Effect of Counterions on the Surface Adsorption and Volume Behavior of Micelle-Forming Local Anesthetics

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The surface tension and densities of aqueous solutions of micelle-forming local anesthetic dibucaine and tetracaine salts having different halide ions as counterions from each other (dibucaine hydrochloride (DC·HCl), hydrobromide (DC·HBr) and hydroiodide (DC·HI), and tetracaine hydrochloride (TC·HCl) and hydrobromide (TC·HBr)) were measured as a function of the molality at 298.15 K under atmospheric pressure. The thermodynamic quantities of adsorption and volume for the anesthetics were evaluated numerically based on the experimental results. The surface densities of the anesthetics increased in the order of chloride, bromide, and iodide salts. This behavior may result from differences in the degree of three factors, that is, a hydration interaction between water molecules and counterions, the counterion distribution in the surface-adsorbed film, and ion-pair formation in the adsorbed film between anesthetic cations and counterions. It was further shown from the surface pressure vs. area per adsorbed molecule curves that the adsorbed films of the anesthetics undergo a phase transition from a gaseous state to an expanded state at low concentrations. On the other hand, the volumes of micelle formation for DC·HCl and DC·HBr have been found to be almost equal to each other. This fact means that the effect of these halide counterions on the volume of micelle formation is considerably small in contrast to the results of surface adsorption.

A tertiary amine local anesthetic is a kind of cationic surfactant, and, hence, exhibits surface activity in an aqueous solution. In our previous works,[1—4] the colloidal properties of local anesthetics in clinical use were investigated by measuring the physicochemical quantities of their aqueous solutions, and characterized thermodynamically. It was shown especially from the results of surface-tension measurements that the anesthetic potency is well correlated with the hydrophobicity of the molecules.[3] On the other hand, most of the local anesthetics in clinical use are only confined to hydrochloride salts. Less attention has been paid to other salts of local anesthetics than the hydrochloride salts, because they are unsuitable as drug compounds; so far, there has been only little information about their properties. Since it is known that the nature of counterions of ionic surfactants has significant influence on the formation of molecular aggregates, such as surface-adsorbed films and micelles,[5—20] we are now interested in exploring the effect of counterions on the thermodynamic behavior of the surface-adsorbed film of local anesthetics and their volume in water.

The present study investigated the surface-adsorption and volume behavior of micelle-forming local anesthetics having different halide ions as counterions from each other, that is, the salts of dibucaine (hydrochloride (DC·HCl), hydrobromide (DC·HBr), and hydroiodide (DC·HI)) as well as those of tetracaine (hydrochloride (TC·HCl) and hydrobromide (TC·HBr)). The surface tension and densities of aqueous solutions of these anesthetics were measured as a function of the concentration at constant temperature under atmospheric pressure. The thermodynamic quantities of adsorption and volume were calculated from the experimental data; the effect of the counterions on both properties is discussed based on these quantities.

Experimental

Materials. Dibucaine (2-butoxy-*N*-[2-(diethylamino)ethyl]-4-quinolinecarboxamide) hydrochloride and tetracaine (2-(dimethylamino)ethyl 4-(butylamino)benzoate) hydrochloride were purchased from Sigma Chemical Company. Dibucaine hydrobromide and tetracaine hydrobromide were synthesized from their free base (Sigma Chemical Company) with hydrobromic acid in an ethanol solution. Dibucaine iodide was obtained by a similar method. The anesthetics were purified by several recrystallizations from a mixture of ethanol and carbon tetrachloride for the salts of dibucaine and from ethanol for the salts of tetracaine, respectively. The molecular structures of dibucaine and tetracaine cations are illustrated in Fig. 1. Water was distilled three times from dilute alkaline permanganate solution after deionization for measurements of the surface tension and twice for measure-

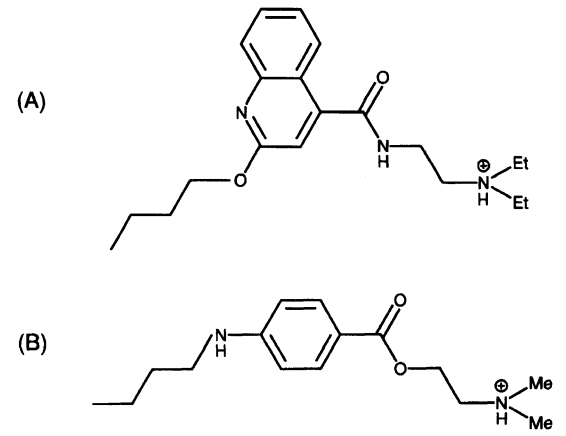

Fig. 1. Molecular structures of local anesthetic cations: (A) dibucaine, (B) tetracaine.

ments of the density.

Methods. The surface tension of the aqueous anesthetic solutions was measured by the drop-volume method (described previously[21]) at 298.15 K under atmospheric pressure. The densities of anesthetic solutions measured were used to calculate the surface tension of the anesthetic solutions. The experimental error for the value of the surface tension was less than 0.05 $mN\,m^{-1}$.

The densities of the aqueous anesthetic solutions were measured by a vibrating-tube density meter (Anton Paar DMA60/602) (described previously[3]) under atmospheric pressure. The temperature of the tube was maintained at 298.15±0.001 K by circulating water thermostated by a PID temperature controller (Yamashita Giken Co., Ltd. (Tokushima, Japan)). The experimental error for the density value was less than 0.002 $kg\,m^{-3}$ (2 ppm).

Results

Figure 2 shows plots of the experimental values of the surface tension (γ) of aqueous anesthetic solutions against their molality (m_1), where measurements of DC·HI solutions at concentrations above 10 $mmol\,kg^{-1}$ and those of TC·HBr above 40 $mmol\,kg^{-1}$ could not be made because these anesthetics precipitate in the solution due to their high Krafft temperatures. The γ vs. m_1 curves of DC·HCl, DC·HBr, and TC·HCl are observed to have distinct break points at the concentration corresponding to the critical micelle concentration (cmc). It is also found that the γ vs. m_1 curves of all anesthetics have other break points in the lower concentration region. The magnification of the curves in the vicinity of the break points at low concentrations is given in Fig. 3. We confirmed in a previous paper[3] stating that the surface-adsorbed films of DC·HCl and TC·HCl exhibit a phase transition by a comparison of their results with those of surfactants.[22] Thus, we may also say that the phase transition occurs in the adsorbed films of these anesthetics even if their counterions are different from each other. Further, it is noticed that the difference in counterions between anesthetics produces a remarkable effect on their surface activity.

The apparent molar volume of anesthetic (ϕ_1) was evaluated from the value of density (ρ) of the aqueous anesthetic solution measured using

$$\phi_1 = (1/\rho - 1/\rho_w)/m_1 + M/\rho, \quad (1)$$

where ρ_w and M are the density of water ($kg\,m^{-3}$) and the molar mass of the anesthetic ($kg\,mol^{-1}$), respectively. The resulting ϕ_1 vs. m_1 curves of anesthetics are illustrated in Fig. 4. It can be clearly seen that the ϕ_1 values of the anesthetics decrease slightly and linearly with increasing m_1 in the concentration range below the cmc, while those of DC·HCl, DC·HBr, and TC·HCl increase with m_1 in the concentration range

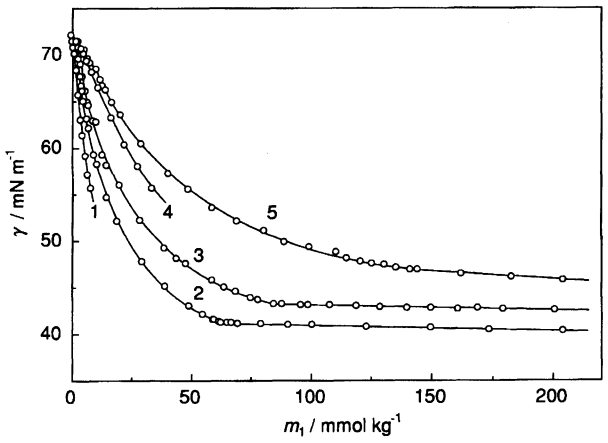

Fig. 2. Surface tension vs. molality curves of local anesthetics: (1) DC·HI, (2) DC·HBr, (3) DC·HCl, (4) TC·HBr, (5) TC·HCl.

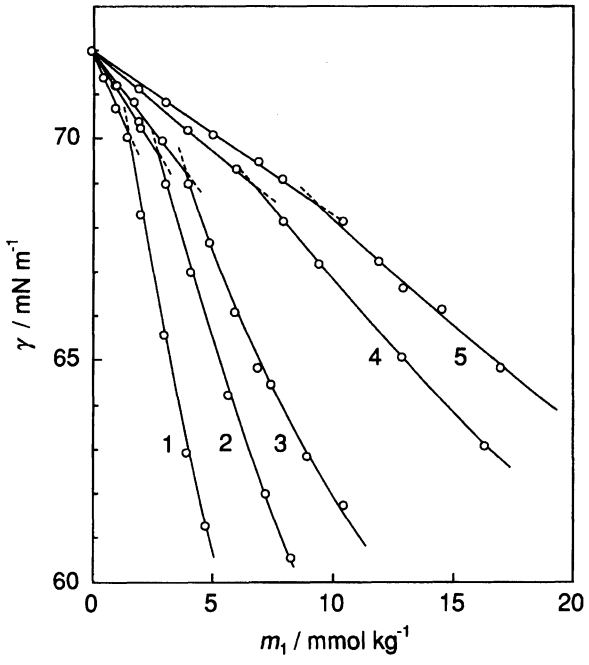

Fig. 3. Surface tension vs. molality curves of local anesthetics: (1) DC·HI, (2) DC·HBr, (3) DC·HCl, (4) TC·HBr, (5) TC·HCl.

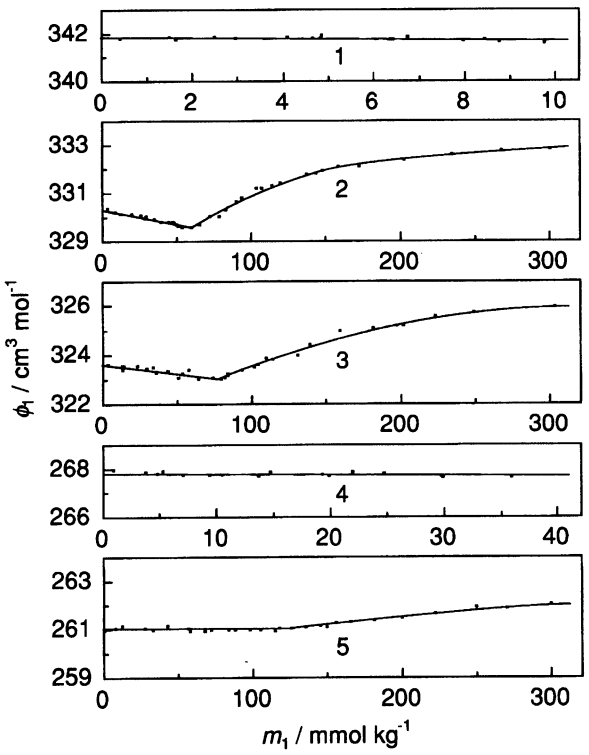

Fig. 4. Apparent molar volume vs. molality curves of local anesthetics: (1) DC·HI, (2) DC·HBr, (3) DC·HCl, (4) TC·HBr, (5) TC·HCl.

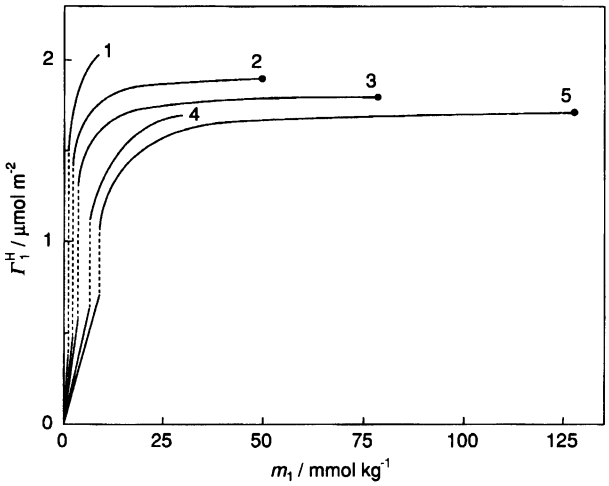

Fig. 5. Surface density vs. molality curves of local anesthetics: (1) DC·HI, (2) DC·HBr, (3) DC·HCl, (4) TC·HBr, (5) TC·HCl, (●) surface density at the cmc.

above the cmc; their curves break sharply at the cmc. The cmc values obtained from ϕ_1 vs. m_1 curves are in good agreement with those obtained from the γ vs. m_1 curves given in Fig. 2.

Discussion

It is assumed that the local anesthetics used in the present study were uni-univalent electrolytes, because of their relatively high pK_a values (as described previously[3,23]), though local anesthetic cations are actually weak electrolytes.

We now evaluate the surface density of anesthetic (Γ_1^H) in order to examine the adsorption behavior of anesthetics at concentrations below the cmc. The value of Γ_1^H can be obtained by making use of the following equation:[24]

$$\Gamma_1^H = -(m_1/2RT)(\partial\gamma/\partial m_1)_{T,p}. \quad (2)$$

The evaluated Γ_1^H values from the γ vs. m_1 curve given in Fig. 2 are drawn as a function of m_1 in Fig. 5. The Γ_1^H values of anesthetics increase with increasing m_1, and those of DC·HCl, DC·HBr, and TC·HCl reach the saturated ones at concentrations around the cmc. It should be noted that the Γ_1^H value increases in the order DC·HCl, DC·HBr, and DC·HI for dibucaine salts, and TC·HCl and TC·HBr for tetracaine salts. This observation indicates that the surface activity of anesthetics is greatly dependent on their counterions. The difference in the surface activities between them seems to be attributable to the differences in the degree of the following three factors: (i) hydration interaction between water molecules and counterions, (ii) counterion distribution in the surface-adsorbed film, and (iii) ion-pair formation in the adsorbed film between anesthetic cations and counterions. The halide ions have a much weaker interaction with water molecules than the alkaline metal ions, such as Li^+ and Na^+ ions, due to their large crystallographic radii;[25,26] they are known as structure-breaking or negative hydration ions. However, the hydration interaction between water molecules and halide ions becomes strong in the order of I^-, Br^-, and Cl^- ions because the hydration Gibbs energy for these halide ions becomes more negative in the same order.[27] This may contribute to the degree of attractive interaction between an anesthetic cation and its counterion. Further, Ikeda et al. showed from surface-tension measurements of the aqueous solutions of dodecyldimethylammonium chloride and sodium bromide mixtures[28,29] that the surface adsorption of the Br^- ion is larger than that of the Cl^- ion; some reports have indicated that the degree of counterion binding of cationic surfactant micelles increases in the order of chloride, bromide, and iodide salts.[7—11] These observations suggest the different degree of counterion distribution in such molecular aggregates as surface-adsorbed films and micelles though the adsorbed film is different only in geometrical shape from the micelle. In addition to these facts, ion-pair formation between the tetraalkylammonium ion and the halide ion was reported by Lindebaum et al.[30] They found that the iodide salts of tetraalkylammonium form an ion-pair in the solution, and that the bromide salts do slightly while the chloride salts don't at all. It is considerable that the above-mentioned factors are all closely related to the degree of electrostatic repulsion between cationic head groups, and that

they reduce the repulsion in the order of chloride, bromide, and iodide salts. Therefore, we may say that the packing of anesthetic molecules in the adsorbed film becomes tighter in this order. On the other hand, there exist discontinuous changes in the Γ_1^H vs. m_1 curves of all anesthetics at concentrations corresponding to the phase-transition points of the adsorbed film in Fig. 3.

Drawing a surface-pressure (π) vs. area per adsorbed molecule (A) curve is useful for investigating the film behavior. The π and A values are calculated, respectively, by

$$\pi = \gamma^0 - \gamma \tag{3}$$

and

$$A = 1/N_A\Gamma_1^H, \tag{4}$$

where γ^0 is the surface tension of the pure water and N_A is Avogadro's number. The π vs. A curves obtained by use of the γ vs. m_1 curves in Fig. 3 and the Γ_1^H values in Fig. 5 are demonstrated in Fig. 6. All of the curves are found to be almost similar in shape, and to show discrete changes in A at the transition pressures. Taking into account of the thermodynamic quantities of DC·HCl and TC·HCl at the transition points in a previous study,[3] it can be said that the adsorbed films of these anesthetics undergo a phase transition from a gaseous state to an expanded state in spite of the difference in their counterions. Table 1 tabulates the thermodynamic quantities for these anesthetics at the phase-transition points. It is important to note that as the transition pressure decreases the intermediate flat region between both states enlarges, and the expanded films of anesthetics become more condensed in the order of chloride, bromide, and iodide salts. These findings may be explained by the degree of interaction between the anesthetic cation and its counterion (as mentioned previous section): the anesthetic cation interacts more strongly with the counterion in the order Cl^-, Br^-, and I^- ions, and thus the anesthetic molecules in the adsorbed film are packed tightly in this order. Furthermore, the expanded films of tetracaine salts are observed to have large A values compared with those of dibucaine salts at a given π value. Since the dibucaine cation has a larger aromatic quinoline ring in the hydrophobic group than the tetracaine cation (Fig. 1), it seems that the dibucaine cation has a stronger affinity for π electron between aromatic rings in the adsorbed film than that of the tetracaine cation.

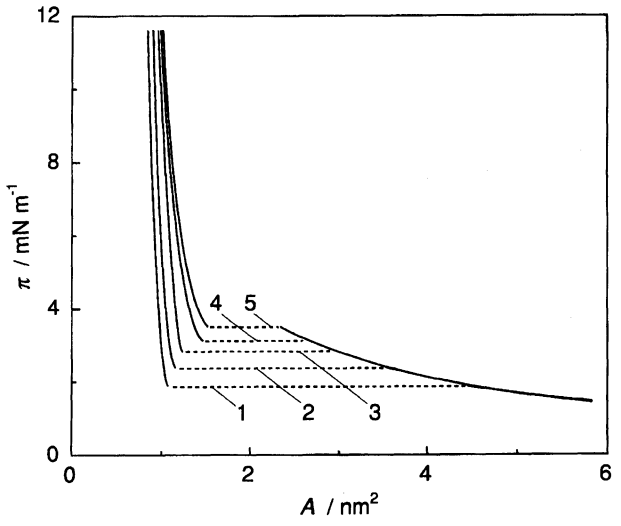

Fig. 6. Surface pressure vs. area per adsorbed molecule curves of local anesthetics: (1) DC·HI, (2) DC·HBr, (3) DC·HCl, (4) TC·HBr, (5) TC·HCl.

We next examine the volume behavior of the anesthetics in water. It has been verified that the derivative of the quantity $m_1\phi_1$ with respect to m_1 at constant T and p is a useful quantity for elucidating the volume behavior of surfactants in solution, and provides a partial molar volume of the monomeric anesthetic (V_1^W) at a concentration below the cmc and the molar volume of micelle per anesthetic molecule (V^M/N_1^M) in a sufficiently high concentration range above the cmc:[31]

$$[\partial(m_1\phi_1)/\partial m_1]_{T,p} = V_1^W, \quad \text{for } m_1 < C, \tag{5}$$

and

$$[\partial(m_1\phi_1)/\partial m_1]_{T,p} = V^M/N_1^M, \quad \text{for } m_1 \gg C, \tag{6}$$

where V^M and N_1^M are the molar volume of the micelle and the aggregation number of the anesthetic molecule in the micelle, which are defined using the excess thermodynamic quantity, respectively,[32] and C denotes the cmc. The value of $\partial(m_1\phi_1)/\partial m_1$ is estimated from the slope of the ϕ_1 vs. m_1 curve in Fig. 4, and is plotted against m_1 in Fig. 7. It can be seen that there is a linear relationship between V_1^W and m_1 for all anesthetics. By extrapolating the V_1^W values to zero concentration, the partial molar volumes of anesthetics at infinite dilution ($V_1^{W,0}$) can be obtained; the resulting values are listed in Table 2. The values of the difference in $V_1^{W,0}$ between DC·HCl and DC·HBr, TC·HCl and TC·HBr, and DC·HCl and DC·HI are 6.6, 6.7, and 18.2 $cm^3\,mol^{-1}$, which are fairly comparable to those between Cl^- and Br^- ions, and Cl^- and I^- ions.[14,33,34] In the case of DC·HCl, DC·HBr, and TC·HCl, the obtained V^M/N_1^M values from Fig. 7 are given in Table 3. Here, the $\partial(m_1\phi_1)/\partial m_1$ values at 300 $mmol\,kg^{-1}$ were taken as the V^M/N_1^M values for micelles of the anesthetics. Taking into account that the degree of counterion binding of the micelles is dependent on the counterions, it is interesting that the value of the difference in V^M/N_1^M between DC·HCl and DC·HBr (6.5 $cm^3\,mol^{-1}$) is nearly equal to that in the monomer state. Desnoyers et al. reported similar results for chloride and bromide salts of cetytrimethylammonium.[34] They described that the free counterion and bound counterion to surfactant micelles have approximately the same volume in the micellar solution. Therefore, the present results may indicate that the volumes of the Cl^- and Br^- ions in the micel-

Table 1. Thermodynamic Quantities Inherent in the Phase Transition at 298.15 K and 0.1 MPa[a)]

	$(m_1)^{eq}$	γ^{eq}	π^{eq}	$\Gamma_1^{H,g}$	$\Gamma_1^{H,e}$	A^g	A^e
	mmol kg^{-1}	mN m^{-1}	mN m^{-1}	μmol m^{-2}	μmol m^{-2}	nm^2	nm^2
DC·HCl	3.95	69.17	2.79	0.56	1.32	2.94	1.26
DC·HBr	2.75	69.62	2.34	0.47	1.41	3.53	1.18
DC·HI	1.52	70.12	1.84	0.37	1.50	4.47	1.11
TC·HCl	9.39	68.49	3.47	0.70	1.07	2.37	1.56
TC·HBr	6.91	68.85	3.11	0.63	1.12	2.65	1.49

a) Notation: $(m_1)^{eq}$, concentration of the phase transition point; γ^{eq}, surface tension of the phase transition point; π^{eq}, surface pressure of the phase transition point; $\Gamma_1^{H,g}$, surface density of the gaseous film; $\Gamma_1^{H,e}$, surface density of the expanded film; A^g, mean area per adsorbed molecule of the gaseous film; A^e, mean area per adsorbed molecule of the expanded film.

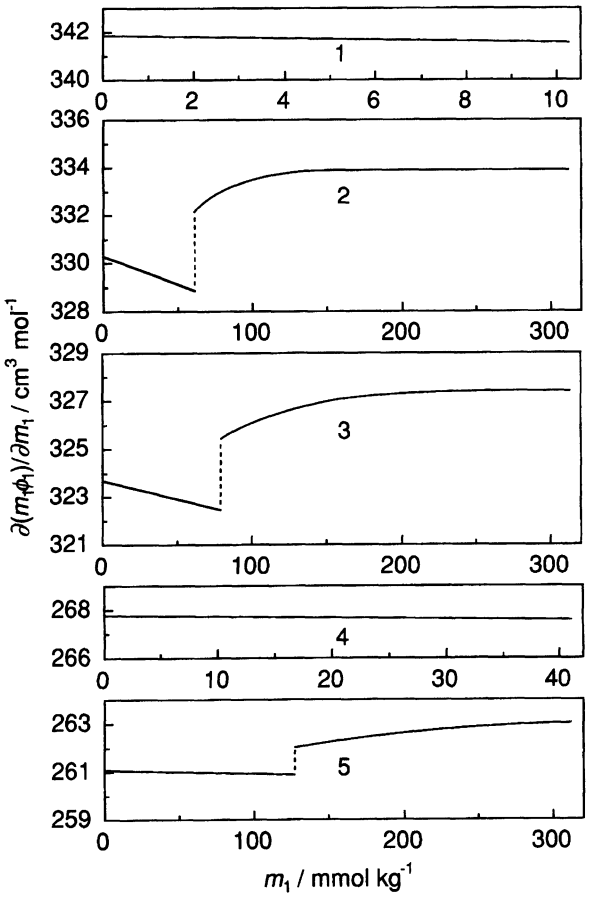

Fig. 7. Partial derivative of $m_1\phi_1$ with respect to molality vs. molality curves of local anesthetics: (1) DC·HI, (2) DC·HBr, (3) DC·HCl, (4) TC·HBr, (5) TC·HCl.

Table 2. Partial Molar Volume of Local Anesthetics at Infinite Dilution at 298.15 K and 0.1 MPa

	DC·HCl	DC·HBr	DC·HI	TC·HCl	TC·HBr
$V_1^{W,0}$/cm^3 mol^{-1}	323.6	330.2	341.8	261.0	267.7

lar state are almost the same as those in the monomer state.

The volume of micelle formation ($\Delta_W^M V$) is calculated by combining Eq. 5 with Eq. 6:

$$\Delta_W^M V = V^M/N_1^M - V_1^W. \quad (7)$$

Table 3. Volume Parameters of Micelle Formation of Local Anesthetics at 298.15 K and 0.1 MPa[a)]

	cmc	$V_1^{W,C}$	V^M/N_1^M	$\Delta_W^M V$
	mmol kg^{-1}	cm^3 mol^{-1}	cm^3 mol^{-1}	cm^3 mol^{-1}
DC·HCl	78.7	322.4	327.3	4.9
DC·HBr	61.6	328.8	333.8	5.0
TC·HCl	127.8	260.8	263.0	2.2

a) Notation: $V_1^{W,C}$, partial molar volume of monomeric local anesthetics at the cmc; V^M/N_1^M, molar volume of micelle per local anesthetic molecule at 300 mmol kg^{-1}; $\Delta_W^M V$, volume of micelle formation.

Table 3 summarizes the numerical values of the volume parameters of micelle formation for DC·HCl, DC·HBr, and TC·HCl. The $\Delta_W^M V$ values of DC·HCl and DC·HBr are almost the same as each other, as expected from the above discussion. Such a behavior was observed in the case of the homologous series of decylammonium salts and dodecyltrimethylammonium salts.[14,19)] This fact means that the effect of these halide counterions on $\Delta_W^M V$ is considerably small in contrast to the results of surface adsorption.

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