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Studies on Absorption and Excretion of Drugs. XI.[1] Relation between Chemical Structure and Absorption Rate. (3). Intramolecular Interaction Constant, Additivity Rule and Prediction for Intestinal Absorption Rate Coefficient

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It was expected that the absorption rate coefficient of the foreign organic compound was, as a first approximation, a simple additive function of its substituent groups and that the absorption rate coefficient should be predicted from the additivity rule.

Furthermore, the following relationship for the intestinal absorption rate of foreign organic compounds was expected from the application of the activated diffusion model, the transition state theory and the formal treatment based on the extrathermodynamic relationships,

$$\log k_{\mathrm{RS}(i)\cdots\mathrm{S}(j)}/k_{\mathrm{RS}(i)\mathrm{S}(j)}=\text{constant}$$

where $k_{\mathrm{RS}(i)\cdots\mathrm{S}(j)}$ or $k_{\mathrm{RS}(i)\mathrm{S}(j)}$ denotes the absorption rate coefficient for the compound with or without the intramolecular interaction, respectively.

The perfusion experiments through the small intestine of anesthetized rats for various benzene derivatives with or without intramolecular interaction were carried out. The logarithmic plots of the residual ratio against the perfusion time gave straight lines and from the slopes the absorption rate coefficients were obtained.

The results indicate that the absorption rate coefficient can be essentially predicted from the additivity rule and that the values of $\log k_{\mathrm{RS}(i)\cdots\mathrm{S}(j)}/k_{\mathrm{RS}(i)\mathrm{S}(j)}$ for a given combination of interacting groups have a proper value which is called the intramolecular interaction constant.

In our previous paper,[1] we studied the effects of substituent groups on intestinal absorption rate of foreign organic compounds. From the results, it was found that there exist the substituent constants for the intestinal absorption rate coefficient under the fixed experimental condition. But in that paper, compounds having strong intramolecular interaction were excluded from the object of study.

The purposes of the present study are to investigate the additivity of the substituent constants and the prediction of the absorption rate coefficients and to study the effects of the intramolecular interaction on the absorption rate coefficient.

In the previous paper,[1] the substituent constant is related to the independent additive term of the activation free energy of transfer. Therefore, the additivity rule for the substituent constant may be expected. When benzene is chosen as the standard compound, logarithm of the ratio of the absorption rate coefficient for polysubstituted benzene (*e.g.* trisubstituted benzene, $\phi S_1S_2S_3$) to the absorption rate coefficient of benzene, ϕH, is shown in equation (1),

$$\begin{aligned}\log\frac{k_{\phi\mathrm{S}_1\mathrm{S}_2\mathrm{S}_3}}{k_{\phi\mathrm{H}}}&=\log\frac{k_{\phi\mathrm{S}_1\mathrm{S}_2\mathrm{S}_3}}{k_{\phi\mathrm{S}_1\mathrm{S}_2}}+\log\frac{k_{\phi\mathrm{S}_1\mathrm{S}_2}}{k_{\phi\mathrm{S}_1}}+\log\frac{k_{\phi\mathrm{S}_1}}{k_{\phi\mathrm{H}}}\\&=\mathrm{K}_{\mathrm{S}_3}+\mathrm{K}_{\mathrm{S}_2}+\mathrm{K}_{\mathrm{S}_1}\qquad(1)\end{aligned}$$

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[1] Part X: H. Nogami, M. Hanano, and H. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 580 (1968).
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where k_i is the absorption rate coefficient for compound i and $K_{S(i)}$ is the substituent constant for group S_i. Thus, logarithm of the absorption rate coefficient for benzene derivative may be calculated from equation (2), when the value of $k_{\phi H}$ and the substituent constants are known.

$$\log k_{\phi S_1 S_2 S_3} = \log k_{\phi H} + \sum_{i=1}^{3} K_{S(i)} \tag{2}$$

Now, let us consider the effect of intramolecular interaction on absorption rate coefficient. By the same way as in the previous paper, Danielli's activated diffusion model,[3] the transition state theory[4–10] and the formal treatment based on the extrathermodynamic relationships[11,12] are applied to the process of the transfer of compounds having strong intramolecular interaction from the luminal solution into the biophase as follows: We shall express the compound with the intramolecular interaction between substituent groups, S_i and S_j by $RS_i...S_j$ and the isomer without it by RS_iS_j. When each of them passes over a transition state in the transfer from the solution into the biophase, the processes are shown as formulae (3) and (4),

$$RS_i\cdots S_{j,\,in\,W} \longrightarrow RS_i\cdots S_{j,\,in\,X^{\neq}} \longrightarrow RS_i\cdots S_{j,\,in\,B} \tag{3}$$

$$RS_iS_{j,\,in\,W} \longrightarrow RS_iS_{j,\,in\,X^{\neq}} \longrightarrow RS_iS_{j,\,in\,B} \tag{4}$$

where $in\ W$, $in\ X^{\neq}$ and $in\ B$ denote "in the luminal aqueous solution," "in the transition state" and "in the biophase," respectively. The standard partial molar free enegy, $\bar{G}^{\ominus}$, for each compound in each state can be described in the form of the following equations,

$$\bar{G}^{\ominus}{}_{RS(i)\cdots S(j),\,in\,W} = G_{R\,in\,W} + G_{S(i),\,in\,W} + G_{S(j),\,in\,W} + I_{S(i)\cdots S(j),\,in\,W} \tag{5}$$

$$\bar{G}^{\ominus}{}_{RS(i)S(j),\,in\,W} = G_{R\,in\,W} + G_{S(i),\,in\,W} + G_{S(j),\,in\,W} \tag{6}$$

where G_i is an independent additive term for i and $I_{S(i)\cdots S(j)}$ is a term resulting from the intramolecular interaction between the groups, S_i and S_j. Thus, the activation free energies for the transfer of these compounds from the luminal solution into the biophase are shown in equations (7) and (8),

$$\begin{aligned} \Delta G^{\neq}{}_{RS(i)\cdots S(j)} &= \bar{G}^{\ominus}{}_{RS(i)\cdots S(j),\,in\,X^{\neq}} - \bar{G}^{\ominus}{}_{RS(i)\cdots S(j),\,in\,W} \\ &= \Delta G^{\neq}{}_{R} + \Delta G^{\neq}{}_{S(i)} + \Delta G^{\neq}{}_{S(j)} + \Delta I^{\neq}{}_{S(i)\cdots S(j)} \end{aligned} \tag{7}$$

$$\begin{aligned} \Delta G^{\neq}{}_{RS(i)S(j)} &= \bar{G}^{\ominus}{}_{RS(i)S(j),\,in\,X^{\neq}} - \bar{G}^{\ominus}{}_{RS(i)S(j),\,in\,W} \\ &= \Delta G^{\neq}{}_{R} + \Delta G^{\neq}{}_{S(i)} + \Delta G^{\neq}{}_{S(j)} \end{aligned} \tag{8}$$

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3) H. Davson and J.F. Danielli, "The Permeability of Natural Membranes," Cambridge, 1952, p. 324.

4) S. Glasstone, K.J. Laidler, and H. Eyring, "The Theory of Rate Processes," Chapter 1, 3, 4, 9, McGraw-Hill Co., 1941.

5) H. Eyring and E.M. Eyring, "Modern Chemical Kinetics," Chapter 2—4, Reinhold, 1963.

6) K.J. Laidler, "Reaction Kinetics," Vol. I, Chapter 2, Pergamon, 1963.

7) H. Eyring, J. Walter, and G.E. Kimball, "Quantum Chemistry," Chapter 16, John Wiley and Sons, 1944.

8) B.J. Zwolinski, H. Eyring, and C.E. Reese, *J. Phys. Colloid Chem.*, 53, 1426 (1949).

9) R.B. Parlin and H. Eyring, in "Ion Transport Across Membrane," ed. H.T. Clark, Academic Press, 1954, p. 103.

10) F.H. Johnson, H. Eyring, and M.J. Polissar, "The Kinetic Basis of Molecular Biology," Chapter 14, John Wiley and Sons, 1954.

11) J.E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reaction," Chapter 1—6, John Wiley and Sons, 1963.

12) A.I. Shatenshtein, in "Advances in Physical Organic Chemistry," ed. V. Gold, Vol. I, Academic Press, 1963, p, 193.

where $\Delta G^{\neq}$ is an independent additive term for the activation free energy and $\Delta I_{S(i)\cdots S(j)}$ is a term resulting from the intramolecular interaction between S_i and S_j.

According to the treatment based on the transition state theory, the following equations are described.

$$\frac{k_{RS(i)\cdots S(j)}}{k_{RS(i)S(j)}}=\exp\left[-\frac{\Delta G^{\neq}{}_{RS(i)\cdots S(j)}-\Delta G^{\neq}{}_{RS(i)S(j)}}{RT}\right] \tag{9}$$

$$\log\frac{k_{RS(i)\cdots S(j)}}{k_{RS(i)S(j)}}=-\frac{0.434}{RT}\Delta I^{\neq}{}_{S(i)\cdots S(j)} \tag{10}$$

To a given interaction, $\Delta I^{\neq}{}_{S(i)\cdots S(j)}$ should have a proper value. So, the intramolecular interaction constant, K_I, is defined by equation (11).

$$\log\frac{k_{RS(i)\cdots S(j)}}{k_{RS(i)S(j)}}=-\frac{0.434}{RT}\Delta I^{\neq}{}_{S(i)\cdots S(j)}=K_I \tag{11}$$

Experimental

Sample Solution——Eleven compounds tested here are listed in Table I and II. The sample solution contained 2 mM of the compound to be tested and 0.9% NaCl. All the sample solutions were adjusted the pH to 6.0 by the addition of NaOH or HCl solution.

Experimental Procedure——The experimental technique employed was the same as that described in our previous paper.[13] The volume of the perfusion solution was 50 ml for sulfanilamide and 200 ml for other compounds.

Analytical Method

a) Sulfanilamide: The sample solution (50 ml) was transferred into a 500 ml–measuring flask, the washings were also collected in this flask and the volume was made up to 500 ml with distilled water. One milliliter of this solution was pipetted into a 20 ml–measuring flask and added 1 ml of 3 N HCl and 4 drops of 0.2% $NaNO_2$. Ten minutes later, 10% $NH_4SO_3NH_2$ (4 drops) was added. Five minutes later, 0.2% N–(2–diethylaminoethyl)–1–naphthylamine solution (4 drops) was added. Then, the volume was made up to 20 ml with distilled water and the optical density was read on a spectrophotometer (Hitachi Co., Ltd., Model EPU–2) at 544 mμ.

b) Other samples: Two hundred milliliter of the sample solution was transferred into a 1 liter–measuring flask, the washings were also collected in the flask and the volume was made up to 1 liter with distilled water. The solutions were diluted with 0.1 N NaOH for compounds No. (44) to (46) and with 0.1 N HCl for compounds No. (47) to (53). The optical densities measured at 414 mμ for (44), at 432 mμ for (45), at 410 mμ for (46), at 273 mμ for (47), at 288 mμ for (48), at 259 mμ for (49), at 299 mμ for (50), at 226 mμ for (51), at 244 mμ for (52), at 241 mμ for (53).

Results and Discussion

The absorption rate coefficients obtained by the same method as in our previous paper[13] are shown in Table I and II.

By the estimations of pK_a values for these compounds with a potentiograph (Metrohm A.G. Model–E336), it was confirmed that the contribution of ionic form of each compound might be negligible at the virtual pH in absorption site. From these results, together with the data in the previous paper,[1] the substituent constants were obtained, as shown in Table III.

The results shown in Table III indicate that the effect of the second OH–group on the absorption rate coefficient is constant ($K_S=-0.05$) but is smaller than that of the first OH–group in the previous paper[1] ($K_S=-0.16$). It appears that an OH–group may decrease the effect of the other OH–group, but the cause of this phenomenon remains obscure.

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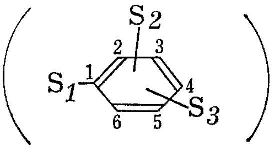
[13] H. Nogami, M. Hanano, and H. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 580 (1968).

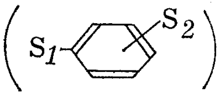
Table I. Absorption Rate Coefficients



No.	Compounds	Substituent groups			Absorption rate coefficients k
		S1	S2[a]	S3[a]	
44	*o*-Nitrophenol	$-NO_2$	-OH(2)		1.00
45	2-Hydroxy-5-methylnitrobenzene	$-NO_2$	-OH(2)	$-CH_3(5)$	1.34
46	*o*-Nitroaniline	$-NO_2$	$-NH_2(2)$		1.13[b] {1.17, 1.16, 1.07}
47	Resorcinol	-OH	-OH(3)		0.48
48	Hydroquinone	-OH	-OH(4)		0.45
49	Ethylprotocatechuate	$-COOC_2H_5$	-OH(3)	-OH(4)	0.85[b] {0.88, 0.81}
50	Salicylamide	$-CONH_2$	-OH(2)		0.77[b] {0.80, 0.74, 0.82, 0.70}

[a] The position is shown in the parentheses.
[b] This is a mean of the values in the brace.

Table II. Absorption Rate Coefficients



No.	Compounds	Substituent groups		Absorption rate coefficients k
		S1	S2[a]	
51	Benzocaine	$-COOC_2H_5$	$-NH_2(4)$	1.00[b] {0.82, 1.19}
52	Phenacetin	$-NHCOCH_3$	$-OC_2H_5(4)$	0.82
53	*p*-Acetaminophenol	$-NHCOCH_3$	-OH(4)	0.43[b] {0.41, 0.45}
54	Sulfanilamide	$-SO_2NH_2$	$-NH_2(4)$	0.14[b] {0.15, 0.13, 0.13}

[a] The position is shown in the parentheses.
[b] This is a mean of the values in the brace.

Table III. Values of Substituent Constant

Substituent groups -S	RS (No.)[a]	$\log k_{RS}$	RH (No.)[a]	$\log k_{RH}$	$\log (k_{RS}/k_{RH})=K_S$		
						(Means)	(Mean deviations)
-OH [II]	(15)	+0.03	(12)	+0.06	−0.03	−0.05	±0.02
	(47)	−0.32	(34)	−0.27	−0.05		
	(48)	−0.35	(34)	−0.27	−0.08		
$-CH_3$	(37)	−0.16	(34)	−0.27	+0.11	+0.12	±0.01
	(45)	+0.13	(44)	0.00	+0.13		
$-COOC_2H_5$	(40)	0.00	(34)	−0.27	+0.27	+0.24	±0.03
	(49)	−0.07	(35)	−0.28	+0.21		

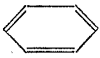
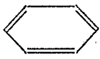
[a] Compounds represented by No. (1) to No. (24) are shown in Part IX of this series of studies, No. (25) to No. (43) shown in Part X and No. (44) to No. (54) shown in this paper.

If the previous considerations are reasonable, the value of $\log k_{\phi H}$ which is obtained from the absorption rate coefficient for a monosubstituted derivative of benzene and the substituent constant by using the following equation should be a proper value.

$$\log k_{\phi H}=\log k_{\phi S}-K_S \qquad (12)$$

In order to check this point, the calculated values from equation (12) are listed in Table IV.

Table IV. Values of $\log k_{\phi H}$

ϕS	$\log k_{\phi S}$	-S	K_S	$\log k_{\phi H}=\log k_{\phi S}-K_S$	(Means)	(Mean deviations)
-OH	-0.27	-OH [I]	-0.16	-0.11	-0.12	± 0.02
-CHO	$+0.09$	-CHO	$+0.23$	-0.14		
$-NO_2$	$+0.11$	$-NO_2$	$+0.22$	-0.11		
$-COOCH_3$	$+0.16$	$-COOCH_3$	$+0.26$	-0.10		

The results indicate that $\log k_{\phi H}$ is constant.

Then, from the value of $\log k_{\phi H}$ and the substituent constants, the absorption rate coefficients for drugs which have never been used in this study can be predicted by using the additivity rule expressed in equation (2). The calculated values are shown in Table V.

Table V. Prediction of k-Values

Compounds	$\log k_{\phi H}$	S_1	K_{S_1}	S_2	K_{S_2}	$\log k_{calc.}$	$k_{calc.}$
Benzocaine	-0.12	$-COOC_2H_5$	$+0.24$	$-NH_2$	-0.15	-0.03	0.93
Phenacetin	-0.12	$-NHCOCH_3$	-0.16	$-OC_2H_5$	$+0.21$	-0.07	0.85
p-Acetaminophenol	-0.12	$-NHCOCH_3$	-0.16	-OH	-0.16	-0.44	0.36
Sulfanilamide	-0.12	$-SO_2NH_2$	-0.82	$-NH_2$	-0.15	-1.09	0.08

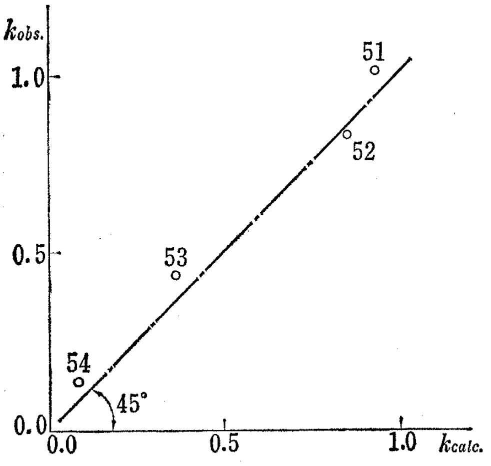


Fig. 1. Comparison of Calculated Values with Observed Values

51 : Benzocaine; 52 : Phenacetin;
53 : *p*-Acetaminophenol; 54 : Sulfanilamide

The comparison of calculated values with observed values is shown in Fig. 1.

The results indicate that the calculated values agree with the observed values. Therefore, it is concluded that under a fixed condition there exists the additivity rule for the intestinal absorption rate coefficient.

In equation (10) and (11), it is expected that the difference between the absorption rate coefficients for a compound with intramolecular interaction and for its isomer without it may be proper to the interaction. The values of $\log k_{RS(i)\cdots S(j)}/k_{RS(i)S(j)}$ can be calculated by using the experimentally obtained value for $k_{RS(i)\cdots S(j)}$ and the calculated value from equation (2) for $k_{RS(i)S(j)}$. These values are shown in Table VI.

These results indicate that when the interacting groups, S_i and S_j are fixed, $\log k_{RS(i)\cdots S(j)}/k_{RS(i)S(j)}$ has a proper value.

The intramolecular interaction constant is related to an effect on the activation free energy in the process of intestinal absorption by equation (11). In this process, as discussed in the previous papers,[1,13] the breakage of the hydrogen bond to the surrounding water molecules may be an important factor. The compound with an intramolecular interaction has

TABLE VI. Values of Interaction Constant

Interaction $S_i \cdots S_j$	$RS_i \cdots S_j$ (No.)[a]	$\log k_{RS(i) \cdots S(j)}$	$\log (k_{RS(i)S(j)})_{calc.}$	$\log k_{RS(i) \cdots S(j)}/k_{RS(i)S(j)\,calc.} = K_I$		
					(Means)	(Mean deviations)
-CHO$\cdots$HO-	(12)	+0.06	−0.05	+0.11	+0.12	±0.01
	(15)	+0.03	−0.10	+0.13		
-$NO_2 \cdots$HO-	(44)	0.00	−0.06	+0.06	+0.07	±0.01
	(45)	+0.13	+0.06	+0.07		
-OH$\cdots$HO-	(35)	−0.28	−0.33	+0.05	+0.04	±0.02
	(49)	−0.07	−0.09	+0.02		
-$CONH_2 \cdots$HO-	(50)	−0.11	−0.51	+0.40	+0.40	……
-$COOCH_3 \cdots$HO-	(18)	+0.16	−0.02	+0.14	+0.14	……
-$NO_2 \cdots H_2N$-	(46)	+0.05	−0.05	+0.10	+0.10	……

a) Compounds represented by No. (1) to No. (24) are shown in Part IX of this series of studies, No. (25) to No. (43) are shown in Part X, and No. (44) to No. (54) shown in this paper.

a tendency toward internal satisfaction of hydrogen bonding capacity so that the interaction with surrounding water may be reduced, and consequently the energy per mole required for the breakage of the solute–solvent interaction may be reduced. So, it is expected that there may be some relationship between the effect of the intramolecular interaction on the activation free energy and the intramolecular hydrogen bond forming power. Of course it is not strictly, because the activation free energy in this process contains the terms for other than the breakage of the interaction with surrounding water. But, as first approximation the intramolecular interaction constant, K_I, may be related to the intramolecluar hydrogen bond forming power.

From the studies on infrared light absorption,[14,15] the decreasing order of the intramolecular hydrogen bond forming powers is estimated as follows:
(-CHO...HO-), (-$COOCH_3$...HO), (-NO_2...HO), (-OH...HO-). This essentially agrees with the order of the values of the interaction constant in Table VI.

From the above results, together with the conclusion of the previous paper, three effects of substituent groups on the intestinal absorption rate coefficient *i.e.* the substituent constant, the intramolecular interaction constant and the additivity rule were experimentally confirmed.

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14) M. Tsuboi, *Bull. Chem. Soc. Japan*, **25**, 60 (1952).

15) S. Seki, H. Chihara, and K. Suzuki, "Suiso Ketsugō" in "Iwanami Kōza Gendai Kagaku," VI G, Iwanami, 1956, p. 24.