

Solubilization of Benzoic Acid Derivatives by Polyoxyethylene Lauryl Ether¹⁾

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The solubilization of 34 benzoic acid derivatives by polyoxyethylene lauryl ether micelles was quantitatively studied by solubility measurement and equilibrium dialysis. The logarithms of partition coefficients (K) of solubilizates between aqueous and micellar phases were directly related to the logarithms of their partition coefficients between aqueous solution and *n*-octanol (P_{octanol}). The plots could be grouped in four parallel linear relationships, each of which was characterized by the intercept b value. When the b value is connected with the positional distribution of hydrophilicity of the palisade layer with reference to *n*-octanol water content, the physical meaning of the value is probably related to the site of incorporation of solutes within the polyoxyethylene mantle. The results show that benzoic acid derivatives examined are classified into dicarboxylic acids, nitro and cyano compounds, the majority of compounds, and salicylic acids group, which are located in order from the outer layer of the mantle toward the hydrocarbon core.

Keywords—solubilization by surfactant; substituted benzoic acids; substituted salicylic acids; polyoxyethylene lauryl ether; solubility; partition coefficient between aqueous and micellar phases; partition coefficient between water and *n*-octanol; linear free energy relationship

In the framework of pharmaceutical applications of solubilization, numerous studies have been carried out to find a certain relationship between the magnitudes of micellar solubilization and the hydrophobicities of solubilizates (*n*-octanol–water partition coefficient). Especially nonionic surfactants have been most frequently investigated as one of the necessary ingredients in the pharmaceutical preparation.

Collett and Koo³⁾ investigated the interaction of *para*-substituted benzoic acid derivatives with polysorbate 20 micelles and obtained a linear relationship between the aqueous-micellar partition coefficients and π values of the substituents. Also, in the case of solubilization of phenolic compounds in cetomacrogol 1000 solution, Azaz and Donbrow⁴⁾ showed that the partition coefficients between micelles and water were directly related to the partition coefficients between heptane or *n*-octanol and water. However, in the former study only seven compounds were selected as solubilizate and in the latter were ten compounds. In such cases the number of compounds chosen may not be enough to generalize a relationship and it is apt to select compounds which satisfied with a single linear relationship.

The structure of micelles of polyoxyethylene surfactants is considered to be such that a hydrocarbon core, containing predominantly the hydrocarbon chains of the surfactant molecules, is surrounded by polyoxyethylene mantle, the palisade layer. These regions of the sphere presumably provide different natures of environment such as water content, density, and the nature of electrical field to solubilizates. Consequently, due to numerous parameters involved, solubilization behaviors for a given system are difficult to predict

- 1) Part of this work was presented at the 97th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1977.
- 2) Location: Tanabe-dori 3, Mizuho-ku, Nagoya, 467, Japan.
- 3) J.H. Collett and L. Koo, *J. Pharm. Sci.*, **64**, 1253 (1975).
- 4) E. Azaz and M. Donbrow, *J. Colloid Interface Sci.*, **57**, 11 (1976).

and a knowledge of the interaction site of the solubilizate in the micelle is necessary for an understanding of the relationship between the magnitudes of the solubilization and the hydrophobicities.

The purpose of this study is to examine the correlation between the magnitudes of solubilization of various benzoic acid derivatives (34 species) in polyoxyethylene lauryl ether (PLE) solution and the hydrophobicities of the solubilizates, pursuing whether the relationship mentioned above can be expressed by a single linear pattern, and to rationalize possible modes of solubilizate incorporation in the micelle.

Experimental

Materials—Benzoic acids were recrystallized from water-ethanol. *m*-Methoxybenzoic acid was synthesized from an equimolar mixture of *m*-hydroxybenzoic acid and dimethyl sulfate refluxing in weak alkaline solution on a steam bath for 5 hours. The product was recrystallized from water-ethanol, mp 104–105°. Polyoxyethylene lauryl ether (PLE) was purified from commercially available Brij 35 as previously mentioned.⁵⁾

Solubility Measurements—An excess of benzoic acids was added to 10 ml volumes of aqueous solutions containing various concentrations of PLE. The solvents used in the solubility, dialysis and partitioning studies were pH 1.0 HCl-KCl buffer for *meta* and *para* substituted benzoic acids and 1.0N HCl for *ortho* substituted ones to depress ionization of the acids. The solutions were shaken for 2 days at a constant temperature, $25 \pm 1^\circ$. After equilibration, sample solutions were pipetted through cotton filters. The samples were suitably diluted with pH 7.0 phosphate buffer and assayed spectrophotometrically. The presence of PLE in the diluted solutions had no influence on the spectrophotometrical assay of benzoic acids.

Equilibrium Dialysis—Visking cellulose tube (20/32) was used as dialysis bag. The bag was filled with 10 ml of aqueous solution containing various concentrations of PLE and soaked in 40 ml of benzoic acids solutions of various concentrations. The flask containing the bag was shaken for 2 days at $25 \pm 1^\circ$. Samples from both sides of the bag were taken and assayed.

Measurements of Partition Coefficients—Partition coefficients between aqueous solution and *n*-octanol were determined similarly to Fujita, *et al.*⁶⁾ 20–200 ml of aqueous solution of benzoic acids were added to 5–20 ml of *n*-octanol and the mixture was agitated vigorously for 30 minutes. The initial concentrations of benzoic acids in the aqueous phase were 1.0×10^{-3} M. For the acids whose solubilities were below it, their saturated solutions were used. After equilibration, the concentration of the sample in the aqueous phase was assayed, and that in the *n*-octanol phase was determined by the subtraction. Partition coefficients between aqueous solution and ether were determined in the same manner as mentioned above.

Determination of Partial Molar Volume—The density of PLE solutions was determined with a Lipkin-Davison type pycnometer. The calculated partial molar volume of PLE was 1.18 l/mol at $25 \pm 0.1^\circ$.

Results and Discussion

In contrast to the earlier study,³⁾ the present one was extended to cover thirty-four benzoic acid derivatives including the *ortho*-, *meta*- and *para*-substituted and dicarboxylic acids in addition. The solubility curves were linear with respect to PLE concentration ranging from 0.002 to 0.02 M in all cases. Fig. 1 shows the typical solubilization curves for *ortho*-substituted benzoic acids. The solubility ratios, expressed in the ratio of the solubility in the micellar solution to that in the nonmicellar solution, were sensitive enough to distinguish the solubilizates examined and the intercepts on the ordinate of linear plots practically converged to unity since the CMC of PLE is very low ($6.0\text{--}9.1 \times 10^{-5}$ M at 25°).

Figure 2 shows the results of the dialysis study on benzoic acid as an example. The concentration of benzoic acid solubilized per molar concentration of PLE, C_b/PLE concentration, was plotted against the free acid concentration, C_f . The closed circle obtained from the solubility data was placed on as well and both results obtained in the unsaturated condition (dialysis) and from the solubility at the corresponding PLE concentration were found located on the same linear relationship. For all other compounds similar linearities were confirmed. These results indicate that the partition theory can be applied to the quantita-

5) K. Ikeda, H. Tomida, and T. Yotsuyanagi, *Chem. Pharm. Bull.* (Tokyo), **25**, 1067 (1977).

6) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).

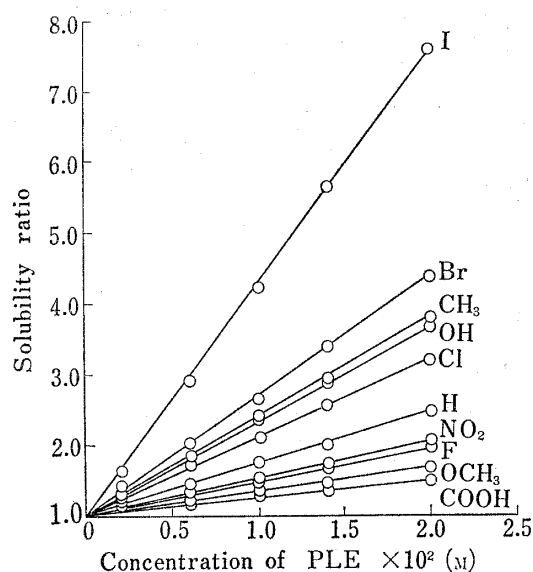


Fig. 1. Solubilization of *ortho*-Substituted Benzoic Acids in Different Concentrations of Polyoxyethylene Lauryl Ether at 1.0 N HCl and $25 \pm 1^\circ$

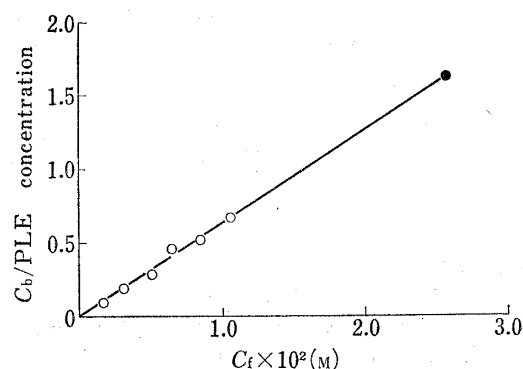


Fig. 2. Dialysis Result for the Interaction between Benzoic Acid and Polyoxyethylene Lauryl Ether at pH 1.0 and $25 \pm 0.1^\circ$

●, solubility point.

tive treatment of the interaction over a wide concentration range up to the saturated system of free acid. The partition coefficient, K , was defined by

$$K = \frac{C_m}{C_a} \quad (1)$$

where C_a and C_m are the concentrations of the solute in aqueous and micellar phases, respectively. K value can be determined by solubility data from the slope of equation 2.

$$\frac{S_t}{S_a} = (K-1) \cdot \text{PMV} \cdot [\text{PLE}] + 1 \quad (2)$$

where S_a is the solubility in water and S_t is the total solubility in the presence of PLE, and PMV is the partial molar volume of PLE. Aqueous solubilities and partition coefficients of benzoic acid derivatives are listed in Table I.

TABLE I. Aqueous Solubilities, S_a and Partition Coefficients of Benzoic Acids, K between Aqueous and Micellar Phases Obtained from Solubility Method

Substituent	<i>ortho</i>		<i>meta</i>		<i>para</i>	
	S_a (M)	K	S_a (M)	K	S_a (M)	K
H			2.61×10^{-2}	57.4		
F	4.05×10^{-3}	43.1	1.65×10^{-2}	91.2	4.98×10^{-3}	94.6
Cl	8.66×10^{-3}	99.8	1.92×10^{-3}	346	3.48×10^{-4}	446
Br	5.29×10^{-3}	150	1.36×10^{-3}	505	1.42×10^{-4}	634
I	1.75×10^{-3}	271	2.74×10^{-4}	1150	9.16×10^{-5}	908
CH ₃	6.55×10^{-3}	120	6.13×10^{-3}	166	2.23×10^{-3}	163
OCH ₃	2.50×10^{-2}	32.0	1.18×10^{-2}	72.8	1.30×10^{-3}	109
OH	1.08×10^{-2}	116	5.71×10^{-2}	38.3	4.17×10^{-2}	42.2
NO ₂	2.53×10^{-2}	47.5	1.57×10^{-2}	96.8	1.01×10^{-3}	117
CN			2.35×10^{-3}	50.1	5.60×10^{-3}	57.0
COOH	2.57×10^{-2}	22.4	4.42×10^{-4}	155	6.50×10^{-5}	69.8

With regard to the derivatives carrying the same substituent, the order of aqueous solubilities was found to be *ortho* > *meta* > *para* and the order of K was just the opposite, except for hydroxybenzoic acids. As shown in Fig. 3, the solubilization of benzoic acid derivatives by PLE micelles is inversely related to their aqueous solubilities, as observed for the phenolic compounds in cetomacrogol 1000 solution.⁴⁾ In the hydroxy derivatives, the *ortho* compound was solubilized most, followed by *para* and *meta* compounds. Patel and Foss obtained the magnitude of interaction of hydroxy, chloro and aminobenzoic acids in polysorbate 80 and cetomacrogol 1000,⁷⁾ and either hydroxy or amino derivatives showed the order of *ortho* > *para* > *meta*. Substitution of hydroxy group in the *ortho* position results in more affinity for any surfactant than *para* and *meta* substituents. This can be explained by the fact that the intramolecular hydrogen bonding brings more proton-donating nature to the carboxylic group.

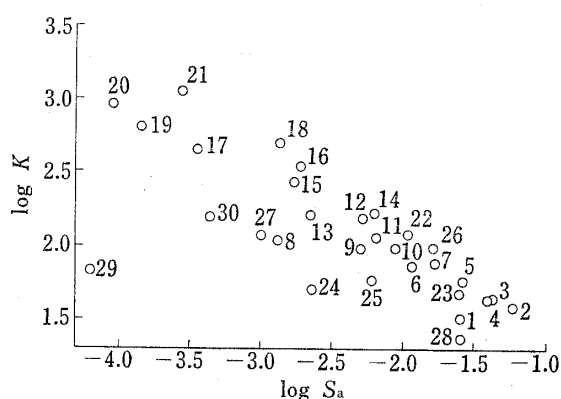


Fig. 3. Relationship between Aqueous Solubilities and Aqueous-Micellar Partition Coefficients for the Benzoic Acids

1) *o*-OCH₃; 2) *m*-OH; 3) *p*-OH; 4) *o*-F; 5) H; 6) *m*-OCH₃; 7) *m*-F; 8) *p*-OCH₃; 9) *p*-F; 10) *o*-Cl; 11) *o*-CH₃; 12) *o*-Br; 13) *p*-CH₃; 14) *m*-CH₃; 15) *o*-I; 16) *m*-Cl; 17) *p*-Cl; 18) *m*-Br; 19) *p*-Br; 20) *p*-I; 21) *m*-I; 22) *o*-OH; 23) *o*-NO₂; 24) *m*-CN; 25) *p*-CN; 26) *m*-NO₂; 27) *p*-NO₂; 28) *o*-COOH; 29) *p*-COOH; 30) *m*-COOH.

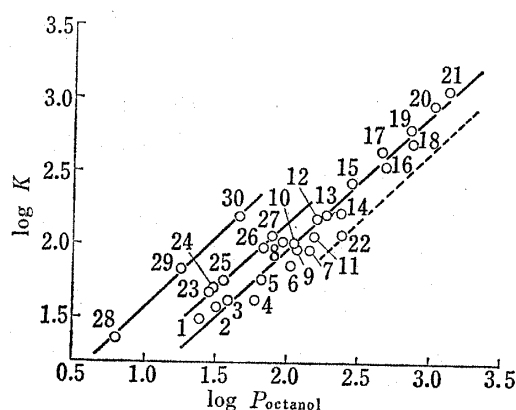


Fig. 4. Relationship between $\log P_{\text{octanol}}$ and $\log K$ for the Benzoic Acids

Numbers are the same as those in Fig. 3.

The dotted line refers to the salicyclic acid derivatives as shown in Fig. 5.

Figure 4 reveals the relationship between $\log K$ and $\log P_{\text{octanol}}$ and plots could hardly be fitted in a single linear relationship.

Leo and Hansch⁸⁾ studied the relationship between the *n*-octanol-water partitioning system chosen as a reference standard and other solvents, based on equation 3 which was first proposed by Collander.⁹⁾

$$\log P_{\text{solvent}} = a \log P_{\text{octanol}} + b \quad (3)$$

where P is the partition coefficient, and the parameters a and b represent a measure of the sensitivity of solvent system to changes in the hydrophobicity of solutes and that of the hydrophobicity of the solvent, respectively. They pointed out that a single equation is sufficient to give an excellent correlation with the *n*-octanol reference system over a variety of solute types, H-donor, H-acceptor and solutes having both donative and acceptable capabilities, if the solvent in question carries both H-donor and H-acceptor functional groups. For example, as reported by Higuchi *et al.*¹⁰⁾ in the case of the cyclohexane-water system in which the organic phase was added a small amount of tributyl phosphate or sarin as hydrogen

7) N.K. Patel and N.E. Foss, *J. Pharm. Sci.*, **54**, 1954 (1965).

8) A. Leo and C. Hansch, *J. Org. Chem.*, **36**, 1539 (1971).

9) R. Collander, *Acta Chem. Scand.*, **5**, 774 (1951).

10) T. Higuchi, J. Richards, S. Davis, A. Kamada, J. Hou, M. Nakano, N. Nakano, and I. Pittman, *J. Pharm. Sci.*, **58**, 661 (1969).

acceptor, the hydrogen bonding ability of solutes was accounted for separately as a term of pK_a . The correction was successful and a good correlation was obtained. In an attempt to apply this consideration to the relationship between the PLE micelle-water and *n*-octanol systems, little significant factor was obtained on the pK_a term when the correction was made for the electrical effect of respective compounds in terms of pK_a value.

On the basis of the data of benzoic acid derivatives, an attempt was made to classify the plots into three linearly parallel categories, each of which renders the gradient approximately unity. The first includes the majority of the derivatives employed, the second the compounds carrying nitro and cyano substituents, and the third the dicarboxylic group. These linear relationships can be expressed by the following equations which were derived by the least-squares method.

$$\log K = 0.921 \log P_{\text{octanol}} + 0.118 \quad \begin{array}{ccc} n & r & s \\ 21 & 0.986 & 0.080 \end{array} \quad (4)$$

$$\log K = 0.881 \log P_{\text{octanol}} + 0.392 \quad \begin{array}{ccc} n & r & s \\ 5 & 0.999 & 0.014 \end{array} \quad (5)$$

$$\log K = 0.968 \log P_{\text{octanol}} + 0.600 \quad \begin{array}{ccc} n & r & s \\ 3 & 0.999 & 0.036 \end{array} \quad (6)$$

where n is the number of points used in the regression, r is the correlation coefficient, and s is the standard deviation.

According to the definition of the parameter a , the slope of unity assigned to the respective groups indicates that the sensitivity of the partitioning to PLE micelles can be assumed to be comparable to the *n*-octanol reference system for any group of the derivatives classified. Besides, there is another parameter b given by the shift of the regression equation. It theoretically indicates the $\log K$ for a set of solutes which assumed to partition equally between *n*-octanol and water.

From a good correlation between the intercept value and the degree of water content at saturation, Leo and Hansch⁸⁾ use the b value as a measure of a solvent's hydrophobicity for acidic solutes: a positive intercept means that the solvent is more hydrophilic than the *n*-octanol saturated with water and a negative value specifies it more hydrophobic. As shown by equations 4, 5 and 6, the b value of the first group was slightly positive and the second and third groups showed more positive deviations than the first. This indicates that the PLE micelle exerts itself to be more hydrophilic than the *n*-octanol phase for nitro and cyano derivatives and to be much more hydrophilic for the dicarboxylic acid group. Accordingly, it is suggested that the solubilizes belonging to the second and third groups favor relatively hydrophilic environment compared to the first group. Moreover, salicylic acid, known to form the second hexagonal ring by intramolecular hydrogen bonding, deviates evidently from the first group (Fig. 4). Further studies were carried out on four substituted salicylic acids and the results are shown in Table II and Fig. 5. A distinct linear relationship was found for the salicylic acid series, which can be expressed by

$$\log K = 0.996 \log P_{\text{octanol}} - 0.303 \quad \begin{array}{ccc} n & r & s \\ 5 & 0.997 & 0.032 \end{array} \quad (7)$$

The regression equation reveals the gradient of nearly unity and a negative intercept value, which implies the PLE micelle exerts itself to be more hydrophobic than the octanol phase. This indicates that PLE micelles offer different environments to a given set of solutes when solubilized in the micellar phase. Thus, characterized by b values, the solubilizes can be ranked in order of the dicarboxylic acid group, nitro and cyano compounds, the majority of benzoic acid derivatives and the salicylic acid series.

Meantime, for the relationship between hydrocarbon-water and *n*-octanol-water system, Leo and Hansch⁸⁾ divided all solutes in two general solute categories (hydrogen donors and acceptors) and successfully calculated solvent regression equations for the two classes, describing a single equation is enough to give a good correlation for a set of properly selected solutes.

TABLE II. Aqueous Solubilities, S_a , Partition Coefficients between Aqueous and Micellar Phases, K , and between Aqueous Solution and n -Octanol, P_{octanol} for the Salicylic Acid Derivatives

Compound	S_a (M)	K	$\log P_{\text{octanol}}$
Salicylic acid	1.08×10^{-2}	116	2.38
5-Chlorosalicylic acid	1.69×10^{-3}	571	3.09
5-Bromosalicylic acid	2.22×10^{-3}	826	3.23
4-Methylsalicylic acid	1.26×10^{-3}	513	2.99
5-Methylsalicylic acid	1.72×10^{-3}	269	2.78

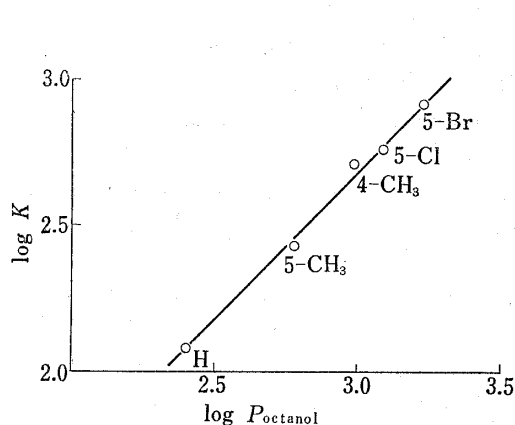


Fig. 5. Relationship between $\log P_{\text{octanol}}$ and $\log K$ for the Salicylic Acid Derivatives

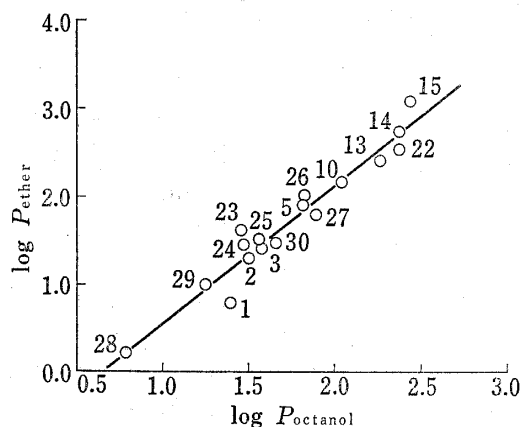


Fig. 6. Relationship between $\log P_{\text{octanol}}$ and $\log P_{\text{ether}}$ for the Benzoic Acids

Numbers are the same as those in Fig. 3.

TABLE III. Partition Coefficients of the Benzoic Acids between Aqueous Solution and n -Octanol, P_{octanol} and Ether, P_{ether}

Substituent	<i>ortho</i>		<i>meta</i>		<i>para</i>	
	$\log P_{\text{octanol}}^a$	$\log P_{\text{ether}}$	$\log P_{\text{octanol}}^b$	$\log P_{\text{ether}}$	$\log P_{\text{octanol}}^b$	$\log P_{\text{ether}}$
H			1.81	1.89 ^{b)}		
F	1.77		2.15		2.07	
Cl	2.05	2.14 ^{b)}	2.68		2.65	
Br	2.20		2.87		2.86	
I	2.44	3.11 ^{b)}	3.13		3.02	
CH ₃	2.18		2.37	2.70 ^{a)}	2.27	2.40 ^{a)}
OCH ₃	1.39	0.78 ^{b)}	2.02		1.96	
OH	2.38	2.53 ^{b)}	1.50	1.32 ^{b)}	1.58	1.42 ^{b)}
NO ₂	1.46	1.59 ^{b)}	1.83	1.97 ^{b)}	1.89	1.80 ^{a)}
CN			1.48	1.44 ^{a)}	1.56	1.50 ^{a)}
COOH	0.79	0.20 ^{b)}	1.66	1.46 ^{b)}	1.25 ^{a)}	1.00 ^{a)}

^{a)} Determined in this study.

^{b)} The values summarized by A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).

Seiler¹¹⁾ reported that the partition coefficient measured in saturated hydrocarbon systems could be converted with good accuracy to the n -octanol system, introducing a parameter I_H regarded as a measure for hydrogen bonding ability.

For the benzoic acid derivatives listed in this study, the relationship between ether-water and n -octanol-water systems was examined as shown in Table III and Fig. 6. It

11) P. Seiler, *Eur. J. Med. Chem.-Chimica Therapeutica*, **9**, 473 (1974).

reveals an excellent correlation with a coefficient of 0.971. The regression equation was given by

$$\log P_{\text{ether}} = 1.57 \log P_{\text{octanol}} - 1.02 \quad \begin{matrix} n \\ 17 \end{matrix} \quad \begin{matrix} r \\ 0.971 \end{matrix} \quad \begin{matrix} s \\ 0.179 \end{matrix} \quad (8)$$

Although some compounds such as halogenated derivatives were excluded because of their extremely high partition coefficients to the ether phase, it should be noted that the solutes examined include dicarboxylic acids, nitro and cyano derivatives which gave appreciable deviations from the majority of the originally given set in the case of PLE micelles and *n*-octanol system. Naturally, one can raise a problem why a single linear correlation is not sufficient to express the relationship between the PLE micelles and *n*-octanol phases for the benzoic acid derivatives, while sufficient between the organic solvents.

The authors noted that the intrinsic difference in the partitioning behavior between PLE micelles and hydrocarbons with reference to *n*-octanol might be due to the difference of the physical structure of respective phases: the former consists of the hydrocarbon core and the palisade layer in contact with or hydrated by a number of water molecules, which may offer rather complicated environment to a solute depending on the site solubilized, while the latter may provide a homogeneous environment, both in physical and chemical situations except for interface between two phases.

It is recognized that the hydration of the palisade layer depends upon the chain length of the oxyethylene unit. For C_{16} polyoxyethylene nonionic surfactant micelles, the degree of hydration per ethylene oxide unit was varied from 5.2 to 10.6 water molecules as the ethylene oxide chain length increased.¹²⁾ This implies that there is a water content distribution from the surface toward the interior core. Similarly, it seems possible that the PLE micelles have a positional distribution of either hydrophilic or hydrophobic nature due to water content for the solutes to be solubilized. Note again here that the term of either hydrophilic or hydrophobic is used with reference to the *n*-octanol phase saturated with water.

Donbrow and Rhodes¹³⁾ reported that benzoic acid, which belongs to the first group in this study, is most probably located at the junction of the palisade layer and the hydrocarbon core of polyoxyethylene monoalkyl ether, and Mukerjee¹⁴⁾ calculated the partition ratio of *p*- and *o*-hydroxybenzoic acids between the core and the oxyethylene mantle, describing that the former resides more in the mantle and the latter does in the core, because the carboxyl group tends to bind to the oxyethylene mantle by hydrogen bonding and bipolar molecules such as *p*-hydroxybenzoic acid carry two hydrogen donor function, while the bonding function of *o*-hydroxybenzoic acid is retarded by intramolecular hydrogen bond.

As mentioned above, the magnitude of the partition coefficient, *K*, generally increases from *ortho* to *meta* to *para* derivatives as to the same kind substitute. Therefore, it can be considered that the position of the substituted is related to its proton-donating ability, making the compound more reactive with the micelles due to the hydrogen bonding with the oxyethylene moiety of the micelle structure. Higuchi and Lach¹⁵⁾ described the possible mechanism of interaction between carboxylic acid and surfactants of polyoxyethylene type. Blaug and Ebersman¹⁶⁾ reported that the aromatic acid is possibly incorporated in the palisade layer of the nonionic micelles. Along with these earlier studies, it is very likely that the site of incorporation of the benzoic acid derivatives is predominantly in the oxyethylene mantle or the surface of micelles by hydrogen bonding, which is a primary interaction mechanism.

12) D.I.D. El Eini, B.W. Barry, and C.T. Rhodes, *J. Colloid Interface Sci.*, **54**, 348 (1976).

13) M. Donbrow and C.T. Rhodes, *J. Chem. Soc.*, **1964**, 6166.

14) P. Mukerjee, *J. Pharm. Sci.*, **60**, 1529 (1971).

15) T. Higuchi and J.L. Lach, *J. Am. Pharm. Assoc., Sci. Ed.*, **53**, 465 (1954).

16) S.M. Blaug and D.S. Ebersman, *J. Pharm. Sci.*, **53**, 35 (1964).

However, because of their highly electronegative nature, the nitro and cyano derivatives would reveal dipole forces in addition to the hydrogen bonding and dicarboxylic acids carry doubly functional activity of hydrogen bonding to the oxyethylene unit. It would be expected, therefore, that respective solutes occupy their favorable configurations in the palisade layer along with oxyethylene unit.

When the nature of PLE micelles is characterized by the water content of the *n*-octanol phase whether hydrophilic or hydrophobic and the solutes solubilized are characterized by *b* value, it is suggested that the distribution of *b* value reflects the relative positions at which the solutes solubilized among a set of selected compounds. Accordingly, it could be qualitatively mentioned that the first, the second and the third groups are located in order from the part close to the core to the micellar surface with their respective reactivities to the oxyethylene unit, resulting in the difference of the *b* value among them. Furthermore, the solubilization site of salicylic acids is well known and seems consistent with the fact that the negative *b* value predicts for these compounds to reside in more hydrophobic portion of the PLE micelle with reference to the *n*-octanol phase, that is in the hydrocarbon core. Although exact positions are not identified, the authors might expect to be able to predict the qualitative behavior of solubilization by nonionic surfactant micelles with the intercept *b* value.