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217. Kiichiro Kakemi, Takaichi Arita, Ryohei Hori, and Ryoji Konishi*1 : Absorption and Excretion of Drugs. XXXI.*2 On the Relationship between Partition Coefficients and Chemical Structures of Barbituric Acid Derivatives.*3

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The partition coefficients, which are known to be an influencing factor in physiological dispositions of drugs, were investigated systematically with three series of barbituric acid derivatives. From the results obtained, the concentration dependence of partitioning, and specific association of molecules in both aqueous and solvent phase were not observed. The latter was supported also by the computed degree of association obtained from the diffusion data. A logarithmic relationship between partition coefficients to two different organic solvents was found to exist, and this relationship provides a useful method or information to elucidate the characterizations of partitioning mechanism and their relation to the absorption phenomena. In respect to the effect of chemical structure on partition equilibrium, it was confirmed with all derivatives and solvent systems that the partition coefficients were predicted from the two parameters of the substituent at 5-position of barbituric acid ring, namely, the mass of the substituent in number of carbon atoms, and Taft's polar constant using the equation related to Hammett's rule.

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In the previous paper, gastric absorption of three series of barbituric acid derivatives in rats was examined and partition coefficient to organic solvent was proved to be a relatively accurate guide to the prediction of gastric absorption of the unionized forms of the drugs. Partition property of drugs is generally known to be an influencing factor not only in absorption processes, but also in other physiological dispositions such as distribution,[1] biotransformation,[2] excretion,[3] drug action,[4] etc. Previous studies on partition coefficient, however, have paid little attention to confirm the correlation with chemical structure and to clarify the relationship among the solvent systems and concentration dependence of partition equilibrium.

Partition coefficients of barbituric acid derivatives have been reported by several workers.[5~7] Lamb and Harris had successfully applied Taft's equation to the relation between chemical structure and partition coefficient using 5,5-disubstituted barbituric acid derivatives, but the solvent examined was only a mixture of chloroform (60%) and isooctane (40%). In order to make partition coefficient a reliable clue to the prediction of the gastric absorption, it was necessary to determine quantitatively the differences exerted by the kind of solvent and the structural features of partitioning molecules.

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*2 Part XXX : This Bulletin, **15**, 1534 (1967).

*3 Presented in part to the 13th Kinki Branch Meeting of Pharmaceutical Society of Japan (November, 1963).

1) B.B. Brodie, H. Kurz, L.S. Schanker : J. Pharmacol. Exptl. Therap., **130**, 20 (1960).
2) L.E. Gaudette, B.B. Brodie : Biochem. Pharmacol., **2**, 89 (1959).
3) M.D. Milne, B.H. Scriber, M.A. Crawford : Am. J. Med., **24**, 709 (1958).
4) E. Overton : Pflüg. Arch. Ges. Physiol., **92**, 115 (1902).
5) A.I. Briggs : J. Chem. Soc., **1956**, 2485.
6) T.C. Butler : J. Am. Pharm. Assoc., **44**, 367 (1955).
7) D.J. Lamb, L.E. Harris : *Ibid.*, **49**, 583 (1960).

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In this report, the partition coefficients of eighteen barbituric acid derivatives, consisting of eight 5,5-disubstituted barbituric acids (abbreviated as oxy series in this report.), six 1-methyl-5,5-disubstituted barbituric acids (N-methyl series) and four 5,5-disubstituted thiobarbituric acids (thio series), were estimated with various solvents, and applicability of the equation related to Hammett's rule was examined. Furthermore, the fundamental problems concerning concentration dependence in partition equilibrium and interrelationship of partition coefficients estimated in two different solvents were examined and correlated with the gastric absorption characteristics previously reported.

Experimental

Materials——Barbituric acid derivatives used in this paper were prepared as previously described.*2 The derivatives designated by an asterisk in Table ⅢB were donated by Dr. Sato,[8] Tanabe Pharmaceutical Co., Ltd., Osaka, Japan. All other materials were of analytical grade. The nomenclature and abbreviation is same as in the previous report.

Analytical Method——Ultraviolet spectrophotometry was used in all assays without solvent extraction.

Apparent Partition Coefficients——The same procedure as previously described was employed.

Result and Discussion

Table I represents the apparent molecular radii calculated from the previously reported diffusion data according to Stokes's equation (1), and the computed values of apparent molecular weights and degrees of association of barbituric acid derivatives in water using equation (2) and (3). ρ_0 value of 1.5[9] in equation (2) was employed. It should be emphasized from these results that there is no specific molecular association

$$r=\frac{KT}{6\pi\eta_0 D} \qquad (1)$$

$$M'=\frac{4}{3}\pi r^3\rho_0 N_0 \qquad (2)$$

$$n=\frac{M'}{M} \qquad (3)$$

r : radius of molecule
K : Boltzman constant
T : absolute temperature
η_0 : viscosity of medium
D : diffusion coefficient
M : molecular weight
M' : apparent molecular weight
ρ_0 : density of molecule
N : Avogadro's number
n : degree of association

of barbituric acid derivatives in aqueous solution. That the molecular states of barbituric acid derivatives are identical in both aqueous and solvent phase, was confirmed by examining the effect of concentration on apparent partition coefficient. Table Ⅱ shows the results obtained with barbital, which is a typical compound. No concentration dependence was observed over an initial concentration range of 50 μg./ml. to 500 μg./ml. both with chloroform and isopentyl acetate.

These suggest that barbital exists as a monomeric molecule in both aqeous and organic phase. This is well correlated with the experimental result that absorption of

8) Y. Sato : Nippon Kagaku Zasshi, **78**, 921 (1957).
9) E. Valko; Trans. Faraday Soc., **31**, 231 (1935).

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Table I. Molecular Radii and Degrees of Association calculated from Diffusion Coefficients[a)]

Barbiturate	Molecular radius (Å)	Apparent mol. wt.	Degree of association
Barbital	2.55	62.72	0.34
Probarbital	2.95	97.11	0.49
Allobarbital	4.12	264.54	1.27
Phenobarbital	3.09	111.60	0.48
Cyclobarbital	3.98	238.48	1.01
Pentobarbital	3.26	131.08	0.58
Amobarbital	3.60	176.51	0.78
Metharbital	2.75	78.69	0.40
Hexobarbital	3.68	188.54	0.80
Mephobarbital	3.08	110.54	0.45
Thiopental	3.45	155.33	0.64
Thiamylal	3.74	197.89	0.78

a) previously reported,*1 37° in water.

Table II. Effect of Concentration on Partition Coefficient of Barbital

Initial drug concentration in buffered phase (μg./ml.)	Partition coefficients (pH 1.1, 37°)	
	Chloroform	Isopentyl acetate
50	0.73	3.68
100	0.75	3.84
200	0.72	3.82
300	0.72	3.79
400	0.75	3.84
500	0.78	3.84

barbituric acid derivatives from rat stomach is a first order process without a characteristic concentration dependence. In assessing partition coefficient as an important factor in absorption of drug, it is necessary to characterize the differences or similarities between organic solvent and lipid component in a biological membrane. Very little, however, was referred to this problem in the reports supporting pH-partition hypothesis of drug absorption. At present, characterization of membrane lipids has not yet been established, and it was felt that a valuable clue may be drawn by comparing the partition coefficients in two different organic sovents. Collander[10)] derived experimentally a mathematical relationship between partition coefficients of some homologous compounds in two different solvent systems, which is generally expressed by equation (4). McGowan[11)] derived theoretically equation (5) exhibiting the relation of partition coefficient to Parachor of solute, and if the association of molecules or interaction with solvent were same in a homologous series of compounds, this equation becomes identical to the empirical equation by Collander as rearranged in the form of equation (6).

$$\log P_m = a \log P_n + b \quad (4)$$

$$\log P_m = K_m(P) + E_m \quad (5)$$

10) R. Collander : Acta. Chem. Scand., **4**, 1085 (1950).
11) J.C. McGowan : J. Appl. Chem., **1**, 120 (1951); **2**, 323, 651 (1952).

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$$\log P_m = \frac{K_m}{K_n} \log P_n + \left(\frac{E_m}{K_m} - \frac{E_n}{K_n} \right) \quad (6)$$

P_m, P_n : partition coefficient to solvent m and n

a, b : constant

K_m, K_n : constant of partitioning system

(P) : parachor

E_m, E_n : correction term betweem the system and drug

Patition coefficients of barbituric acid derivatives for various solvents are summarized in Table Ⅲ (A) and Table Ⅲ (B), including the previously reported data. Figs. 1, 2, and

Table Ⅲ. (A) Partition Coefficients[a] of Barbituric Acid Derivatives for Various Organic Solvents (A) Oxy Series

Barbiturate	CCl_4, ×10	$CHCl_3$	Isopentyl acetate	C_6H_6	*n*-Octyl alcohol
Barbital	0.35	0.72	3.82	0.17	4.54
Probarbital	0.61	1.60	8.81	0.26	9.42
5-Allyl-5-ethylbarbituric acid	0.63	1.31	9.59	0.31	8.57
Allobarbital	1.09	2.13	16.8	0.45	15.6
Phenobarbital	2.33	4.44	34.4	0.97	24.7
Pentobarbital	9.27	24.1	106	3.23	106
Amobarbital	21.6	53.0	134	5.17	117

a) pH 1.1, 37°

Table Ⅲ. (B) Partition Coefficients[a] of Barbituric Acid Derivatives for Various Organic Solvents (B) N-Methyl Series and Thio Series

Barbiturate	CCl_4, ×10	$CHCl_3$	Isopentyl acetate
Metharbital	20.2	34.7	20.6
N-Methylallobarbital	68.9	140	85.5
Mephobarbital	63.6	95.5	55.8
Hexobarbital	76.0	129	73.2
N-Methylcyclobarbital	308	301	187
N-Methylamobarbital	895	545	402
5-Allyl-5-ethyl-2-thiobarbituric acid*	227	305	824
5-(Cyclohexen-1-yl)-5-ethyl-2-thiobarbituric acid*	149	188	568
Thiopental	378	321	991
Thiamylal	689	688	1700

a) pH 1.1, 37°

3 represent the correlation of partition coefficients of barbituric acid derivatives for two different organic solvents. Fig. 1, in which the combination of chloroform and carbon tetrachloride was examined, indicates that a logarithmic relationship exists and equation (4) is applicable to the description of this relationship. In Fig. 2 and Fig. 3 where isopentyl acetate was plotted as one of the solvents, some deviations are seen among a group of oxy series, thio series, and N-methyl series, although the same logarithmic

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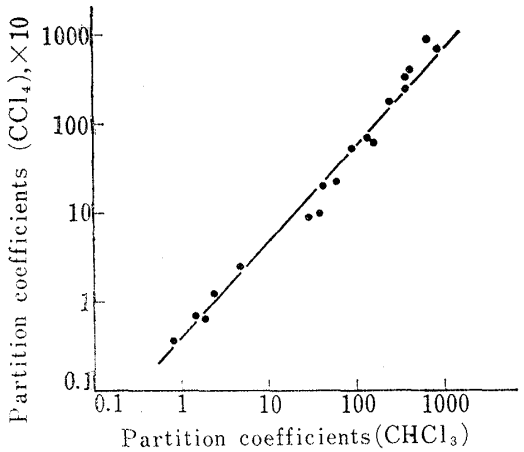

Fig. 1. Logarithmic Correlation between Partition Coefficients for Different Organic Solvents (Carbon Tetrachloride–Chloroform)
Data in Table III (A) and (B) were plotted.

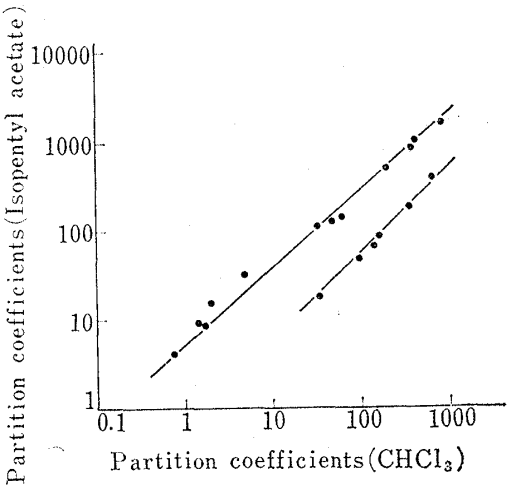

Fig. 2. Logarithmic Correlation between Partition Coefficients for Different Organic Solvents (Isopentyl Acetate–Chloroform)
Data in Table III (A) and (B) were plotted.

relationship hold in any one homologous series. This fact indicates that partition to chloroform or carbon tetrachloride is different in the contributing factor from isopentyl acetate. According to Sandell,[12] in the former solvents, contribution of hydrogen bonding in partition is less than the latter. If the assumption that lipids in the absorptive membrane behave as an organic solvent to bartituric acid derivatives was valid, there would exist a logarithmic relationship between partition coefficient to organic solvent and absorption, in which partition process is mediating. These consideration are in good agreement with the experimental results of absorption reported previously and in the following paper. Relation between partition equilibrium and chemical structure in barbituric acid derivatives was examined with three series according to the method of Lamb and Harris.[7] Lamb and Harris dealt with only oxy series and one solvent system and they derived equation (7) which was originally applied to methanolysis of *l*-menthyl esters by Pavelich and Taft.[13] An attempt was made to extend the application of this equation to N-methyl series and thio series which are both considered to be same as oxy series in respect to the effect of the substituent attached to 5-position in barbituric acid ring. The value of Taft's polar substituent constants were cited from the reported

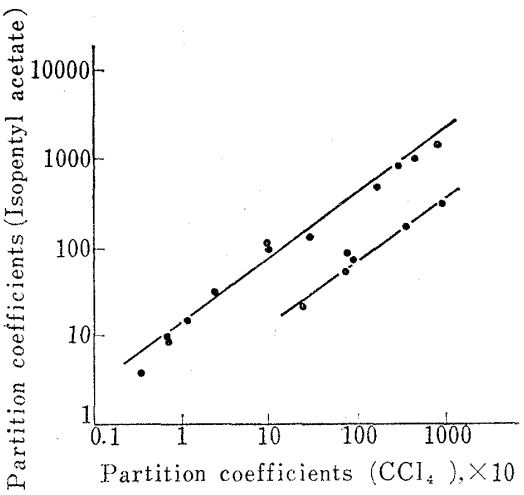

Fig. 3. Logarithmic Correlation between Partition Coefficients for Different Organic Solvents (Isopentyl Acetate–Carbon Tetrachloride)
Data in Table III (A) and (B) were plotted.

$$\log P=\rho\sum\sigma^*+\delta N+\log P_0 \qquad (7)$$

P, P_0 : partition coefficients of 5,5-disubstituted, and unsubstituted barbituric acid derivatives

ρ, δ : reaction constants

12) K.B. Sandell : Monatsh. Chem., **89**, 36 (1958).
13) W.A. Pavelich, R.W. Taft, Jr. : J. Am. Chem. Soc., **79**, 4935 (1957).

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σ^* : Taft's polar substituent constants

N : number of carbon atom in substituent

data,[7,14] except that for the substituent cyclohexen-1-yl, which was calculated using equation (8)[15] from the acid ionization constant of cyclohexenylacetic acid.[16]

$$\sigma^* = \frac{\log\left(\frac{k}{k_0}\right)}{\rho'} \qquad (8)$$

ρ' : reaction constant for ionization of carboxylic acids (1.721)

k_0 : ionization constant of acetic acid

k : ionization constant of appropriate carboxylic acid

Table Ⅳ summarizes partition coefficients to carbon tetrachloride, values for $\sum\sigma^*$ and N of oxy series derivatives. As shown typically in Fig. 4, the correlation between partition coefficients and number of carbon atoms in substituent was not satisfactory in all three series, but by determining the best fit of the data to equation (7) using standard least squares method[17] for a bivariant regression plane, the satisfactory linear relationship was found to exist in not only oxy series, but also in N-methyl and thio

Table Ⅳ. Taft's Constants, Number of Carbon Atoms in Substituents and Partition Coefficients

Barbiturate	Number of C Atom	$\sum\sigma^*$	log P_{CCl_4}
Barbital	4	−0.225	−0.456
Probarbital	5	−0.240	−0.215
5-Allyl-5-ethylbarbituric acid	5	−0.172	−0.201
Allobarbital	6	−0.114	0.037
Phenobarbital	8	0.040	0.367
Pentobarbital	7	−0.255	0.967
Amobarbital	7	−0.245	0.975
Secobarbital	8	−0.197	1.334

series. And furthermore, it was varified that this correlationship exists in all organic solvents examined as shown in Figs. 5, 6 and 7. From the results obtained, it is practically possible to predict quantitatively partition coefficients of an arbitrary barbituric acid derivative to a given organic solvent investigated in the present paper from the mass and Taft's polar constants of the substituents at 5-position. The values obtained for ρ^*, δ and P_0 of three series with various organic solvents are listed in Table Ⅴ. In all systems, ρ^* is negative, which means that the greater the electron-releasing potency of a substituent on the reaction site which is assumed carboxy group in 2- or 6-position of barbituric acid ring, the larger become the partition coefficients to a organic solvent. The reaction constants for this polarization effect ρ^* were relatively similar in all cases. However, the reaction constants for the substituent bulk were found to differ from

14) M.S. Newman : "Steric Effects in Organic Chemistry," 619 (1956). John Wiley & Sons, Inc., New York, N.Y.
15) *Idem* : *Ibid.*, p. 606.
16) A. Ellinger : Diss. Greifswald (1911).
17) see Appendix in the reference 13).

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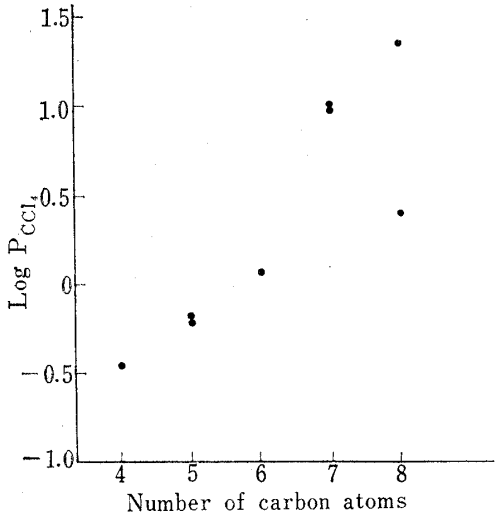

Fig. 4. Correlation between Partition Coefficients and Numbers of Carbon Atoms in Substituents

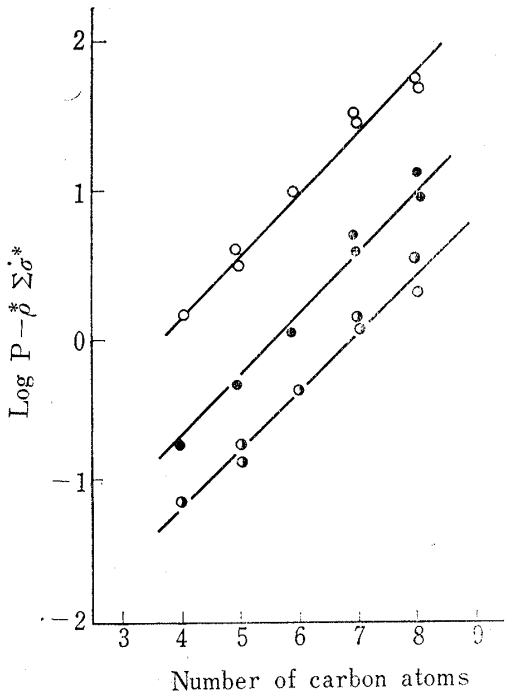

Fig. 5. Taft Type Relationship for Partition Coefficients of Oxy Series
○ Isopentyl acetate
● Chloroform
◑ Carbon tetrachloride

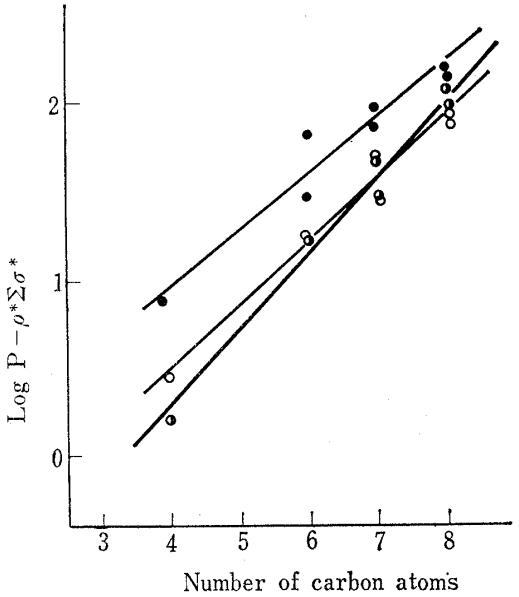

Fig. 6. Taft Type Relationship for Partition Coefficients of N-Methyl Series
○ Isopentyl acetate
● Chloroform
◑ Carbon tetrachloride

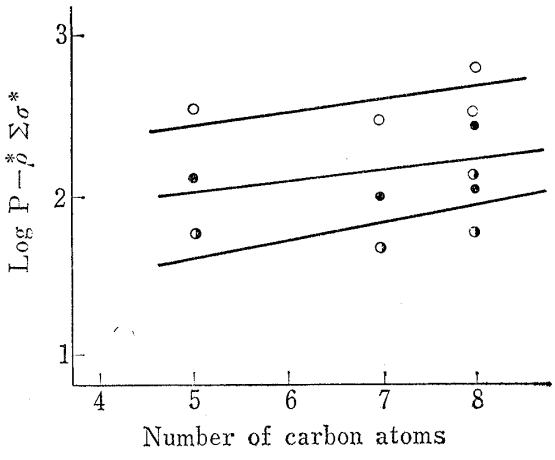

Fig. 7. Taft Type Relationship for Partition Coefficients of Thio Series
○ Isopentyl acetate
● Chloroform
◑ Carbon tetrachloride

series to series. Especially in thio series, the values of δ were smaller compared to those of oxy series and N-methyl series. This suggests that sulfur atom in thiobarbituric acid ring participates greatly in partition to organic solvents. This phenomenon is in agreement with the experiments of Mautner, *et al.*[18] demonstrated from the isosterism

18) H.G. Mautner, E.M. Clayton : J. Am. Chem. Soc., 81, 6270 (1959).

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viewpoints. Further experiments should be contemplated on the quantitative relationship between solvents, and the difference in partitioning into lipids of biophases and organic solvents.

Table V. Constants for Equation (7) calculated from Partition Coefficients

Barbiturate	Solvent	ρ^*	δ	P_0
Oxy series	CT	−2.72	0.438	0.14×10^{-3}
	CF	−3.44	0.465	1.63×10^{-3}
	IA	−2.06	0.392	42.4×10^{-3}
	BZ	−2.38	0.256	1.34×10^{-3}
	OA	−2.49	0.368	47.3×10^{-3}
N-Methyl series	CT	−5.38	0.444	2.38×10^{-3}
	CF	−3.44	0.316	411×10^{-3}
	IA	−3.83	0.334	170×10^{-3}
Thio series	CT	−3.65	0.066	2.24
	CF	−2.15	0.033	79.1
	IA	−2.19	0.035	211

ρ^*: Constants for Substituent Constant
δ: Constants for Carbon Atom Number in Substituent
P_0: Partition Coefficient of Non-Substituted Barbituric Acid
CT: Carbon Tetrachloride CF: Chloroform IA: Isopentyl Acetate
BZ: Benzene OA: *n*-Octyl Alcohol

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