Biochimica et Biophysica Acta, 777 (1984) 75–83
Elsevier

BBA 72256

BENZYL ALCOHOL PENETRATION INTO MICELLES, DIELECTRIC CONSTANT OF THE BINDING SITE, PARTITION COEFFICIENT AND HIGH-PRESSURE SQUEEZE-OUT

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(Received May 1st, 1984)

Key words: Anesthesia theory; Surfactant micelle; Local anesthetic; Dielectric constant; Partition coefficient; High pressure

The absorbance maximum, λ_{max}, of a local anesthetic, benzyl alcohol, is shifted to longer wavelengths when solvent polarity is decreased. The shift was approximately a linear function of the dielectric constant of the solvent. This transition in electronic spectra according to the microenvironmental polarity is used to analyze benzyl alcohol binding to surfactant micelles. A facile method is devised to estimate the micelle/water partition coefficient from the dependence of λ_{max} of benzyl alcohol on surfactant concentrations. The effective dielectric constants of the sodium decyl sulfate, dodecyl sulfate and tetradecyl sulfate micelles were 29, 31 and 33, respectively. The partition coefficient of benzyl alcohol between the micelles and the aqueous phase was 417, 610 and 1089, respectively, in the mole fraction unit. The pressure dependence of the partition coefficient was estimated from the depression of the critical micelle concentration of sodium dodecyl sulfate by benzyl alcohol under high pressure up to 200 MPa. High pressure squeezed out benzyl alcohol molecules from the micelle until about 120 MPa, then started to squeeze in when the pressure was further increased. The volume change of benzyl alcohol by transfer from the aqueous to the micellar phase was calculated from the pressure dependence of the partition coefficient. The volume change, estimated from the thermodynamic argument, was 3.5 ± 1.1 $cm^3 \cdot mol^{-1}$ at 298.15 K, which was in reasonable agreement with the partial molal volume change determined directly from the solution density measurements, 3.1 ± 0.2 $cm^3 \cdot mol^{-1}$. Benzyl alcohol apparently solvates into the micelles close to surface without losing contact with the aqueous phase.

Introduction

Surfactant micelles and phospholipid vesicles have been successfully used as models for biological macromolecules and membranes. To elucidate the molecular mechanisms of anesthesia, we have reported in a series of articles [1–4] on the interactions between anesthetics and surfactant micelles, and revealed that the partition coefficient of anesthetics between a model structure and water represents an important thermodynamic quantity for the physicochemical interpretation of anesthetic actions. Recently, several papers appeared concerning the partition coefficient of small molecules between the micelle and aqueous phases. Various methods have been used to estimate the partition coefficients, including vapor pressure change [5],

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Abbreviations: SDeS, sodium decyl sulfate; SDS, sodium dodecyl sulfate; STS, sodium tetradecyl sulfate.

gel filtration [6], fluorescence [7] and radioactive tracer [8]. We reported a simple method for determining partition coefficients from the depression of the Krafft point [2] or critical micelle concentration [4].

The absorbance maximum, λ_{max}, of a local anesthetic, benzyl alcohol, in ultraviolet spectrum changes according to the solvent polarity where benzyl alcohol molecules are solublized. In the present paper, another facile method is described to determine the micelle/water partition coefficient of benzyl alcohol by the shift in the wavelength of the absorbance maximum when bound to micelles. The method also reveals the microenvironmental polarity of micelles where benzyl alcohol molecules reside.

The pressure effect on the partition coefficient was determined in the range up to 200 MPa by the previously described method [4] of depression of the critical micelle concentration. The pressure dependence of the partition coefficient represents the volume change accompanying the transfer of anesthetic molecules from the aqueous to the micellar phase according to the following equation:

$$RT(\partial \ln K/\partial P)_T = -\Delta V \quad (1)$$

To evaluate the thermodynamically derived values, the partial molal volume of the anesthetic was measured by solution densimetry in water, micelle and *n*-decane. The position of the anesthetic-binding site, estimated from the volume studies, was in reasonable agreement with the results obtained from the shift of the absorbance maximum.

Experimental

Materials

Sodium decyl sulfate (SDeS), dodecyl sulfate (SDS) and tetradecyl sulfate (STS) were obtained from Eastman Organic Chemicals (Rochester, NY) and recrystallized three times from an acetone/water mixture (95 : 5, v/v). The critical micelle concentration values, determined by the conductivity method, were 31.9, 8.30 and 2.10 mmolal, respectively, at 298.15 K. Concentrations are expressed by molality (mol solute in 1 kg solvent) because molarity (mol solute in 1 l solution) is a temperature- and pressure-dependent variable. These values are in good agreement with those found in the literature [9]. Benzyl alcohol was obtained from Fluka. Hexane (MCB, Cincinati, OH), dioxane (Mallinckrodt, St. Louis, MO), 1-butanol (Sigma), ethanol (IMC Chemical Agnew, CA) and methanol (Fisher Scientific, Fair Lawn, NJ) were of the highest grade available and were used without further purification. Decane was obtained from Sigma. The density of decane measured by an Anton-Paar oscillation densimeter was 0.726413 at 298.150 K, which was in good agreement with the literature value [10]. Water was purified by triple distillation, once from alkaline potassium permanganate solution. The specific conductivity of water was $1.1 \cdot 10^{-6}\ \Omega^{-1} \cdot cm^{-1}$.

Ultraviolet spectroscopy

Ultraviolet absorbance spectra were obtained by a Perkin-Elmer Model 554 spectrophotometer (Norwald, CT). The absorbance spectra of benzyl alcohol in various solvents and micellar solution were measured in the region of 250–280 nm, in matched 1.00-cm lightpath cuvettes. Reference cell contained solvents without benzyl alcohol. The concentration of benzyl alcohol was kept at 3 mmolal throughout the experiments. The cuvette temperature was maintained at 25.0 ± 0.1°C by thermostatted cell holders.

Determination of critical micelle concentration

The critical micelle concentration of SDS with and without benzyl alcohol under various pressures was measured by the conductivity method. The high pressure apparatus for the conductivity measurements was previously described [11]. The cell constant was 0.7026 cm^{-1} at atmospheric pressure. Pressures were generated by a hand-operated hydraulic pump and measured within an accuracy of approx. 0.3 MPa by a Heise pressure gauge. The temperature of the water bath, in which the high pressure vessel was immersed, was kept at 298.15 ± 0.01 K.

Density measurement and estimation of partial molal volume

The densities of solutions containing various amounts of benzyl alcohol were measured using an Anton-Paar oscillation densimeter DMA60/601

(Mettler, Hightstown, NJ) at 298.150 ± 0.001 K. Because thermal expansibility is the main source of error in estimating the solution density, the temperature was controlled by a Hart Scientific Iso-therm Model 5003 (Provo, UT) with an ±0.0005 K stability, and was monitored by a Hart Scientific Microtherm Model 1006 with 0.0001 K resolution. The reproducibility of the density measurements was within approx. $1 \cdot 10^{-6}$ g · cm^{-3}.

The apparent molal volume, ϕ_2, of solute (i.e., anesthetic) was calculated from the equation:

$$\phi_2 = \frac{1}{m_2}\left(\frac{1000 + m_2 M_2}{d} - \frac{1000}{d_1}\right) \quad (2)$$

where m_2 and M_2 are the molality and molecular weight of solute (anesthetic), and d and d_1 are the densities of the solution and the reference solvent, respectively. The partial molal volume, $\bar{V}_2$, of solute is calculated from the equation:

$$\bar{V}_2 = \phi_2 + m_2\left(\frac{\partial \phi_2}{\partial m_2}\right)_{T,P,n_1} \quad (3)$$

The partial molal volumes of benzyl alcohol in water and in *n*-decane were determined from the density measurements at six solute concentrations up to 20 mmolal.

The apparent molal volume of anesthetic in the surfactant solution can be estimated from the following equation:

$$\phi_2 = \frac{1}{m_2}\left(\frac{1000 + m_2 M_2 + m_3 M_3}{d} - \frac{1000 + m_3 M_3}{d'}\right) \quad (4)$$

where m_3 and M_3 are the molality and molecular weight of surfactant, and d and d' are the densities of the ternary solution and of the reference surfactant solution, respectively. In this system, the partial molal volume, $\bar{V}_2$, of anesthetic can be calculated from the equation:

$$\bar{V}_2 = \phi_2 + m_2\left(\frac{\partial \phi_2}{\partial m_2}\right)_{T,P,n_1,m_3} \quad (5)$$

Eqn. 5 states that at infinite dilution, apparent molal volume and partial molal volume are equal.

In the ternary solution, the concentrations of SDS were kept at 4.95, 24.82 and 49.95 mmolal. The apparent molal volume of benzyl alcohol was determined from the density measurements at six concentrations for each surfactant solution. The partial molal volume at infinite dilution was obtained by extrapolating these values.

Datum points were stored in an Apple II microcomputer interfaced with a PDP 11/23 minicomputer. All computations, including linear and nonlinear curve fittings with the least-square method, slope and intercept values, standard deviations, correlation coefficients, etc., were performed by the computer system.

Results

Ultraviolet spectroscopy

The wavelength of the absorbance maximum, λ_{max}, of benzyl alcohol was 256.5 nm in water at 298.15 K and was shifted toward longer wavelengths in other solvents in a solvent polarity-dependent manner (Fig. 1). The λ_{max} values in hexane, dioxane, alkanols, methanol/water and dioxane/water mixtures are shown in Fig. 2 in relation to the solvent dielectric constants, D, of these solvents. The D values were measured at 298.15 K with a General Radio capacitor bridge 1620A (Santa Clara, CA) at 5 kHz as previously reported [12] and were in good agreement with the literature values [13–18]. It can be seen that the λ_{max} of benzyl alcohol is approximately a linear function of the dielectric constants of the solvents. Rehfeld [19,20] reported that the shift of the λ_{max} of benzene in polyhydric alcohols deviates from

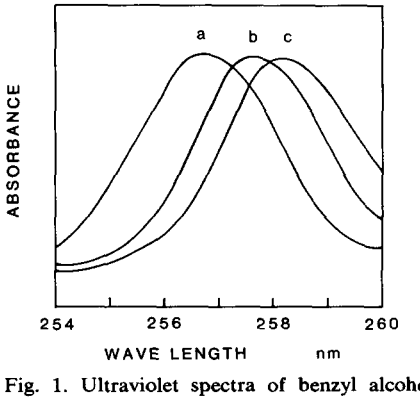

Fig. 1. Ultraviolet spectra of benzyl alcohol in solvents of varying polarity; a, water; b, methanol; and c, dioxane. The absorbance is normalized to the same magnitude by a computer system and plotted on an arbitrary scale.

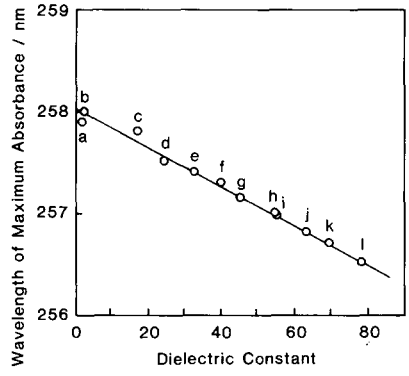

Fig. 2. Wavelength of absorbance maximum of benzyl alcohol in various solvents as a function of dielectric constant of solvents at 298.15 K. Solvents: a, hexane; b, dioxane; c, 1-butanol; d, ethanol, e, methanol; f, 50% (v/v) dioxane/water; g, 70% (w/w) methanol/water; h, 35% (v/v) dioxane/water; i, 50% (w/w) methanol/water; j, 25% (v/v) dioxane/water; k, 15% (v/v) dioxane/water; and l, water.

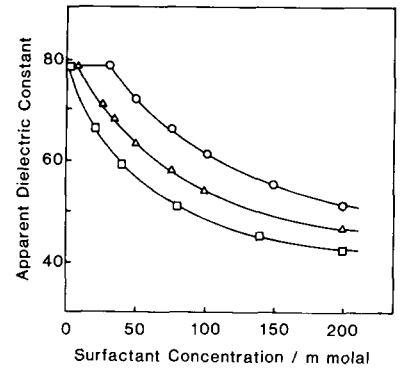

Fig. 3. Apparent dielectric constant of micellar solution as a function of concentration of surfactants. ○, SDeS; △, SDS; and □, STS, at 298.15 K.

the linear relation, but a straight line is usually obtained between the shift of λ_{max} and the solvent dielectric constant, especially in homologous series of drugs, such as *n*-alcohols.

In the present case, the linear relationship between the shift of λ_{max} and the solvent dielectric constant is expressed by the following equation:

$$\lambda_{max} = 258.02 - 0.01914D \quad (6)$$

The two constants were determined by the least-square method.

This relationship is used to estimate the dielectric constant of the micellar microenvironment where benzyl alcohol molecules are bound. Ultraviolet spectra of benzyl alcohol were obtained in the aqueous solutions of surfactants with varying hydrocarbon chain-lengths. The wavelength of the absorbance maximum did not change until the surfactant concentration reached the critical micelle concentration, and then shifted toward the longer wavelength as the surfactant cocentration increased.

Fig. 3 shows the apparent dielectric constant, D_{app}, of micellar solutions, which is estimated from λ_{max} using the linear relation shown in Fig. 2, as a function of surfactant concentration. The value of D_{app} remained constant until the surfactant concentration reached the critical micelle concentration. An abrupt reduction in the D_{app} value occurred above the critical micelle concentration, approaching a limiting value as the surfactant concentration increased. The dependence of the apparent dielectric constant upon the micellar concentration may be attributable to the micelle/water distribution of benzyl alcohol, because the value is an average of benzyl alcohol molecules bound to the micelle and dispersed in water.

Pressure and anesthetic antagonism on the critical micelle concentration

When the specific conductivity, measured at a constant pressure and at an constant benzyl alcohol concentration, was plotted against the varying concentration of SDS, two straight lines were

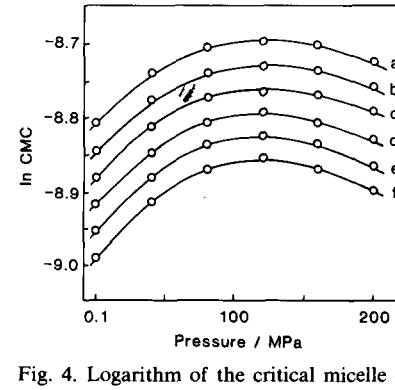

Fig. 4. Logarithm of the critical micelle concentration (CMC) (in mole fraction) as a function of pressure at 298.15 K. Benzyl alcohol concentration; a, 0; b, $0.9 \cdot 10^{-4}$; c $1.8 \cdot 10^{-4}$; d, $2.7 \cdot 10^{-4}$; e, $3.6 \cdot 10^{-4}$; and f, $4.5 \cdot 10^{-4}$ in mole fraction.

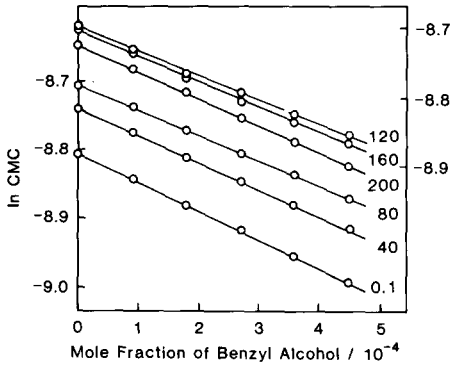

Fig. 5. Logarithm of the critical micelle concentration (CMC) (in mole fraction) as a function of mole fraction of benzyl alcohol at 298.15 K at various pressures. Numerical values refer to pressure in MPa. Right-hand scale is for lines at 120, 160 and 200 MPa.

TABLE I

PARTIAL MOLAL VOLUME OF BENZYL ALCOHOL IN VARIOUS SOLVENTS AT 298.15 K

Solvent	Partial molal Volume ($cm^3 \cdot mol^{-1}$)
Water	101.8 ± 0.2
SDS solution (mmolal)	
4.98	101.8 ± 0.2
24.82	102.2 ± 0.2
49.95	102.7 ± 0.2
SDS micelle	104.9 ± 0.2 [a]
Benzyl alcohol (pure liquid)	103.8 ± 0.05
n-Decane	108.8 ± 0.3

[a] Estimated from Eqn. 13 in the text.

produced. The critical micelle concentration was taken as the intersection point of the two straight lines.

The critical micelle concentration values of SDS in the presence of various concentrations of benzyl alcohol at 298.15 K are shown in Fig. 4 as a function of pressure. A maximum was observed at about 120 MPa. The maxima in the critical micelle concentration versus pressure curves are in agreement with previous reports [21–24], and seem to be independent of the presence of benzyl alcohol in the concentration range presently studied.

The depression of the critical micelle concentration by alcohols is well known. At ambient pressure, the logarithm of the critical micelle concentration (in mole fraction) decreases linearly with the mole fraction of added benzyl alcohol as in the case of normal-chain alcohols [25,26]. The linear relation between $\log_e$ critical micelle concentration (ln CMC) and the mole fraction of benzyl alcohol was obtained under high pressures, as well as at ambient pressure. The results are shown in Fig. 5. The magnitude of the critical micelle concentration depression is evidently dependent on pressure.

Partial molal volume

The values of the partial molal volume of benzyl alcohol at infinite dilution in water, SDS solutions and *n*-decane were calculated from solution density data and are summarized in Table I.

Discussion

The anesthetic molecules, solubilized into micellar solutions, are distributed between the micellar and aqueous phases. The fact that the absorbance maximum does not split indicates that the exchange rate of the solute molecules between the two phases is faster than the resolution of spectrophotometry. Hence, the apparent dielectric constants estimated from the shift of λ_{max} are weighted averages in two phases.

Let the total anesthetic concentration expressed as C_A be solubilized into the micellar phase by xC_A, where x is the fraction of anesthetics distributed into the micellar phase. The micelle/water partition coefficient (K) is defined by the ratio of anesthetic mole fractions in each phase.

$$K = \frac{xC_A}{(C - C_0) + xC_A} \Big/ \frac{(1-x)C_A}{55.5 + (1-x)C_A} \tag{7}$$

where C and C_0 are the total and critical micelle concentrations of surfactant in molality, respectively. The fraction of anesthetic molecules partitioned into the micellar phase can be represented under the condition of $C - C_0 \gg C_A$

$$x = \frac{K(C - C_0)}{55.5 + K(C - C_0)} \tag{8}$$

As seen in Eqn. 8, x is solely described by the

partition coefficient and the micellar concentration when the anesthetic concentration is sufficiently low compared to the surfactant concentration.

The apparent dielectric constant of the surfactant solution, D_{app}, can be expressed as:

$$D_{app} = xD_m + (1-x)D_w \quad (9)$$

where D_m is the effective dielectric constant at the microenvironment around the aromatic ring of benzyl alcohol in the micelle, and D_w is the dielectric constant of water, which is 78.5 at 298.15 K.

From Eqns. 8 and 9, one obtains:

$$\frac{1}{D_w - D_{app}} = \frac{1}{D_w - D_m} + \frac{55.5}{K(D_w - D_m)} \cdot \frac{1}{C - C_0} \quad (10)$$

The data shown in Fig. 3 are plotted in Fig. 6 according to Eqn. 10. The plots of $(D_w - D_{app})^{-1}$ versus $(C - C_0)^{-1}$ showed straight lines for all surfactant micelles presently employed. From the slopes and the intercepts in Fig. 6, one can obtain the effective dielectic constant D_m in the micelle, and the micelle /water partition coefficient, K, of benzyl alcohol, respectively. The values of D_m and K are summarized in Table II.

With the SDS micelle, the partition coefficient of benzyl alcohol was 610 (in the mole fraction unit), and the effective dielectric constant at the binding site of benzyl alcohol was 31. The dielectric constant was intermediate between the aqueous and nonpolar environments.

The partition coefficient was larger with surfactants having longer hydrocarbon chain. On the other hand, the microenvironmental polarity of the anesthetic-binding site was little affected by the chain-length of the surfactants.

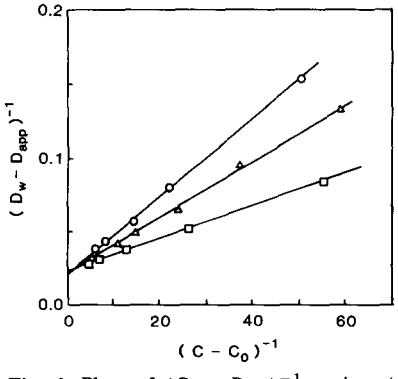

Fig. 6. Plots of $(D_w - D_{app})^{-1}$ against $(C - C_0)^{-1}$ for three surfactants (see text). ○, SDeS; △, SDS; and □, STS.

TABLE II

EFFECTIVE DIELECTRIC CONSTANTS (D_m) OF SURFACTANT MICELLES AND MICELLE/WATER PARTITION COEFFICIENT (K) OF BENZYL ALCOHOL AT 298.15 K

Surfactant	D_m	K
SDeS	29	417
SDS	31	610
STS	33	1089

There are a number of studies on the ultraviolet spectra of benzene and its derivatives in micellar solutions, which led to diverse conclusions (see Ref. 27). Rehfeld [28] concluded that benzene is located in the hexane-like environment in the micelles. Cardinal and Mukerjee [29] suggested that benzene, ethylbenzene and β-phenethyl alcohol ($C_6H_5CH_2CH_2OH$) are, on the average, in SDS micelles in a region that has effective dielectric constants of 49, 41 and 47, respectively. According to the procedure described by Cardinal and Mukerjee [29], Simon et al. [8] used ratio of the absorbance intensities of benzene at two wavelengths and reported that the data do not correlate well to the dielectric constants of reference solvents. They [8] argued that the ultraviolet spectroscopic technique is not very useful in determining the location of benzene in micelles, became multiple numerical values can be obtained for the effective dielectric constant according to the method of constructing the calibration curves. Simon et al. [8], however, did not consider the partition of benzene between the micellar and aqueous phases in estimating the effective dielectric constant. In addition, the absorbance intensity ratio may not be a good parameter in estimating the solvent dielectric property.

In the present study, the shift in the wavelengths of the absorbance maximum, λ_{max}, is used to estimate the dielectric constants of solvents. The datum points in Fig. 2 show excellent correlation between the dielectric constant and λ_{max} with a correlation coefficient of $r = 0.969$. The present method of estimating effective dielectric constant

of the anesthetic-binding site in micelles should be more reliable than those reported previously.

Depression of the critical micelle concentration by the addition of alcohol has been analyzed quantitatively by several authors [25,26,30]. The 'critical micelle concentration-decreasing power' defined as $-\mathrm{d}\ln \mathrm{CMC}/\mathrm{d}Y_a$, where Y_a is the mole fracton of added alcohol in the aqueous phase, has been related to the micelle/water partition coefficient, K, of alcohol as follows:

$$-\frac{\mathrm{d}\ln \mathrm{CMC}}{\mathrm{d}Y_a} = \theta K \tag{11}$$

where θ is a constant and $\theta = 0.69$ is used for a homologous series of alcohols. The critical micelle concentration-decreasing power of benzyl alcohol was 414 ± 16 from the slope at one atmospheric pressure in Fig. 5. If one accepts $\theta = 0.69$ for benzyl alcohol, the micelle/water partition coefficient of benzyl alcohol becomes 600 for the SDS micelle, which is in good agreement with the presently obtained value by the ultraviolet method shown in Table II. Judging from the magnitude of the critical micelle concentration-decreasing power, the effect of benzyl alcohol is equivalent to normal alcohol with an alkyl chain-length of carbon number 4.7.

The critical micelle concentration-decreasing power of benzyl alcohol varies in a pressure-dependent manner as seen in Fig. 5. The pressure dependence of the critical micelle concentration-decreasing power is related to the volume change, ΔV_p^0, associated with the transfer of benzyl alcohol from the aqueous to the micellar phases, via the pressure dependence of an equilibrium constant such as the partition coefficient, K, as follows:

$$\left[\frac{\partial \ln(-\mathrm{d}\ln \mathrm{CMC}/\mathrm{d}Y_a)}{\partial P}\right]_T \approx \left(\frac{\partial \ln K}{\partial P}\right)_T = -\frac{\Delta V_p^0}{RT} \tag{12}$$

where the pressure dependence of θ may be negligible, since the constant θ is only dependent on the combination of surfactant and added alcohol.

The critical micelle concentration-decreasing power at various pressures was obtained from the slopes in Fig. 5. According to Eqn. 12, the logarithm of the critical micelle concentration-decreasing power was plotted against pressure in Fig. 7.

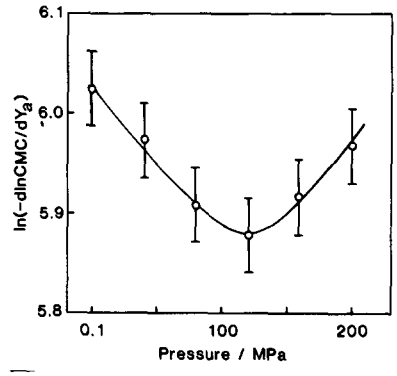

Fig. 7. Critical micelle concentration-decreasing power of benzyl alcohol as a function of pressure at 298.15 K. Datum points are obtained from the slope shown in Fig. 5. The critical micelle concentration (CMC) values in Fig. 5 contain approx. 0.05 mmolal error which is within the size of the symbol. The effect of this error on the slope ($\mathrm{d}\ln \mathrm{CMC}/\mathrm{d}Y_a$) is expressed by the vertical bars. For instance, at 0.1 MPa, $\mathrm{d}\ln \mathrm{CMC}/\mathrm{d}Y_a = 414 \pm 16$ (S.E.).

As seen in Fig. 7, the sign of the pressure dependence of the partition is reversed at about 120 MPa; the logarithm of the critical micelle concentration-decreasing power decreases with a pressure increase until about 120 PMa, then starts to increase according to further pressure increase. This means that the solubilized benzyl alcohol is partially squeezed out of SDS micelles by the applied pressure below 120 MPa, but further increase in pressure squeezes benzyl alcohol molecules into micelles from water.

The phenomenon of the pressure-anesthetic antagonism has been known since the early reports of Johnson and co-workers [31–33], who demonstrated restoration of the light intensity of anesthetic-doped luminous bacteria by hydrostatic pressure ranging from 10 to 15 MPa. This antagonism was confirmed later by demonstration of the awakening effect of pressure upon anesthetized tadpoles [34] and mice [35]. The pressure effect on anesthesia is also biphasic and displays a maximum. When the pressure exceeds about 15 to 20 MPa, the antagonizing effect changes into an enhancement of anesthetic action. The inversion of pressure effect upon anesthetic action is in a pressure range one order of magnitude lower than that in the micellar system. Therefore, the inversion phenomenon in the micellar system may not be directly relevant for understanding the pressure

antagonism of anesthesia in the biological system. In the model system, however, the inversion phenomenon can be analyzed by thermodynamics, in contrast to the complicated biological systems.

The SDS micelle with solubilized benzyl alcohol may be regarded as a mixed micelle, consisting of ionic SDS molecules and nonionic benzyl alcohol molecules. At one atmospheric pressure, the partial molal volume of micellar surfactants is known to be larger than that of singly dispersed surfactants in the aqueous phase [36]. As is seen in Table I, the partial molal volume of benzyl alcohol solubilized into the micelle is larger than that in the aqueous phase. Furthermore, partial molal compressibility of the micellar species is known to be larger than that of the singly dispersed species [37–39]. The former is almost the same magnitude as the compressibility of the liquid state, whereas the latter exhibits sometimes negative values [37–39]. Because of the difference in the compressibility between the micellar and the singly dispersed species, the partial molal volume versus pressure curves may inflect at about 120 MPa. Thus, the changes in partial molal volume on micellization and on the transfer process change the sign from plus to minus at about 120 MPa. The inversion phenomenon of volume change under high pressure is also reported in the micelle formation of SDS [38] and sodium decanoate [39]. Consequently, a minimum in the logarithm of the critical micelle concentration-decreasing power versus pressure curve shown in Fig. 7 may be explained by the inversion of the pressure effect upon the partial molal volume of benzyl alcohol in the micellar and aqueous phases.

The volume change of benzyl alcohol associated with the transfer ΔV_p^0 from the aqueous phase to the SDS micellar phase can be calculated from the slope at one atmospheric pressure in Fig. 7 and Eqn. 12. The value of ΔV_p^0 was 3.5 ± 1.1 $cm^3 \cdot mol^{-1}$ at 298.15 K. To check the validity of Eqn. 12, this value was compared with the volume change determined directly from the solution density meaurements.

The partial molal volumes of benzyl alcohol in water, decane and SDS solutions are summarized in Table I. The partial molal volume of benzyl alcohol in 4.99 mmolal SDS solution, which is below the critical micelle concentration, is the same as that in water, 101.8 $cm^3 \cdot mol^{-1}$. In the micellar solution, the partial molal volume of benzyl alcohol was not constant and increased with an increase in the micellar concentration. This inconstancy of partial molal volume is attributable to the partition of benzyl alcohol between the micellar and aqueous phases. By analogy to Eqn. 9 in ultraviolet spectra, the obtained partial molal volume is expressed by the summation of the partial molal volumes in the micelle and aqueous phases.

$$\bar{V}_2 = x\bar{V}_2^m + (1-x)\bar{V}_2^w \qquad (13)$$

where $\bar{V}_2^m$ and $\bar{V}_2^w$ are the partial molal volume of benzyl alcohol in the micelle and in the aqueous phase, respectively. We can estimate the value of x from Eqn. 8. When $c = 24.82$ mmolal, $x = 0.15_3$ and when $c = 49.95$ mmolal, $x = 0.31_4$. The values of $\bar{V}_2^m$ and $\bar{V}_2^w$ can be calculated from Eqn. 13 using the values of x and $\bar{V}_2$ in the two micellar solutions shown in Table I. We obtained 104.9 $cm^3 \cdot mol^{-1}$ for V_2^m and 101.7 $cm^3 \cdot mol^{-1}$ for $\bar{V}_2^w$. The value of $\bar{V}_2^w$ coincides with the partial molal volume in water and SDS solution below the critical micelle concentration, 101.8 $cm^3 \cdot mol^{-1}$. The partial molal volume change according to the transfer of benzyl alcohol from the aqueous to the micellar phase was 3.1 ± 0.2 $cm^3 \cdot mol^{-1}$, which is in reasonable agreement with the value calculated from Eqn. 12. Note that the partial molal volume in the micelle, 104.9 $cm^3 \cdot mol^{-1}$, is very close to that in the egg phosphatidylcholine/cholesterol (2 : 1) vesicles, 105.3 $cm^3 \cdot mol^{-1}$ [40]. The partial molal volumes of benzyl alcohol in various solvents are in the order: *n*-decane > vesicles ≈ micelles > water. It is established that nonpolar hydrocarbons like alkanes are solubilized into the micelle core, while more polar hydrocarbons like alkanols are solubilized at the micelle surface [41]. The partial molal volume for benzyl alcohol in micelles is much smaller than that in *n*-decane, and is larger than that in water. Since the partial molal volume of a solute varies according to the difference in the solvent property surrounding the solute molecule, these results indicate that benzyl alcohol molecules solvate into the surfactant micelles close to the interface without losing contact with the aqueous phase. This conclusion is

supported by the effective dielectric constants around benzyl alcohol molecules solubilized into the micelles that showed intermediate values between the aqueous and nonpolar phases.

This idea of interfacial adsorption of anesthetics is consistent with our previous report [4] on the proton nuclear magnetic resonance study which showed that one end of an inhalation anesthetic, methoxyflurane, did not lose contact with water when solubilized into a cationic surfactant micelle. Tokiwa and Aigami [42] also used nuclear magnetic resonance spectroscopy to locate the position of aromatic alcohols in SDS micelles by using chemical shifts of the phenyl protons and reported that the phenyl alcohols were solubilized in the micelle with the polar head near the micellar surface and with the phenyl moiety in the hydrophobic mid-methylene region of the micelle. Miyagishi and Nishida [43] used proton chemical shifts of SDS and Brij-35 micelles to identify the position of solubilized phenyl alkyl alcohols and reached the same conclusion.

Acknowledgments

This study was supported by the Medical Research Service of the Veterans Administration and United States Public Health Service grants GM26950 and GM27670. The authors thank Professor S.J. Rehfeld for helpful discussions, and Mr. H.L. Blue for his assistance in preparing the manuscript.

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