[Chem. Pharm. Bull. 19(12)2510—2517(1971)] UDC 547.854.5-26:03

Solubilization of Barbiturates by Polyoxyethylene Lauryl Ether[1]

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(Received April 30, 1971)

Micellar solubilization of barbiturates by polyoxyethylene lauryl ether was investigated by the methods of solubility measurement, equilibrium and dynamic dialyses, potentiometric titration and molecular sieve. Amount of solubilized barbiturate was found to be proportional to free concentration in aqueous phase. Evaluating volume fraction of micelle, partition coefficient between aqueous and micellar phases, K, was used as the quantitative indication of micellar solubilization. Results obtained by various methods were in good agreement. Phenobarbital alone showed specific interaction with polyoxyethylene lauryl ether in solubility study at temperature below 45°. To see the effect of chemical structure on solubilization attempt was made to subdivide log K into terms concerning Taft's substituent constant, carbon number of substituents and unsubstituted barbituric acid. These considerations suggest that major portion of barbiturate is localized in polyoxyethylene layer of micelle.

Studies on solubilization of barbiturates by surfactant have been reported by a number of investigators and also the resultant effects on biological activities have been studied by some workers.[3] Most of the studies on barbiturate solubilization, however, have been aimed at practical formulation using unpurified surfactants and quantitatively precise and detailed study has not been reported. Meanwhile, recently various methods for the quantitative study on micellar solubilization have been developed and the comparison of these is of interest and worthy.

In this study using purified polyoxyethylene lauryl ether (PLE) the solubilization of various barbiturates was quantitatively investigated by various methods and the effect of chemical structure on micellar solubilization is discussed. In the literature hitherto micellar solubilization has been interpreted as adsorption or complexation. Recently, however, evaluating volume fraction of micell, v, solubilization has been quantitatively represented as partition and the effects of solubilization on various phenomena have been successfully interpreted with quantitative equations. Mitchel studied on the effect of solubilization on the hydrolysis of acetylsalicylic acid and the decrease of the hydrolysis rate was quantitatively elucidated.[4] The equations used by Mitchel was based on Yamada, *et al.*'s equation by which the effect of solubilization on the decrease of biological absorption was accounted for.[5] As will be shown later, the result of this study on micellar solubilization of barbiturate by PLE was also found to be able to quantify as partition. In the discussion on the result, therefore, apparent partition coefficient, K, defined as

$$K = \frac{D_m/v}{D_w/(1-v)} \tag{1}$$

was used as the quantitative indication of micellar solubilization, where D_m and D_w are amounts (mole) of barbiturate in micellar and aqueous phases, respectively. For the calculation of

1) Main part of this study was presented at the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July 1970.
2) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
3) P.H. Elworthy, A.T. Florence and C.B. Macfarlane, "Solubilization by Surface Active Agents" Chapman and Hill Ltd., London, 1968.
4) A.G. Mitchel, *J. Pharm. Sci.*, **56**, 1261 (1967).
5) H. Yamada and R. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1279 (1965).

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value K from the result obtained by various methods, some newly derived equations which involve v term were used.

Experimental

Material——Barbiturates used were recrystallized from dilute aqueous alcohol with the least concentration required for dissolution. In preliminary study some solubility difference depending upon recrystallization medium was found, which may be attributed to polymorphism. Purified PLE was obtained from commercially available Brij 35 by the modification of Nakagawa, *et al.*'s method, by which mainly free polyethylene glycol is removed.[6] Brij 35 was dissolved in n-butanol saturated with water and passed through dried silica gel column. Butanol was evaporated at reduced pressure and the residue was used as purified PLE. For potentiometric titration, however, it was found that further purification was necessary for some lots of Brij 35. In these cases the aqueous solution of PLE prepared as above passed before use through ion exchange resin column[4] composed of anion exchanger, Dowex 1-x 4, and cationic exchanger, Amberlite IR-120. The membrane used for equilibrium and dynamic dialysis was Visking cellulose tube, which was boiled in distilled water three times respectively for 30 minutes. In preliminary study it was ascertained that PLE permeated through cellulose membrane during 48 hours under experimental condition of equilibrium dialysis amounts in receiving solution merely far below c.m.c. of PLE (0.011 or 0.014 %[7]). For the determination of PLE Uno's method[8] was used. The apprehension for surfactant permeation through cellulose membrane[9] seems to be due to impurities of low molecular weight owing to the lack of purification. For a molecular sieve method Sephadex G-25 fine, Pharmacia, Uppsala, Sweeden, was used. The internal water volume of swelled molecular sieve was found to be 2.30 ml/dry gel using Blue Dextran 20,000.

Determination of Barbiturate——UV spectral method was used according to Hasegawa, *et al.*[10] For the determination of barbiturate the interference by PLE was not observed.

Determination of Volume Fraction of Micelle——Ostwald-Sprengel pycnometer was used for the determination of density of aqueous PLE solution. The density incresaes linearly with the concentration of PLE and value v at various temperature was calculated.[4] Partial molar volume of PLE was found to be 1028.8 ml/mole.

Solubility Measurement——In a stoppered flask 0.005 M HCl containing various amount of PLE was taken and excess amount of barbiturate was added. Hydrochloric acid added prevents the dissociation of barbiturate. The amount dissolved was determined after being shaken for 48 hours in a thermostat. Amount in micelle, D_m was estimated from the increase of solubility due to the presence of PLE.

Equilibrium Dialysis——Dialysis bag was made of Visking cellulose tube (20/32) with the length of 15 cm and filled with 10 ml of 0.005M HCl containing varying amount of PLE. The bag was soaked in 40 ml of barbitutate solution of varying concentration. The flask containing the bag was shaken for 48 hours in a thermostat. Amount in micelle, D_m, was calculated from the difference of the concentrations inside and outside of the bag at equilibrium.

Dynamic Dialysis——Following to the method of Ågren, *et al.*[11] two connected 300 ml flasks holding dialysis membrane at the joint were used. The diameter of connecting tubes and dialyzing membrane was 2.5 cm. In one flask 250 ml of 0.005 M HCl containing barbiturate and varying amount of PLE was loaded and in the other same volume of plain 0.005 M HCl was supplied. Both flasks were stirred vigorously with same speed using a couple of identical stirrers and the amount permeated was determined at appropriate intervals. As the experiment was confined to the initial stage of permeation, *i.e.* only 2% barbiturate permeated at most, backward permeation can be neglected. The cummulative amount permeated increases linearly with time as will be shown. Value K can be calculated by equation 2, where permeation rate was defined as the slope of the increasing concentration in receiving flask.[12]

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6) T. Nakagawa and K. Shinoda, "Colloidal Surfactant" ed. by K. Shinoda, T. Nakagawa, B. Tamamushi, T. Isemura, Academic Press, New York and London, 1963, p. 166.
7) P. Becher and N.K. Clifton, *J. Colloid Sci.*, **14**, 519 (1959).
8) T. Uno, *Yakuzaigaku*, **22**, 223 (1962).
9) *a*) N.K. Patel and H.B. Kostenbauder, *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 289 (1958); *b*) C.K. Bahal and H.B. Kostenbauder, *J. Pharm. Sci.*, **53**, 1027 (1964).
10) J. Hasegawa, K. Ikeda and T. Matsuzawa, *Chem. Pharm. Bull.* (Tokyo), **6**, 36 (1958).
11) A. Ågren, R. Elofsson, *Acta Pharm. Suetica*, **4**, 281 (1967).
12) The permeation rate is proportional to D_w assuming that barbiturate entrapped in micelle is impermeable. Denoting the total amount of barbiturate in surfactant solution by D_{total}, which is equal to D_w+D_m, equation 3 is obtained from equation 1.

$$\frac{D_w}{D_{\text{total}}} = \frac{1-v}{Kv+1-v} \tag{3}$$

Ratio D_w/D_{total} is equal to the ratio of permeation rates in the presence and the absence of PLE.

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$$\frac{\text{Permeation Rate in the Presence of PLE}}{\text{Permeation Rate in the Absence of PLE}} = \frac{1-v}{Kv+1-v} \quad (2)$$

Potentiometric Titration——The experimental procedure is essentially the same as that of Donbrow, *et al.*[13] In 10 ml of PLE solution 60 mg of phenobarbital sodium was dissolved and titration was carried out with 0.005 M HCl under the stream of N_2. The water used was degassed by bioling and stored in a flask provided with soda lime tube. Value K was calculated with equation 4[14] which is the modification of Donbrow, *et al*'s equation involving v term.

$$\Delta\text{pH} = \log\left(\frac{Kv}{1-v} + 1\right) \quad (4)$$

Molecular Sieve Method——The experiment was carried out following to that of Ashworth, *et al.*[15] and Donbrow, *et al.*[16] After the swelling of 4 g Sephadex G-25 fine with 15 ml of 0.005 M HCl for 2 hours, 10 ml of 0.005 M HCl containing varying amount of PLE was added. Equilibrium is attained during stirring for one hour at 25° and supernatant solution was analyzed. Value K can be calculated by equation 6 which involves v term.[17]

$$\frac{D_{\text{total}}}{D_g} = \frac{Kv}{1-v}\cdot\frac{1}{K'}\cdot\frac{V_w}{V_g} + \frac{1}{K'}\cdot\frac{V_w}{V_g} + 1 \quad (6)$$

where D_g represents the amount of barbiturate in gel phase, and V_w and V_g are volumes of bulk water and water in gel phase, respectively. In this experiment V_g was 2.30 ml × 4 = 9.20 ml, and V_w was 25.0 ml—9.20 ml = 15.80 ml. The value K' for phenobarbital at 25° was found to be 1.32.

Result and Discussion

Free Barbiturate Concentration and Amount Solubilized

In the literature on micellar solubilization some instances have been represented as partition and the others as adsorption or complexation depending upon the relationship between free concentration in aqueous phase and the amount solubilized. To see this relationship covering wide concentration range, an equilibrium dialysis method is most suitable. The result of this method on various barbiturates is shown in Fig. 1 illustrating Langmuir (A) and Freundlich (B) type plots, which are expressed by equations 9 and 10.

$$\frac{S}{d_m} = \frac{1}{K_1} + \frac{1}{K_1K'C} \quad (9)$$

$$\frac{d_m}{S} = K_fC^n \quad (10)$$

In these equations K_f, K_1, K'_1, and n are constants, d_m is the amount of barbiturate solubilized (μg), S is the amount of PLE (g) and C is the concentration of barbiturate in sur-

13) *a*) M. Donbrow and C.T. Rhodes, *J. Chem. Soc.*, **1964**, 6166; *b*) *idem*, *ibid.*, **1967** A, 561.

14) The equation 3 in Donbrow, *et al*'s report in 1964[13a] can be simplified into equation 5 assuming $[A^-]_1 = [A^-]_2$ and the activity coefficients are identical.

$$\Delta\text{pH} = \log\frac{[HA_{\text{water}}]_1}{[HA_{\text{water}}]_2} \quad (5)$$

The ratio of $[HA_{\text{water}}]_1/[HA_{\text{water}}]_2$ is equal to D_{total}/D_w which is the reciprocal of equation 3.

15) R.W. Ashworth and D.D. Head, *J. Pharm. Pharmacol.*, **18**, 98 S (1966).

16) M. Donbrow, E. Azaz and R. Hamberger, *J. Pharm. Sci.*, **59**, 1427 (1970).

17) The partition coefficients of barbiturate between water in gel phase and bulk water, K', can be expressed as

$$K' = \frac{D_g/V_g}{D_w/V_w} \quad (7)$$

Equation 6 is obtained by the substitution of equations 1 and 7 into equation 8.

$$D_{\text{total}} = D_w + D_m + D_g \quad (8)$$

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factant free solution (μg/ml). As is shown in Fig. 1 A all straight lines pass the origin of co-ordinates and as seen in Fig. 1B n is considered to be 1 within the experimental error for all barbiturates studied, which means that there is no limitation of solubilization within the results of this study. It is however not conceivable that barbiturate molecules solubilized in micelles are freely distributed between aqueous phase and micelles as the common partition between water and organic solvent. Barbiturate molecule itself has relatively hydrophilic portion, barbituric acid ring, and lipophilic group, 5,5-substituted group, and actually it is known that barbiturates have surface activity.[18] Accordingly it is natural to presume that barbiturate is fixed and orientated at some position in micelle. Approximate calculation from d_m/S value in the experiment shown in Fig. 1, *i.e.* from 25 to 500 μg barbiturate/g PLE, reveals that number of barbiturate molecules distributed per micelle ranges from 0.007 to 0.135. This calculation is based on Becher's data that 40 PLE molecules compose one micelle and molecular weight of micelle is 48×10^3.[19] On the system where much more barbiturate is solubilized will be discussed in the paragraph on solubility study. Value K defined by equation 1 and Kf or $K_1K'_1$ in equation 9 and 10 can be considered equivalent as the indication of micellar solubilization, because v is proportional to S, n is 1 and $1\text{-}v \simeq 1$ at low concentration of PLE.

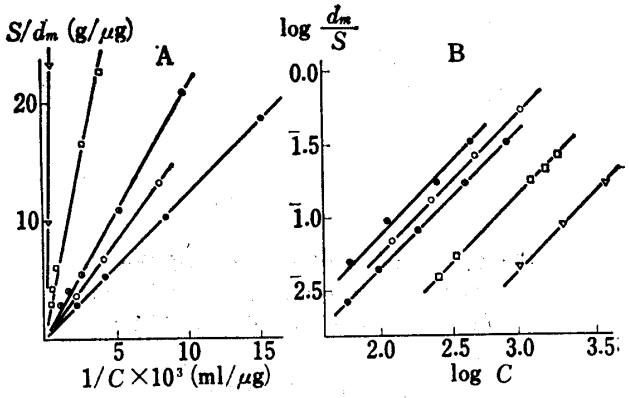

Fig. 1. Langmuir (A) and Freundlich (B) Type Plots of the Result Obtained by Equilibrium Dialysis Method at 25°

▽: barbital □: allobarbital ⊙: phenobarbital
○: amobarbital ●: pentobarbital

Comparison of Various Methods

The results obtained by various methods on phenobarbital at 25° are summarized in Fig. 2, which is illustrated by Langmuir type plots. The result of solubility study is not presented in Fig. 2 because solubility study on phenobarbital brought unordinary result at temperature below 45° as will be shown later. As seen in Fig. 2 the results obtained by various methods are in good agreement and the straight line through plots passes the origin of co-ordinates.

Remarks on the comparison of various methods studied are as follows. Dynamic dialysis method which has been used recently for the study of interaction between drug and macromolecule[11,20] was found to be usefull also for micellar solubilization study. Comparing to an equilibrium dialysis method which has been widely used the dynamic dialysis can be carried out within shorter period and marked difference of permeation rate was observed with simple apparatus as will be shown. Potentiometric titration method can be used exculsively for weak acid or base and the solubilizate should have aqueous concentration sufficient for titration and the difference of pH, Δ pH, is not always large enough for accurate calculation of K. Molecular sieve method will be used further widely because accurate result is obtained neatly without special apparatus in short period. On solubility method discussion will be given in the following section.

Effect of Temperature

Value K at various temperature was determined by dynamic dialysis and solubility study. An example of dynamic dialysis is shown in Fig. 3. As this example all barbiturates

18) R.J. Kuffner, M.T. Bush and L.J. Bircher, *J. Am. Chem. Soc.*, **79**, 1587 (1957).
19) P. Becher, "Nonionic Surfactant" ed. by M.J. Schick, Marcell Decker Inc., New York, 1967, p. 495.
20) M.C. Meyer and D.E. Guttman, *J. Pharm. Sci.*, **59**, 33,39 (1970).

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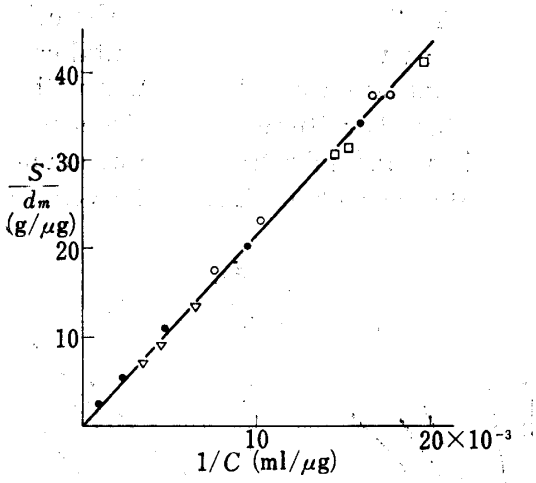

Fig. 2. Langmuir Type Plot of the Results Obtained by Various Methods on Solubilization of Phenobarbital by PLE at 25°

○: potentiometric titration
●: equilibrium dialysis
△: dynamic dialysis
□: molecular sieve method

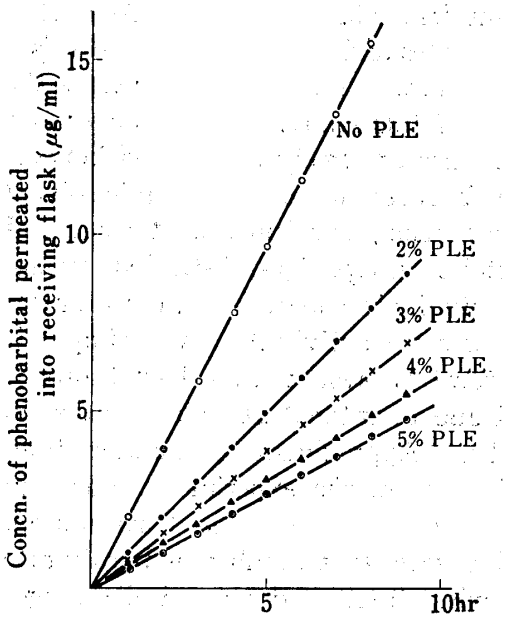

Fig. 3. Permeation of Phenobaribital at Various Concentration of PLE at 25°

permeat linearly with time and the slope of permeation decreases with the increase of PLE concentration. Table I summarizes the value K determined by dynamic dialysis at various temperature and thermodynamic functions calculated by conventional equations 11—13. Value N in Table I is the carbon atom number of 5,5-substituted groups of barbiturates which will be discussed later

$$\Delta G = -RT \ln K \tag{11}$$

$$\Delta H = -R \frac{\partial \ln K}{\partial (1/T)} \tag{12}$$

$$T\Delta S = \Delta H - \Delta G \tag{13}$$

As seen in Table I all ΔH values are negative, viz. micellar solubilization of barbiturates is an exothermic process. Entropy change is largely negative for some barbiturates and slightly positive for others. As the solubilizate is assumed to be fixed in micelle the negative entropy change due to solubilization is convincing. For the elucidation of some positive entropy change observed there can be assumed entropy increasing factors such as destruction ice–berg structure around the substituted groups and/or increasing of flexibility of substituents in micelle. Similar discussion was made by some investigators.[9b] As seen in Table I the larger the negative enthalpy change the larger the negative entropy change and there is linear relationship between ΔH and $T\Delta S$, which means thermodynamic contributions due to enthalpy and entropy changes counteract for solubilization process. Value K determined by solubility method and the molar ratio of solubilized barbiturate to PLE added are shown in Table II. The ratio was calculated from the slope of solubility increase owing to the increase of PLE. Except for the case on phenobarbital at temperature below 45° linear solubility increasing with the increasing of PLE concentration was observed. As seen in Table II value K determined by solubility method is not far from those obtained by dynamic dialysis or other methods which were performed at lower concentration of barbiturate. At the saturated condition which is inherent and inevitable in solubility study barbiturate is solubilized to the extent that the solubilizate is approximately equimolar to PLE as is seen from the ratio in Table II. In these states the composition and structure of micellar complex would be quite

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different from that in the condition where only about one tenth micelles contain barbiturate molecule as was seen in the result of equilibrium dialysis. It must be kept in mind, therefore, that in spite of the approximation of K values determined by solubility study and the other methods the actual figure of the micellar complex may be markedly different in the former and

Table I. Value K Determined by Dynamic Dialysis at Varous Temperature and Thermodynamic Functions Calculated

No.	Barbiturate	N	°C	K	ΔG	ΔH (kcal/mole)	$T\Delta S$
1	barbital	4	25	11.0	−1.4	−3.3	−1.9
			45	7.9	−1.3		−2.0
			60	6.1	−1.2		−2.1
2	5-allyl-5-ethylbarbituric acid	5	25	13.4	−1.6	−7.7	−6.1
			35	9.5	−1.4		−6.3
			45	6.0	−1.1		−6.6
3	allobarbital	6	25	23.6	−1.9	−4.4	−2.5
			35	18.8	−1.8		−2.6
			45	13.8	−1.7		−2.7
			60	10.7	−1.6		−2.8
4	pentobarbital	7	25	78.5	−2.6	−1.7	+0.9
			35	70.0	−2.6		+0.9
			45	62.0	−2.6		+0.9
			60	57.6	−2.7		+1.0
5	amobarbital	7	25	74.0	−2.6	−1.7	+0.9
			35	70.0	−2.6		+0.9
			45	64.5	−2.6		+0.9
			60	55.0	−2.6		+0.9
6	cyclobarbital	8	25	36.0	−2.1	−1.9	+0.2
			35	32.2	−2.1		+0.2
			45	29.4	−2.2		+0.2
7	phenobarbital	8	25	60.8	−2.4	−3.0	−0.6
			35	52.0	−2.4		−0.6
			45	45.0	−2.4		−0.6
			60	33.6	−2.4		−0.6
8	secobarbital	8	25	176	−3.1	−1.6	+1.5
			35	162	−3.1		+1.5
			45	147	−3.1		+1.5

Table II. Value K Determined by Solubility Measurement at Various Temperature and Molar Ratio (Barbiturate Solubilized/PLE)

Barbiturate	°C	K	Molar ratio
Barbital	25	15.6	0.57
	35	14.1	0.65
	45	12.3	0.76
	60	11.5	0.97
Allobarbital	25	19.0	0.20
	35	16.5	0.23
	45	17.1	0.33
	60	15.8	0.54
Amobarbital	25	96.9	0.27
	35	78.4	0.30
	45	80.5	0.34
	60	70.9	0.58
Phenobaribital	60	36.0	0.68
Cyclobarbital	25	41.7	0.32
	35	39.9	0.39
	45	37.8	0.48
	60	29.7	0.86

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the latter. To seek for the realized figure of micellar complex at the saturated condition may be an aim of the study hereafter.

When there is any specific molecular interaction between solubilizate and surfactant and this surpasses beyond the ordinary solubilization process an anomalous phenomenon will be observed. Such condition is apt to be attained especially in solubility study where solubilization occurs to the limitting and the system contains excess solubilizate. Figure 4 shows an instance of such unusual result observed on phenobarbital and PLE at 25°. Above 45°, however, such particular solubilization curve was not observed and ordinary linear solubility increase was observed as an example at 60° shown in Fig. 4. At temperature below 45° in the presence of excess phenobarbital white sticky mass is formed. This particular phenomenon was observed exclusively on phenobarbital among various barbiturates studied. The plots at 25° in Fig. 4 were obtained from the analysis of supernatant solution. The other experimental methods, which were carried out appreciably below saturation, brought no anomalous result on phenobarbital as in the solubility method. This specific interaction must be caused from the same mechanism of the interaction between phenobarbital and polyethyleneglycol which was reported by Higuchi, *et al.*[21] In their study also such peculiar complexation was observed only on phenobaribital. Solubility measurement has been regarded for long time as the fundamental and direct method for solubilization study, but sometimes unusual results have been reported[22] and Donbrow, *et al.* pointed out that such problem is the disadvantage of the solubility method.[16]

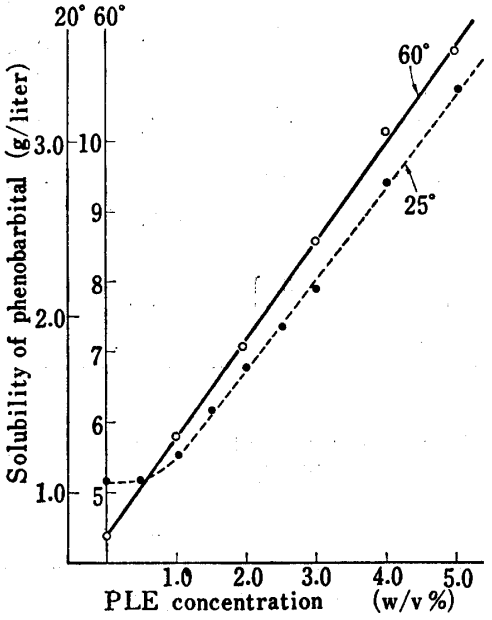

Fig. 4. Unordinary Solubility Increase at 25° and Ordinary Solubility Curve at 60° on Phenobarbital

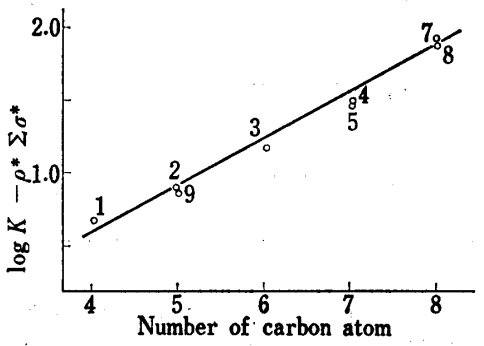

Fig. 5. Relationship between Number of Carbon Atoms of Substituted Groups and log $K - \rho^* \sum \sigma^*$

1—8: number in Table I 9: probarbital

Chemical Structure and Solubilization

As was seen in Table I the larger the carbon number of 5,5-substituted groups the larger the value K, which indicates that solubilization is affected primarily by N. About the effect of substituents on partition coefficient of barbiturate Lamb, *et al.*[23] and later Kakemi, *et al.*[24] interpreted quantitatively by equation 14.

21) T. Higuchi and J. Lack, *J. Am. Pharm. Assoc., Sci. Ed.*, 43, 465 (1954).
22) W.P. Evance, *J. Pharm. Pharmacol.*, 16, 323 (1963).
23) D.J. Lamb and L.E. Harris, *J. Am. Pharm. Assoc., Sci. Ed.*, 49, 583 (1960).
24) K. Kakemi, T. Arita and R. Konishi, *Chem. Pharm. Bull.* (Tokyo), 15, 1705 (1960).

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$$\log K = \delta N + \rho^* \sum \sigma^* + \log K_0 \quad (14)$$

In this equation K_0 is the partition coefficient of unsubstituted barbituric acid, σ^* is Taft's substituent consatnt,[25] ρ^* is the constant specific to partition, δ is the constant concerning with N. Similar calculation for value K obtained in this study may be significant because apparent stoichiometric relationship which is analogy to partition was found in general. Figure 5 is the relationship between log K-$\rho\sum^*\sigma^*$ and N, in which ρ^* was estimated to be -1.55 by the least square procedure. Table III is the comparison of values log K_0, ρ^* and δ obtained in this study and those in literature, which may elucidates the characteristic of micellar solubilization of barbiturates comparing with the partitions between H_2O and organic solvents. Value K_0, an indirectly estimated partition coefficient of unsubstituted barbituric acid, is large for polar solvent. Value K_0 for H_2O-PLE micelle partition is largest in Table III

Table III. Comparison of Constants Concernign Partition of Barbiturates

Phases partitioned	log K_o	ρ^*	δ	ΔE_c (cal/C)	Ref.
H_2O-PLE micelle	−0.65	−1.55	0.330	−458	This study
H_2O-isopentylacetate	−1.37	−2.06	0.392	−540	24)
H_2O-$CHCl_3$	−2.78	−3.44	0.465	−640	24)
H_2O-CCl_4	−3.85	−2.72	0.438	−605	24)
H_2O-isoctate+$CHCl_3$ (Vol. ratio 40:60)	−4.35	−5.38	0.546	−755	23)[a]

a) The definition of the partition coefficient in 23) is reciprocal to the others and the reculculated result is shown.

and has a value of 0.225, which indicates that barbituric acid is essentially hydrophilic. Value ρ^* which is the indication for the effect of polarity of substituents is smallest for micellar solubilization among the partitions shown. This suggests that in micelle the polarity of substituent is mitigated by the surroundings. Vale δ which represents the dependency on N is also smallest for micellar solubilization. These results suggest that the environment where 5,5-substituted groups are localized is not purely hydrocarbon. From δ value the standard free energy change per carbon, which is due to transfer of substituents from aqueous to organic solvent or micellar environment, is calculable. This free energy change, ΔE_c, is shown in Table III, which was calculated by equation 15.

$$\Delta E_c = 2.303RT\delta = 2.303RT\frac{\partial(\log K - \rho^*\sum\sigma^*)}{\partial N} \quad (15)$$

Value ΔE_c for H_2O- nonpolar organic solvent is close to −825 cal/carbon which was obtained form the transfer of long chain alkyl group from aqeous phase to hydrocarbon.[26] As the polarity of partitioned phase increases ΔE_c becomes small. Value ΔE_c for micellar solubilization is fairly smaller than that of partition between water and organic solvents. From these considerations it may be said that solubilized barbiturate molecule is not located in the central hydrocarbon phase but probably major portion is in the polyoxyethylene layer of micelle.

Our thanks due to Professor Dr. Hiroshi Kishimoto for his helpfull discussion.

25) R. W. Taft, Jr., "Steric Effects on Organic Chemistry," ed. by N.S. Newman, John Wiley & Sons Inc., New York (1956) Chaptor 13.
26) P. Mukerjee, *Advan. Colloid Interface Sci.*, **1**, 241 (1967).

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