 40 mM SLS solution containing 6.42 mM ethylparaben and 50 mM NaCl. The height of the higher plateau

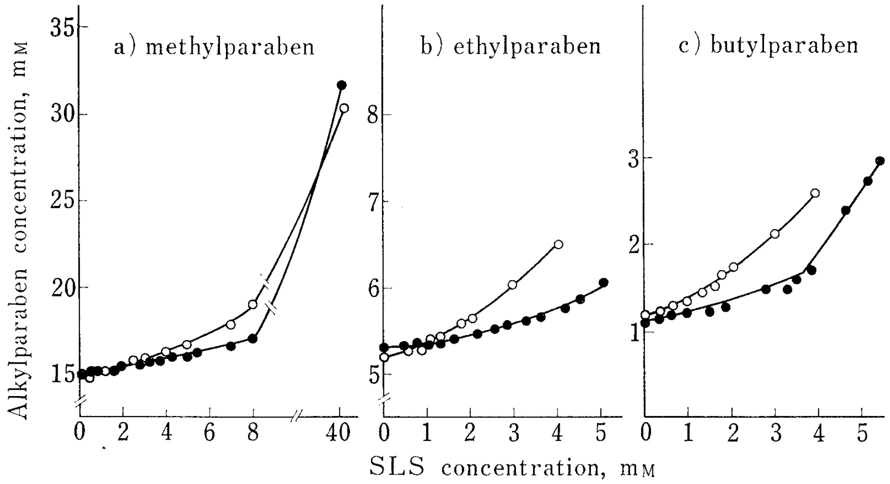

Fig. 1. Effects of Added Sodium Chloride on the Solubilities of Alkylparabens in SLS Solutions at 27°

○, 50 mM NaCl. ●, without NaCl.

Table I. Solubilization of Alkylparabens in 40 mM SLS Solution at 27°

Alkylparaben	No addition (mM)	Addition of 50 mM NaCl (mM)
Methylparaben	33.9	31.6
Ethylparaben	22.7	21.9
Butylparaben	24.3	26.7

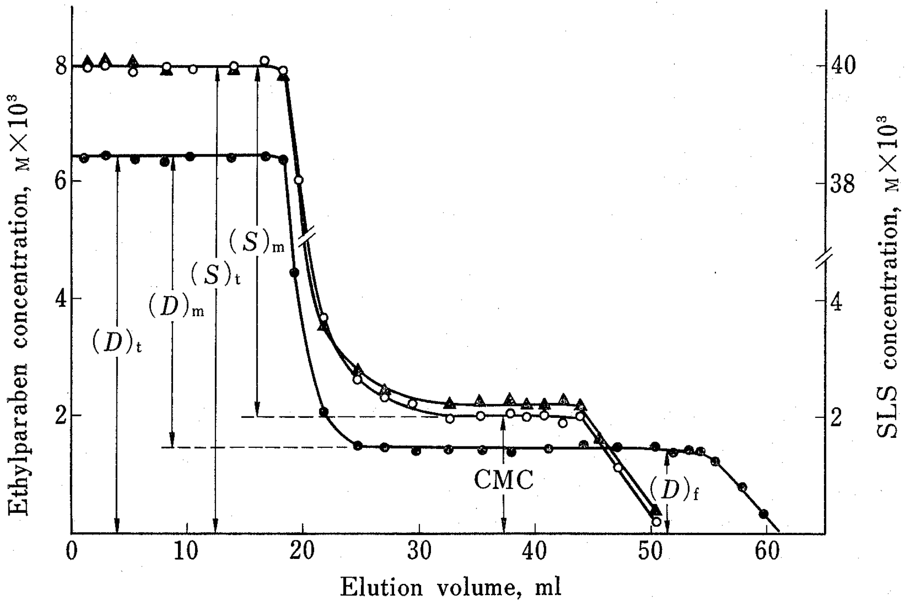

Fig. 2. Tail Analysis of the Elution Curves of 6.42 mM Ethylparaben in 40 mM SLS Containing 50 mM NaCl on Bio-Gel P-4

The sample was eluted with 50 mM NaCl on a gel column preequilibrated with the sample solution.
●, ethylparaben concentration in the eluate.
○, SLS concentration in the eluate.
▲, SLS concentration in the eluate without any alkylparaben.
$X_s{}^a=(D)_f\ 18/1000$
$X_s{}^m=(D)_m/\{(S)_m+(D)_m\}$
$K_a=X_s{}^m/X_s{}^a$

of the SLS elution curve, $(S)_t$, corresponds to the total concentration of SLS in the original sample. The height of the lower plateau is considered to correspond to the CMC of SLS in the solubilized system.[11,12] The elution curve of SLS solution in 50 mM NaCl containing no alkylparaben under the same conditions is shown in Fig. 2. The lower plateau corresponds to the CMC in 50 mM NaCl without any solubilizate. The CMC is nearly equal to that obtained by Stigter.[13] Figure 2 showed that the CMC in the solubilized system is lower than that without solubilizates in the presence of NaCl. $(S)_m$ is obtained by subtracting the CMC from $(S)_t$. The height of the higher plateau on the elution curve of ethylparaben, $(D)_t$, corresponds to the total concentration of ethylparaben in the original sample. $(D)_m$ and $(D)_f$ are the concentrations of ethylparaben solubilized in the micellar phase, and of free ethylparaben in the aqueous phase, respectively.[9,10] Ethylparaben as a complex with SLS[9] was not observed in the elution curve of ethylparaben in the presence of NaCl.

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The apparent distribution coefficient, K_a, was defined as $K_a = X_s^m/X_s^a$,[10] where X_s^m is the molar fraction of a solubilizate in the micellar phase, and X_s^a is the molar fraction of a solubilizate in the aqueous phase. The apparent distribution coefficient, K_a, was calculated from $(D)_m$, $(D)_f$, and $(S)_m$ based on the elution curves of alkylparabens and SLS according to the following equations:

$$X_s^a = (D)_f \cdot 18/1000 \tag{1}$$

$$X_s^m = (D)_m/\{(S)_m + (D)_m\} \tag{2}$$

and

$$K_a = X_s^m/X_s^a \tag{3}$$

Figures 3, 4, and 5 show the effects of added NaCl on the apparent distribution coefficients, K_a, of alkylparabens. The abscissa shows the molar fraction of the alkylparaben in the micellar phase, X_s^m, while the ordinate shows the apparent distribution coefficients, K_a. Addition of NaCl resulted in a decrease in the K_a values. Since K_a is a function of X_s^m and decreases linearly with X_s^m in the presence of NaCl as well as in the absence of NaCl, as shown in Figs. 3, 4, and 5, it should be possible to estimate the apparent distribution coefficients at zero X_s^m.

The CMC obtained from the elution curve of SLS was plotted against $(D)_f$ (Fig. 6). On addition of alkylparabens, the CMC in the presence of NaCl tended to decrease with increase in $(D)_f$ in the same way as in the absence of NaCl.[10]

Tail Analysis of the Solubilized Solutions in the Presence of NaCl on Sephadex G-75

Figure 7 shows elution curves of 40 mM SLS solutions containing 50 mM NaCl, 10 mM NaCl, and without any electrolytes on Sephadex G-75, where V_{m50}, V_{m10}, and V_{m0} are, respectively, the tail volume of SLS micelles in 50 mM NaCl, that in 10 mM NaCl, and that in the system without any electrolytes. Sephadex G-75 (effective in the molecular weight

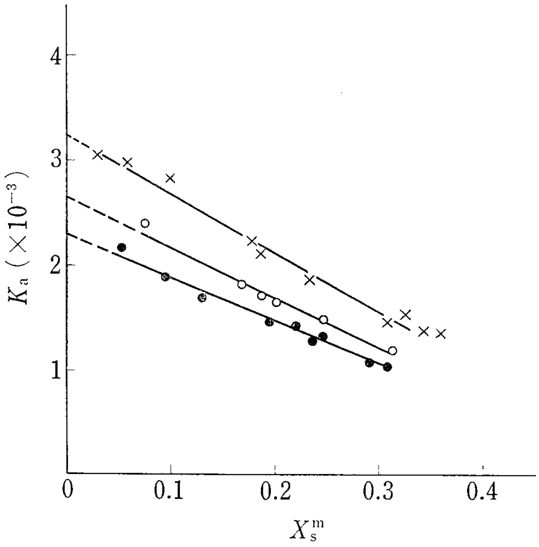

Fig. 3. Effects of Added Sodium Chloride on the Apparent Distribution Coefficient for Methylparaben between the SLS Micellar and Aqueous Phases

●, 50 mM NaCl.
○, 10 mM NaCl.
×, without NaCl.

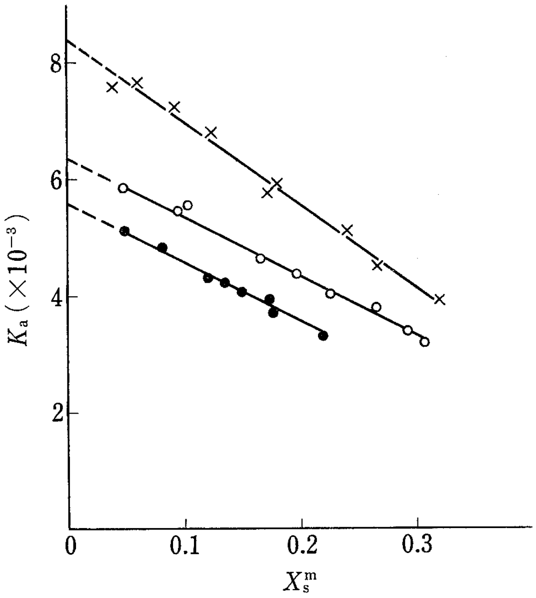

Fig. 4. Effects of Added Sodium Chloride on the Apparent Distribution Coefficient for Ethylparaben between the SLS Micellar and Aqueous Phases

●, 50 mM NaCl.
○, 10 mM NaCl.
×, without NaCl.

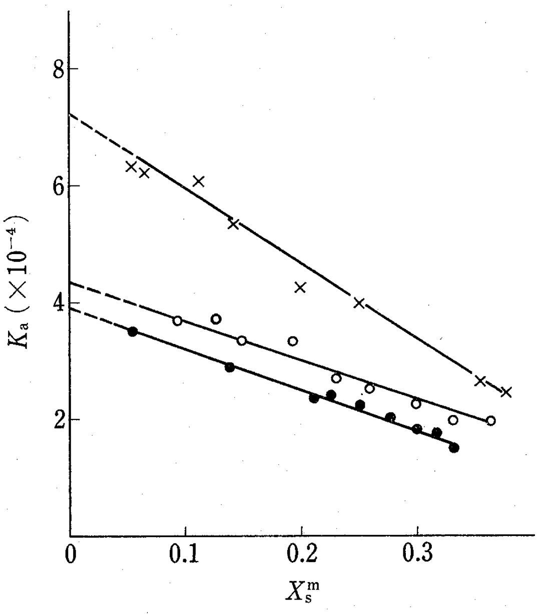

Fig. 5. Effects of Added Sodium Chloride on the Apparent Distribution Coefficient for Butylparaben between the SLS Micellar and Aqueous Phases

●, 50 mM NaCl.
○, 10 mM NaCl.
×, without NaCl.

range of 3000 to 70000) was used because the micellar weight of SLS at 25° has been estimated to be 18000 by light scattering.[14] The tail volume corresponds to the elution volume of the micelles.[1,11,12] The V_m values of micelles solubilizing alkylparabens of various concentrations were obtained by the same method. The V_m values were plotted against $(D)_m$, as shown in Fig. 8. The values of $(D)_m$ were obtained by tail analysis of the solubilized system on Bio-Gel P-4, as described above. The V_m values of micelles solubilizing alkylparabens increased with $(D)_m$ in the presence of NaCl as well as in the absence of NaCl.[1] If the shape of the micelles does not change markedly on adding NaCl or solubilizing alkylparabens, the elution volume of micelles, V_m, is a parameter of the volume of the hydrated micelles.[11,12] Figure 7 shows that the volume of hydrated micelles increased with increase in the concentration of NaCl from 0 to 50 mM NaCl. Furthermore, Fig. 8 shows that the volume of hydrated micelles solubilizing alkylparabens decreased with $(D)_m$ in the presence of NaCl as well as in the absence of NaCl.

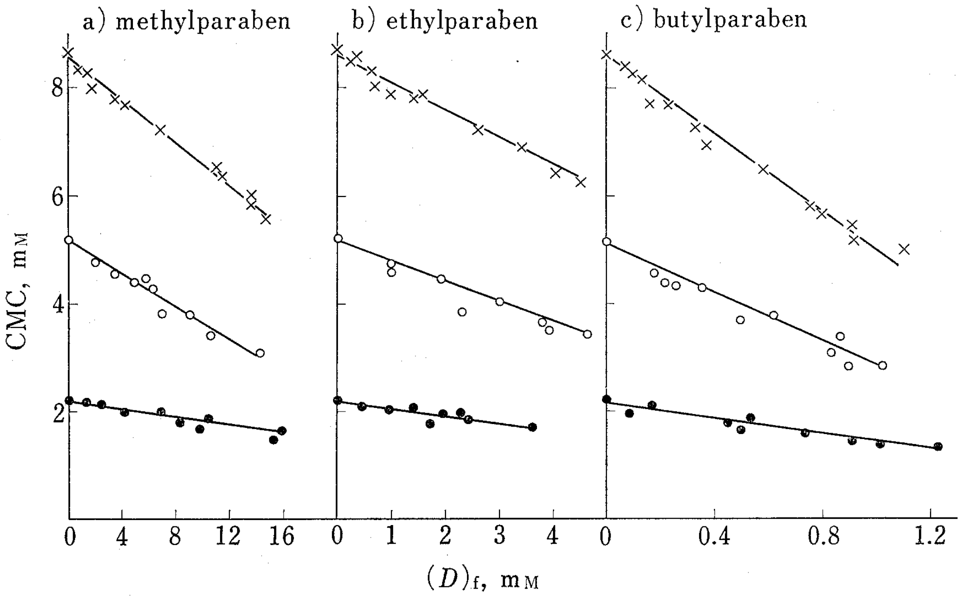

Fig. 6. The CMC's of SLS Solution in the Presence of Alkylparabens

●, 50 mM NaCl.
○, 10 mM NaCl.
×, without NaCl.

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[14] K. Mysels and L.H. Princen, *J. Phys. Chem.*, **63**, 1699 (1959).

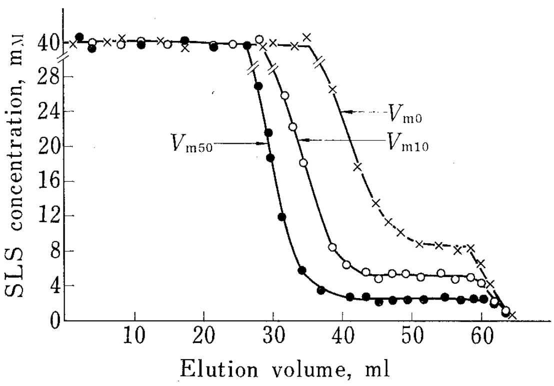

Fig. 7. Tail Analysis of the Elution Curves of 40 mM SLS in the Presence of Sodium Chloride on Sephadex G-75

The samples were eluted with 50 mM NaCl, 10 mM NaCl, and water on a gel column of Sephadex G-75 preequilibrated with 120 ml of the samples.
●, 50 mM NaCl.
○, 10 mM NaCl.
×, without NaCl.

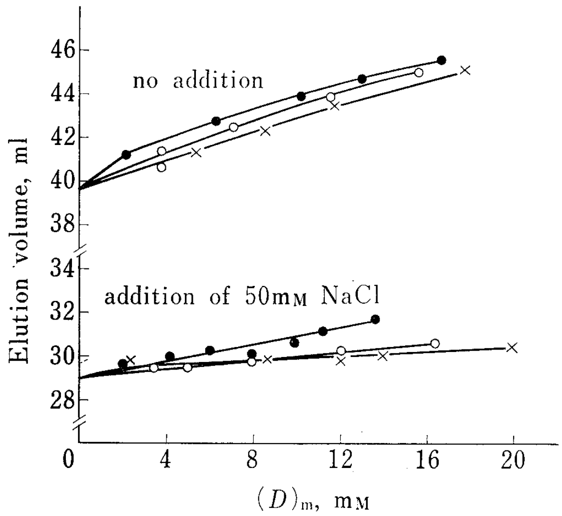

Fig. 8. Variation of the Elution Volume of SLS Micelles with Concentration of Alkylparaben in the Micells in the Presence of 50 mM NaCl

Elution volumes of the SLS micelles in absence of NaCl, as reported in the preceding paper,[1] are included.
●, methylparaben.
○, ethylparaben.
×, butylparaben.

Discussion

It has been confirmed by the various methods that micellar size increases[14,17–19] and CMC decreases[15–20] on addition of electrolytes. In the present investigation, a decrease in the CMC and an increase in the size of hydrated SLS micelles were directly observed with increase in the concentration of NaCl from 0 to 50 mM by gel filtration on Sephadex G-75 (Fig. 7). It is of interest to investigate the effects which such a change in the solution state of SLS micelles has on the solubilized state of a solubilizate because the phenomenon is important for pharmaceutical applications, as well as in colloid chemistry.

The effects of electrolytes on the solubilized systems have been investigated partly by the solubility method.[4,20] The authors also used the solubility method initially. Figure 1 shows that the addition of NaCl apparently resulted in increases of the solubilities of alkylparabens in low concentrations of SLS. The increase of the micellar portion due to the decrease of CMC on addition of NaCl may largely account for this. On the other hand, it is not adequate to consider that the addition of NaCl resulted in increases in the solubilities of alkylparabens in 40 mM SLS solutions (Table I), since the increase in the micellar portion due to the decrease of CMC represents only a small part of the total micellar portion at high concentrations of SLS. The effects of added NaCl on the solubilized system are thus likely to be more complex.[15–20] It is necessary to investigate the effects of electrolytes on the distribution of a solubilizate between the micellar and aqueous phases in order to clarify the

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17) P. Mukerjee, K.J. Mysels, and K. Kapauan, *J. Phys. Chem.*, **71**, 4166 (1967).
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20) H.B. Klevens, *J. Am. Chem. Soc.*, **72**, 3780 (1950).

real effects of electrolytes on solubilized systems. However, the solubility method cannot be used for this purpose.

The gel filtration of solubilized systems on Bio–Gel P-4 can provide information about the distribution of a solubilizate between micellar and aqueous phases.(10) Gel filtration was therefore applied in a similar manner to solubilized systems containing NaCl. The results show that the addition of NaCl decreased the apparent distribution coefficients of alkylparabens between the micellar and aqueous phases (Figs. 3—5). The authors consider that the pseudo phase theory reported by Mukerjee(21) may be useful for solubilized systems in the presence of NaCl as well as in the absence of NaCl.(10)

Since an approximately linear relationship exists between K_a and X_s^m (Figs. 3—5), it seems reasonable to apply ideal solution theory to the solubilized systems.(10) The distribution coefficient of a solubilizate between the micellar and aqueous phases was defined as follows:

$$K_t = X_s^m \gamma_s^{*m} / X_s^a \gamma_s^{*a} \quad (4)$$

where γ_s^{*m} is the activity coefficient of a solubilizate in the micellar phase, γ_s^{*a} is the activity coefficient of a solubilizate in the aqueous phase, and* refers to the ideal dilute solution standard state.

The solubilities of alkylparabens in 10 and 50 mM NaCl at 27° are nearly equal to those in water, and are low. Therefore, the addition of NaCl should have little effect on γ_s^{*a}. It seems reasonable to consider that the values of γ_s^{*a} in the aqueous phase are unity for these alkylparabens, even when the concentrations of alkylparabens are near the solubility limits in SLS micellar solutions. The K_a values which permit extrapolation to zero X_s^m may correspond to a distribution coefficient, K_t. Table II shows the effects of added NaCl on the distribution coefficients for alkylparabens. The addition of NaCl decreased the distribution coefficients, K_t, of the alkylaparabens.

Table II. Effect of NaCl on the Distribution Coefficients, K_t, for Alkylparabens

Alkylparaben	Added NaCl conc. (mM)		
	0	10	50
Methylparaben	3240	2630	2250
Ethylparaben	8450	6340	5640
Butylparaben	72900	44300	39300

The factors responsible for these phenomena were further investigated. The activity coefficients of alkylparabens in the aqueous phase seem to be scarcely influenced by the addition of NaCl, as described above. Therefore, it is not considered likely that a change in the activity coefficients of alkylparabens in the aqueous phase on addition of NaCl reduced the distribution coefficients of alkylparabens.

It is possible to estimate γ_s^{*m} according to equation[4]. Furthermore, we estimated the activity coefficient of SLS in the mixed micelles from γ_s^{*m} according to the Gibbs-Duhem equation.(1) The values of ln γ_s^{*m} and ln γ^{*m} were plotted against X_s^m as shown in Fig. 9. The values of ln γ_s^{*m} increased with increasing X_s^m. This suggests that alkylparabens in the mixed micelles might become unstable thermodynamically with increasing X_s^m. The values of ln γ^{*m}, on the other hand, decreased with increasing X_s^m, suggesting that SLS in the mixed micelles might become thermodynamically more stable with increasing X_s^m. Therefore, the SLS-alkylparabens interaction in the mixed micelles was assumed to be larger than the

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21) P. Mukerjee, *J. Pharm. Sci.*, **60**, 1531 (1971).

alkylparaben-alkylparaben interaction or the SLS–SLS interaction.[1,10] The changes in ln $\gamma^*{}_s{}^m$ and ln γ^{*m} for methyl-, ethyl-, and butylparabens are similar in tendency. This suggests that the state of alkylparabens in the micelles varied only slightly. In other words, the interaction of the hydrophilic part of alkylparaben and SLS in the mixed micelles can be assumed to play an important part in the SLS-alkylparaben interaction.

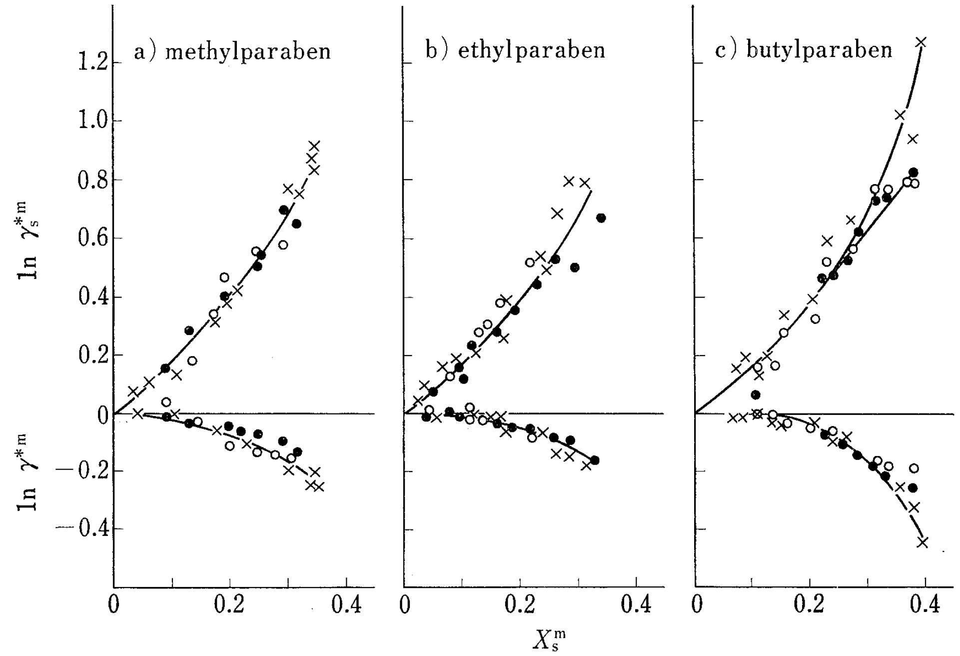

Fig. 9. Activity Coefficients of Alkylparaben and SLS in the Mixed Micelles

●, 50 mM NaCl.
○, 10 mM NaCl.
×, without NaCl.

The values of ln γ_s^{*m} and ln γ^{*m} for methyl-, ethyl-, and butylparabens varied only slightly on addition of NaCl except that butylparaben showed higher X_s^m. This suggests that the SLS-alkylparaben interaction in the mixed micelles was little influenced by the addition of NaCl.

On the other hand, the values of the activity coefficient of butylparaben at high X_s^m were undoubtedly low compared with those in the absence of NaCl, as shown in Fig. 9. This suggests that the degree of SLS-butylparaben interaction decreased slightly at high X_s^m on the addition of NaCl.

The addition of electrolytes to an ionic surfactant solution is known to have the following consequences[22,23]: i) decrease in the CMC,[15–20] ii) increase in the micellar size,[14,17–19] and iii) decrease in the effective charge per monomer surfactant on the surface through decreased ionization.[24,25] Since it is expected that a decrease in the effective charge on addition of electrolytes will tend to concentrate the head groups of surfactant molecules,[26] it seems likely that the contraction of charged head groups enhances the interaction of the hydrocarbon chains. This will result in a more rigid micellar interior.[26] Such a contraction of the micelles may decrease the permeability of the micelle-water interface to a solubilizate. This effect may improve the solubilization of butylparaben, which has a larger alkyl chain than the other alkylparabens. However, further studies are required.

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It was assumed on the basis of gel filtration that the addition of NaCl increased the volume of hydrated SLS micelles (Fig. 7). Furthermore, it was shown that the solubilization of alkylparaben decreased the volume of hydrated SLS micelles in the presence of NaCl. In the preceding paper,[1] the alkylparabens were assumed to penetrate only slightly on the basis of ultraviolet, *etc*. Therefore, a larger surface area of the micelles may solubilize a larger amount of alkylparabens. The increase in the number of small micelles in the solubilized system leads to a larger micelle surface area for the incorporation of alkylparabens.

Tanford[27] assumed that as the aggregation number of a micelle increases, it will move from a more spherical shape to a more ellipsoidal shape. As this occurs, the surface area per molecule decreases, resulting in an increase in charge density. Leibner and Jacobus[28] assumed that the surface area per monomer decreases with increase in the aggregation number. Therefore, it seems reasonable to consider that the addition of NaCl will lead to a decrease in the surface area per SLS molecule.

On addition of NaCl and alkylparabens, the CMC decreased as shown in Fig. 6. The concentrations of SLS taking part in micelle formation, $(S)_m$, are also affected. It is necessary to compare the effects of added NaCl on the amount of alkylparaben solubilized per 1 mol of SLS taking part in micelle formation in order to discuss the decrease in the distribution coefficient in relation to the decrease in micelle surface area.

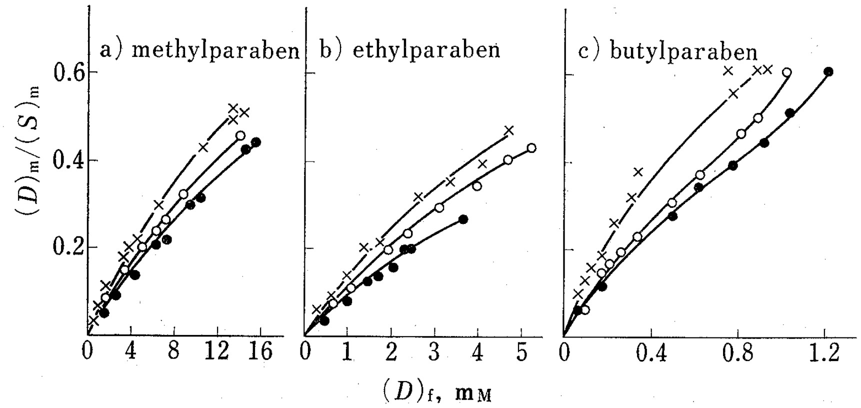

Fig. 10. Plots of $(D)_m/(S)_m$ against $(D)_f$

●, 50 mM NaCl.
○, 10 mM NaCl.
×, without NaCl.

Figure 10 shows plots of $(D)_m/(S)_m$ against $(D)_f$. $(D)_m/(S)_m$ is the amount (mol) of alkylparaben solubilized in 1 mol of SLS. $(D)_m/(S)_m$ decreased with increase in concentration of NaCl for all the alkylparabens.

Thus, the decrease in the surface area on addition of NaCl may be considered as an important factor in the decrease of the distribution coefficient of alkylparabens between the micellar and aqueous phases. Klevens[6] reported that for the solubilization of hydrocarbon, *i.e.*, entry into the core of a micelle, an enhancement of the solubilization upon addition of electrolytes can be expected. On the other hand, the solubility of polar compounds in micellar solution decreases in the presence of electrolytes, since there would be a decrease in the effective volume of the palisade layer available for polar compounds. Our results show that the solubilization of alkylparabens in SLS micelles corresponds to the latter case.

Acknowledgement Grateful acknowledgement is made to Miss K. Mizoguchi for technical assistance.

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28) J.E. Leibner and J. Jacobus, *J. Phys. Chem.*, **81**, 130 (1977).