Syntheses of 2-(N-alkyl-N,N-dimethylammonio)ethyl Hydrogen Phosphates and Their Physicochemical Properties

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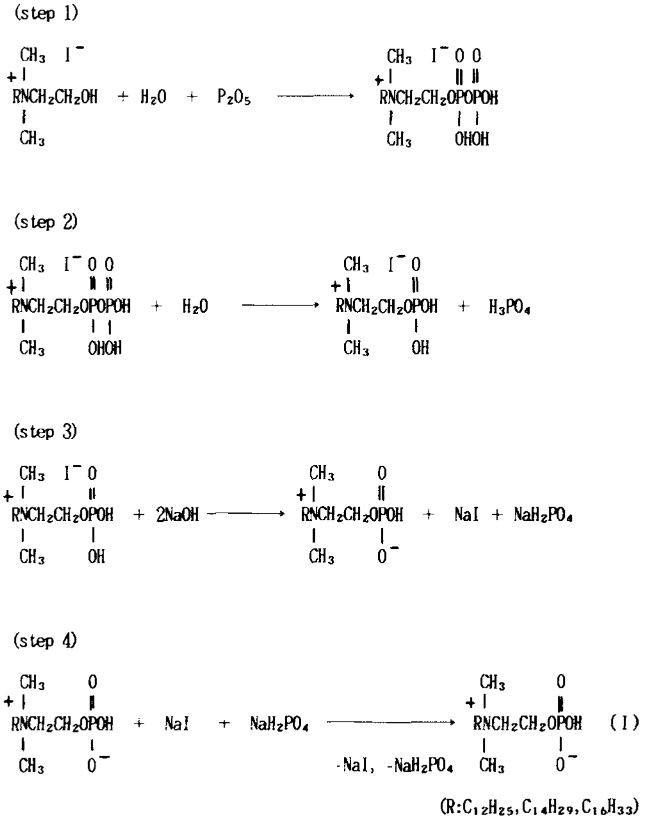
A series of new amphoteric surfactants, having a quaternary ammonium group and a phosphoric acid group, 2-(N-alkyl-N,N- dimethylammonio)ethyl hydrogen phosphates (alkyl: dodecyl, tetradecyl, hexadecyl), were prepared by introducing a phosphoric acid group into N-alkyl-N,N-dimethyl-(N-2-hydroxyethyl) ammoniumiodide, followed by neutralization with sodium hydroxide and removal of inorganic salts. By the evaluation of the physicochemical properties, it was found that the phosphobetaines behave like "nonionic" surfactant in the zwitterionic region, having very small CMC values in comparison with sodium 2-(N-alkyl-N-methylamino)ethyl hydrogen phosphates. Additionally, similar trends were also observed in the experiments from the point of the effect of electrolyte and temperature on CMC, respectively. It should be considered that the hydrophobicity of the surfactant molecule is increased by the electronic interaction between the quaternary ammonium group and a phosphoric acid group. On the other hand, the phosphobetaines gave the smaller values of the occupied area per molecule at the air/water interface than sodium 2-(N-alkyl-N-methylamino)ethyl hydrogen phosphates. Therefore, it is clear that the phosphobetaines have higher surface-active properties than the amphoteric surfactants.

The amphoteric surfactants, which consist of a quaternary ammonium group and an anionic group in each molecule, exist as zwitterions over a certain broad pH range in their aqueous solution. It is known that N-alkyl-N,N-dimethyl glycines (1), 3-(N-alkyl-N,N-dimethylammonio)propane sulfonates (2) are amphoteric surfactants.

Phosphatidylcholine, a typical natural occurring phospholipid, contains a phosphoryl choline group having a quaternary ammonium group and a phosphoric acid group: these groups form a zwitterionic structure.

On the other hand, many synthetic phospholipids—for example, alkylphosphorylcholines (3), 1-alkyl-2-methylglycero-3- phosphocholines (4), 2-(N-dialkyl-N-methylammonio)ethyl sodium phosphates (5), 3-(N-alkyl-N,N-dimethylammonio)propane ethyl phosphonates (6) and 3-(N-alkyl-N,N-dimethylammonio)propane phenyl phosphonates (7)—have been studied from various points of view.

In a previous paper (8), we described the preparation and the basic physicochemical properties of sodium 2-(N-alkyl-N- methylamino)ethyl hydrogen phosphates. The most important features of these amphoteric surfactants are that they exhibit zwitterionic characteristics in the pH range from ca. 5-9, and that they demonstrate good surface-active properties over a wide pH range (pH 4~10) because they have a tertiary amino group and a phosphoric acid group with a long-chained alkyl group in each molecule.



SCHEME 1. **Preparation of 2-(N-alkyl-N,N-dimethylammonio) ethyl hydrogen phosphates.**

In this paper, for the purpose of the development of the phosphate type of amphoteric surfactants, we described the syntheses and the physicochemical properties of a series of new phosphobetaines: 2-(N-alkyl-N,N-dimethylammonio)ethyl hydrogen phosphates (alkyl: dodecyl, tetradecyl, hexadecyl; I in Scheme 1). These phosphobetaines have two points of structural characteristics. First, they have a single long-chained alkyl group as a hydrophobic moiety, which differ entirely from the dialkyl compounds developed by Okahata (5). Secondly, they have a quaternary nitrogen adjacent to the hydrophobic moiety and a phosphoric acid group at the terminus of the hydrophilic part, respectively, which differ from the generally known phospholipids. The main purposes of this study were to investigate the physicochemical properties shown by the aqueous solution of these new phosphobetaines—such as pKa value, surface tension, critical micelle solution (CMC), occupied area per molecule at the air/water interface (A value) and free energy change of micellization—and to compare these data with the corresponding sodium 2-(N-alkyl-N-methylamino)ethyl hydrogen phophates.

EXPERIMENTAL METHODS

Analytical data for procedure—for example, IR, NMR, thin-layer and column chromatographs, and elemental analyses—were performed as previously described (8).

In this study, the following abbreviations are used: DMEP for (N-alkyl-N,N-dimethylammonio)ethyl hydrogen phosphate; the notations, C_{12}-, C_{14}- and C_{16}- in front of the abbreviations denote the carbon numbers, 12, 14 and 16 in alkyl chain, respectively. For example, C_{12}-DMEP represents 2-(N-dodecyl-N,N-dimethylammonio)ethyl hydrogen phosphate.

Synthesis of 2-(N-dodecyl-N,N-dimethylammonio) ethyl hydrogen phosphate (C_{12}-DMEP). C_{12}-DMEP was synthesized from N-dodecyl- N,N-dimethyl-(N-2-hydroxyethyl)ammoniumiodide (DDMHA, m.p. 143°C), as shown in Scheme 1. DDMHA (19.25 g, 0.05 mole), distilled water (0.9 g, 0.05 mole) and diphosphorous pentaoxide (9.94 g, 0.07 mole) were mixed in tetrahydrofuran (300 ml) and stirred until a clear solution was obtained. The solution was then refluxed for 8 hr with stirring. The reaction mixture was cooled to room temperature, water (3.4 g, 0.19 mole) was added, and the mixture was stirred for 30 min. NaOH (5.6 g, 0.14 mole) was then added, followed by stirring for 20 min. After evaporation of the solvent from the reaction mixture, the residue was dissolved in 50 ml of water, followed by the performance of the ion-exchanger gel column chromatography by mixed bed resins (AG501-X8(D), Bio-Rad Laboratories) with a water eluent for the purpose of removing ionic impurities. The colorless eluent was dried to give crude C_{12}-DMEP by using a freeze dryer. In order to purify, the crude product was applied to silica gel column chromatography using ethanol-water (1:1, v/v) as an eluent resulting in 3.9 g of C_{12}-DMEP. The compound showed one spot on TLC, yield 20%; IR: 3452, 2925, 1464, 1379, 1180, 1080, 974, 926, 748 cm^{-1}; ^{1}H-NMR (CD_3OD; δ): 0.87 (3H, t, $CH_3(CH_2)_{11}$-), 1.28~1.80 (22H, m, $CH_3(CH_2)$ 11-), 3.18 (6H, s, $N(CH_3)_2$), 3.45 (2H, t, CH_2N), 3.63 (2H, t, CH_2O), 4.29 (1H, s, OH); ^{13}C-NMR (CD_3OD; δ): 14.44 (CH_3), 23.65 (CH_2), 27.35 (CH_2), 30.24~30.72 (CH_2), 32.99 (CH_2), 52.11 ($N(CH_3)_2$), 59.92 (NCH_2), 66.91 (CH_2O); analysis calculated for $C_{16}H_{36}N_1O_4P_1$: C,56.95; H,10.75; N,4.15. Found: C,57.03; H,10.72; N,4.10.

Other DMEP homologues, C_{14}-DMEP and C_{16}-DMEP, were prepared by similar procedures and showed one spot on TLC; yields and analytical data are as follows:

C_{14}-DMEP; IR: 3453, 2925, 1465, 1378, 1180, 1080, 974, 926, 748 cm^{-1}; ^{1}H-NMR (CD_3OD, δ): 0.88 (3H, t, $CH_3(CH_2)_{13}$-), 1.28~1.79 (26H, m, $CH_3(CH_2)_{13}$-), 3.17 (6H, s, $N(CH_3)CH_2$), 3.44 (2H, t, CH_2N), 3.62 92H, t, CH_2O), 4.26 (1H, s, OH); ^{13}C-NMR (CD_3OD, δ): 14.34 (CH_3), 23.54 (CH_2), 27.29 (CH_2), 30.13~30.60 (CH_2), 32.88 (CH_2), 52.10 ($N(CH_2)_2$), 59.84 (NCH_2), 67.04 (CH_2O); analysis calculated for $C_{18}H_{40}N_1O_4P_1 \cdot H_2O$: C,56.37; H,11.04; N, 3.65. Found: C,55.57; H,10.56; N,3.45.

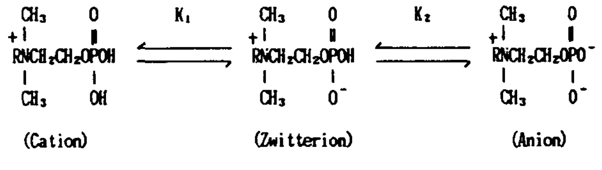
C_{16}-DMEP; IR: 3452, 2924, 1464, 1378, 1180, 1080, 974, 926, 748 cm^{-1}; ^{1}H-NMR (CD_3OD, δ): 0.89 (3H, t, $CH_3CH_2)_{15}$-), 1.29~1.80 (30H, m, $CH_3(CH_2)_{15}$-), 3.19 (6H, s, $N(CH_3)_2$), 3.44 (2H, t, CH_2N), 3.65 (2H, t, CH_2O), 4.28 (1H, s, OH); ^{13}C-NMR (CD_3OD, δ): 14.21 (CH_3), 23.50 (CH_2), 27.24 (CH_2) 30.06~33.53 (CH_2), 32.82 (CH_2), 52.07 ($N(CH_3)_2$), 59.72 (NCH_2), 66.94 (CH_2O); analysis calculated for $C_{20}H_{44}N_1O_4P_1$: C,61.04; H,11.27; N,3.56. Found: C,61.00; H,11.30; N,3.60.

Measurements of physicochemical properties. The pKa values were determined in water at 20°C, according to the potentiometric method. The Krafft point and other surface active properties of aqueous solution of those phosphobetaines were measured by a previously reported method (8). The pH of aqueous solutions was adjusted by the addition of hydrochloric acid or sodium hydroxide.

RESULTS AND DISCUSSION

DMEP-homologues in this study were all white crystals and hygroscopic. Their Krafft points were below zero, as were those of sodium 2-(N-alkyl-N-methylamino)ethyl hydrogen phosphates (MEP) (8), and they are readily soluble in water at room temperature. The pH values of these aqueous solutions (0.1 wt%) were 5.5~5.8 at 20°C. These are lower than MEP-homologues, because DMEP-homologues have a quaternary ammonium group instead of a tertiary amino group. The compounds are soluble in ethanol and methanol but almost insoluble in acetone and benzene.

The results of potentiometric titrations are shown in Table 1. The differential curves indicate two minima, which are due to the formation of cation (ammonioethyl dihydrogen phosphate) by protonation to phosphate group and to the formation of anion (ammonioethyl sodium phosphate) by deprotonation of phosphate group. The two minima of those curves correspond to pK_1 (4.8~4.9)and pK_2 (9.3~9.4). The isoelectric points of DMEP-homologues occurred at pH 7.0~7.1. Thus, it is clear that DMEP-homologues exist in three ionic forms, depending upon the pH values of aqueous solutions. These forms are shown in the following equilibrium.



The cationic structure is formed predominantly in acidic solution of pH below 4.8. The zwitterion exists in the range of pH ca. 4.8~9.3. The anionic form presents in alkaline solution of pH above 9.3. Therefore, DMEP is considered to be a zwitterion in the range of pH 4.8~9.3.

In order to assess the surface-active property of these compounds, the surface tensions of their aqueous solutions were measured. The formations of micelles were demonstrated by the presence of break points in the surface tension-log concentration plots for aqueous solutions of DMEP-homologues at pH 5.5 (Fig. 1). It can be seen that all compounds reduce the surface tension of water and the effects of the length of the alkyl chain upon the surface activity is clear. Their CMC and γCMC values are summarized in Table 2. The CMC values of DMEP-homologues were found to be much smaller than corresponding MEP-homologues (8). This means that the zwit-

TABLE 1

Isoelectric Points of Surfactants[a]

Surfactant	pk_1	pK_2	pK_3	pHI_1	pHI_2
C_{12}-DMEP	4.9	9.4	—	7.2	—
C_{14}-DMEP	4.7	9.3	—	7.0	—
C_{16}-DMEP	4.8	9.4	—	7.1	—
C_{12}-MEP[b]	4.7	8.8	9.4	6.8	9.1

[a] Measured in water + ethyl alcohol (1:1, v/v) at 20°C.

[b] Reference 8.

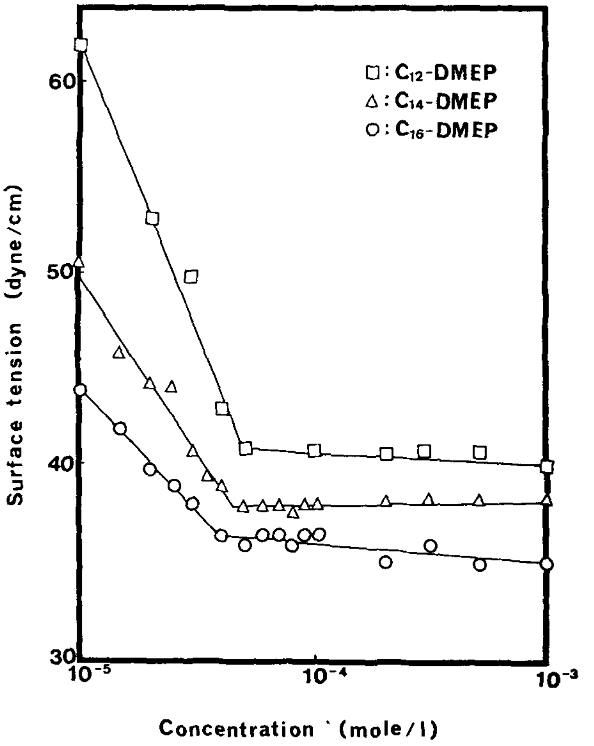


FIG. 1. Surface tensions-concentration plots.

TABLE 2

Interfacial Properties of Surfactants

Surfactant	CMC mmole/l (°C)	γ cmc dyne/cm	A × 10^2 nm^2
C_{12}DMEP	0.050 (25)	41.0	31.7
C_{14}DMEP	0.045 (25)	38.5	51.4
C_{16}DMEP	0.040 (25)	36.5	76.1
C_{12}MEP[a]	0.36 (25)	39.2	51.4
C_{14}MEP[a]	0.20 (25)	38.0	59.3
C_{16}MEP[a]	0.10 (25)	37.0	79.4
N-dodecyl-β-alanine[b]	0.9 (30)	35	45
Sodium dodecyl sulfate[c]	7.2 (20)	35.0	40

[a] Reference 8.
[b] Reference 12.
[c] Reference 11.

terions of DMEP-homologues bear much resemblance to nonionic surfactant in comparison with those of MEP-hommologuges. It should be considered that the hydrophobicity (9) of this phosphobetaine molecule is increased in the zwitterionic region owing to the electronic interaction between the quaternary ammonium group and the phosphoric acid group. The difference of the CMC values between DMEP and MEP indicates that the interaction in DMEP molecule is stronger than in MEP.

The longer the alkyl chain, the lower the CMC values from 0.05 mmole/l to 0.04 mmole/l. This trend agrees with Traube's rule. The relation of logarithm of the CMC values against the carbon number (N) of its alkyl chain in Figure 2 gave the following equation:

$$\mathrm{Log(CMC)} = -4 - 0.025N.$$

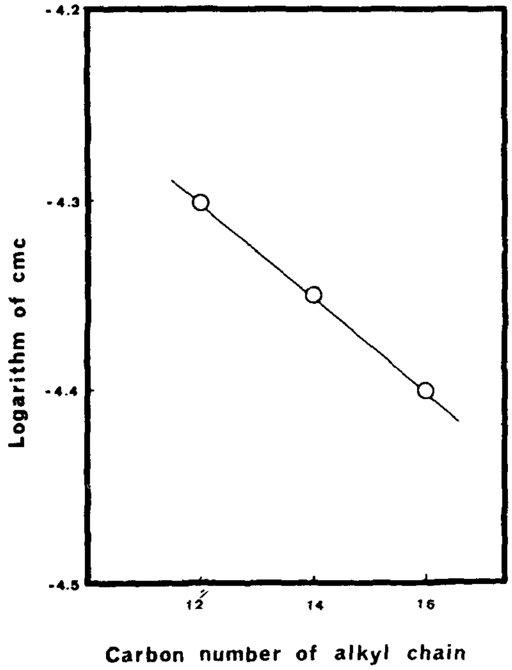


FIG. 2. Plots of logarithm of CMC against carbon number of alkyl chain.

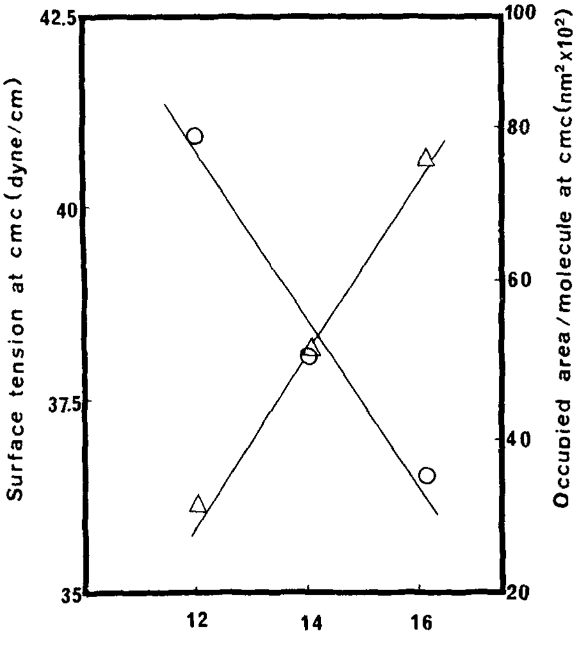


FIG. 3. Plots of surface tension (○) and occupied area per molecule at the air-water interface (△) against carbon number of alkyl chain.

It is interesting to note that the value of this slope means that the dependency of carbon number of alkyl chain upon CMC is small in comparison with MEP-homologues, which are smaller than other amphoteric surfactants (10).

Figure 3 showed the linear decrease in surface tension at the CMC as the alkyl chain length is increased. C_{16}-DMEP showed a minimum surface tension of 36.5 dyne/

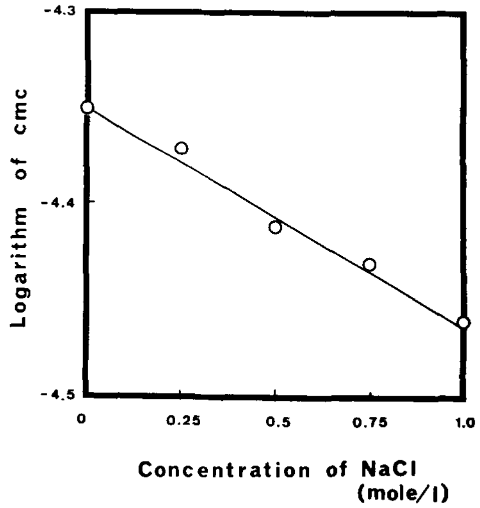


FIG. 4. Effect of electrolyte (NaCl) on CMC value of C_{14}-DMEP.

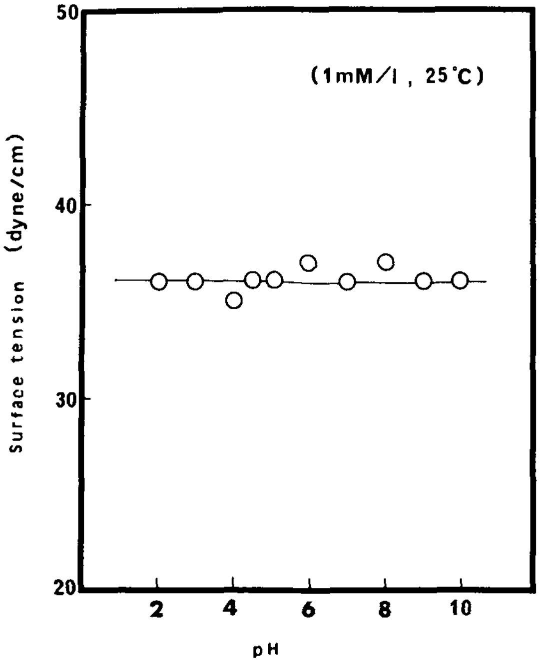


FIG. 5. Effect of pH on surface tension of C_{14}-DMEP.

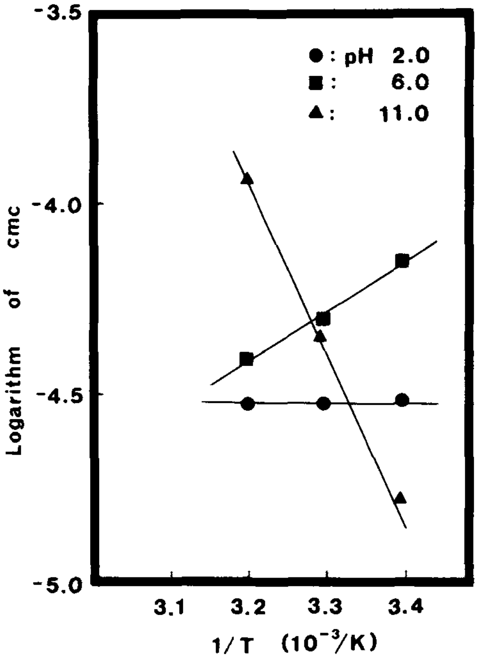


FIG. 6. Effect of temperature on CMC value of C_{14}-DMEP.

cm, which is the same with that of sodium dodecyl sulfate (11) and N-dodecyl-β-alanine (12).

The occupied areas per molecule at the air/water interface (A value) were 31.7×10^{-2} nm^2 for C^{12}-DMEP, 51.4×10^{-2} nm^2 for C_{14}-DMEP and 76.1×10^{-2} nm^2 for C_{16}-DMEP (Table 2), which was estimated by applying the Gibb's adsorption equation to the straight line immediately prior to the CMC as in the case of our previous study (8). These values increase linearly with the increase of alkyl chain length (Fig. 3). It should be noted that this trend is the same in the case of MEP-homologues. However, it is interesting that these values for DMEP-homologues are smaller than those of corresponding MEP-homologues. This difference between them implies that DMEP molecule adsorbs stronger at the air/water interface by hydrophobic effect (9) than the MEP molecule. This behavior should account for the strong effect of an electronic neutralization by the quaternary ammonium group upon the negative charge of the phosphoric acid group in the DMEP molecule in comparison with the MEP molecule having a tertiary amino group and a phosphoric acid group.

Additionally, it is clear that A value of C_{12}-DMEP is smaller than those of N-dodecyl-β-alanine (12) and sodium dodecyl sulfate (11).

The effect of electrolyte (NaCl) on CMC values of C_{14}-DMEP in aqueous solutions (pH 5.5) is shown in Figure 4. The logarithm in the CMC decreases linearly with increasing concentration of NaCl as is the case with nonionic surfactants, whereas for ionic surfactants the logarithm of the CMC decreases linearly with the logarithm of concentration of NaCl (13,14). The behavior may be explained by the zwitterionic property of C_{14}-DMEP in the isoelectric region where ionic charges are neutralized in a molecule and the surfactant considered to be nonionic. Mukerjee (15) showed that the influence of added electrolyte on the CMC of nonionic association colloids in aqueous solution could be understood in terms of salting-out and salting-in equilibria.

The effect of pH on surface tension of C_{14}-DMEP is shown in Figure 5. No specific change was observed over a wide pH range (2~10) at the concentration above the CMC, while the surface tension of the amino acid type surfactant was dependent upon pH (16). C_{14}-DMEP has an excellent surface tension lowering ability within an extremely narrow zone. Even in acidic (pH 2) or alkaline (pH 10) solutions the surface tension lowering ability changed little in comparison with the pH behavior of MEP. Thus, it can be seen that on the surface tension lowering ability of DMEP, the sensitivity to pH is lower than is MEP.

In order to characterize the micellization process at several pH values, the effects of temperature on CMC value of C_{14}-DMEP under acidic (pH 2.0), neutral (pH 6.0) and basic (pH 11.0) conditions, are shown in Figure 6. The

TABLE 3

Foaming Power and Foam Stability of Surfactants

	Foam height (mm)		
Surfactamt	Immediately after the test solution was dropped (A)	After standing for 5 min (B)	Foam stability B/A
C_{12}-DMEP	205	190	0.92
C_{14}-DMEP	155	140	0.90
C_{16}-DMEP	90	80	0.89
C_{12}-MEP[a]	250	235	0.94
Sodium dedocanoate	255	243	0.94

[a] Reference 8.

changes of free energy of micellization (10,17) $\delta G^{\circ}cmc$, were calculated from the following equation:

$$\delta G^{\circ}cmc = 2.303\ RT\ (\log(CMC) - \log w)$$

where w is the molar concentration of water.

At pH 6 the CMC decreased with the increasing temperature as in the case of nonionic surfactant (18) and $\delta G^{\circ}CMC$ was 5.7 Kcal/mol. At pH 11 the CMC increased with the increasing temperature and $\delta G^{\circ}CMC$ was -19.0 Kcal/mol. On the other hand, at pH 2 the CMC is unaffected by a change in temperature.

We studied the foaming properties of surfactants in reference to performance properties. As shown in Table 3, the foaming properties of C_{12}-DMEP are somewhat inferior to those of C_{12}-MEP, whose foaming power and foam stability are almost the same as sodium dodecanoate (soap). This shows that ionic property of C_{12}-MEP is stronger than that of C_{12}-DMEP. This phenomenon seems to be explained by the electric double layer theory (19,20).

In conclusion, it was shown that the phosphobetaines developed in this study, 2-(N-alkyl-N,N-dimethylammonio)ethyl hydrogen phosphates, differ fundamentally from 2-(N-alkyl-N- methylamino)ethyl hydrogen phosphates (8) and that the surface-active properties of the former were much better than those of the latter, because of their increased hydrophobicity by the electronic interaction between the positive change and the negative charge in the zwitterionic region.

More detailed discussions on the relation between the physicochemical properties and the structural characteristics of these phosphobetaines will be presented in future papers describing other analogues.

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