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van der Waals Volume and the Related Parameters for Hydrophobicity in Structure-Activity Studies[1]

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The correlations of Hansch's hydrophobic constant (log P) with van der Waals volume (V_W) and with van der Waals surface area (A_W) were studied using 60 molecules including apolar organic compounds and inert gases, and superiority of V_W over A_W was recognized. From the obtained highly significant relation of V_W to log P and a great number of log P values for polar molecules, hydrophilic effects (V_H) of various polar groups were evaluated. These parameters (V_W and V_H) could be satisfactorily applied to the regression analysis of water-solubility of 156 organic liquids and frog muscle narcosis of 39 drugs. These parameters may especially be useful for drug design because they can easily be calculated for a wide variety of molecules.

Hydrophobicity is one of the most important characters affecting the action of drugs. The previous paper[1b] has described that on the basis of the Hildebrand-Scott solubility theory[3] the hydrophobicity of apolar molecules may be correlated with their volume, and demonstrated that Hansch's hydrophobic constant[4] (log P) can be factored into two intrinsic components, *i.e.* molecular volume and polar effect. In the paper[1b] parachor has been used as a parameter for molecular volume. However, the physical meaning of parachor seems somewhat obscure in respect to a measure of volume. On the other hand, Namethy and Scheraga[5] have pointed out that a dominant energy source for hydrophobic behavior of solutes in water is the cluster of water molecules surrounding the solute surface. This suggests that hydrophobicity of molecules is dependent on their surface area.

In this paper, therefore, the correlations of log P with van der Waals volume (V_W) and with van der Waals surface area (A_W) have been studied using 60 molecules including apolar organic compounds and inert gases, and superiority of V_W over A_W has been recognized in the linearity with log P. Further, from the obtained relation of V_W to log P and a great number of log P values for polar molecules, hydrophilic effects (V_H) of various polar groups have been evaluated. These parameters have been successfully applied to the regression analysis of some physicochemical and pharmacological data.

Method

van der Waals Volume (V_W)——Spherical shapes were assumed for all atoms according to Bondi,[6] because of the absence of generally accepted pear shapes. The values of van der Waals radii used and calculated volume of atoms are listed in Table I. Since van der Waals radii are greater than covalent radii, a correction for sphere overlapping due to covalent bonding between atoms was needed for the calculation of V_W for polyatomic molecules. The covalent bond lengths and correction values are tabulated in Table II, along with a correction for branching, of which the details will be described in the text.

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[1] *a*) This forms Part II of "Quantitative Structure-Activity Studies"; *b*) Part I: I. Moriguchi, *Chem. Pharm. Bull.* (Tokyo) **23**, 247 (1975).

[2] Location: *Shirokane, Minato-ku, Tokyo*, **108**, *Japan*.

[3] L.P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1970, p. 248.

[4] logarithm of partition coefficient between octanol and water: C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).

[5] G. Nemethy and H.A. Scheraga, *J. Chem. Phys.*, **36**, 3401 (1962); *idem*, *J. Phys. Chem.*, **66**, 1773 (1962).

[6] A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).

Table I. van der Waals Radius and Volume of Atoms

Atom	Radius, Å	Sphere volume, 10^2 Å^3	Atom	Radius, Å	Sphere volume, 10^2 Å^3
C	1.7[a]	0.206	I aliphatic	2.0[b]	0.335
H	1.1[b]	0.056	aromatic	2.1[b]	0.388
N	1.5[a]	0.141	B	2.1[d]	0.388
O	1.4[a]	0.115	He	1.2[d]	0.072
S	1.8[c]	0.244	Ne	1.6[d]	0.171
F	1.4[a]	0.115	Ar	1.9[d]	0.287
Cl aliphatic	1.7[b]	0.206	Kr	2.0[d]	0.335
aromatic	1.8[b]	0.244	Xe	2.2[e]	0.446
Br aliphatic	1.8[b]	0.244			
aromatic	1.9[b]	0.287			

[a] round value from L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, 1960, Chapter VII

[b] round value from the intermolecular contact radii in Table III or XII in ref. *c*.

[c] A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964)

[d] round value from J.A. Dean (ed.), "Lange's Handbook of Chemistry," McGraw-Hill Book Co., New York, 1973, pp. 3—118

[e] intermolecular contact radius, Chemical Society of Japan (ed.), "Kagaku Benran," Maruzen Co., Tokyo, 1966, p. 1259

Table II. Correction Values of van der Waals Volume for Sphere Overlapping Due to Covalent Bonding and for Branching

Bond	Bond length,[a] Å	Correction value,[b] 10^2 Å^3	Bond	Bond length,[a] Å	Correction value,[b] 10^2 Å^3
C-C	1.5	−0.078	O-H	1.0	−0.034
C-H	1.1	−0.043	O-B	1.5	−0.079
C-N	1.4	−0.065	S-H	1.3	−0.040
C-O	1.4	−0.056	S-S	2.0	−0.062
C-S	1.8	−0.066	S-F	1.6	−0.052
C-F	1.4	−0.056	C=C	1.3	−0.094
C-Cl(aliphatic)	1.8	−0.058	C=N	1.3	−0.072
C-Cl(aromatic)	1.8	−0.066	C=O	1.2	−0.068
C-Br(aliphatic)	1.9	−0.060	C=S	1.6	−0.081
C-Br(aromatic)	1.9	−0.068	N=N	1.2	−0.061
C-I (aliphatic)	2.1	−0.063	N=O	1.2	−0.053
C-I (aromatic)	2.1	−0.072	S=O	1.5	−0.057
C-B	1.6	−0.113	C≡C	1.2	−0.101
H-H	0.7	−0.030	C≡N	1.2	−0.079
N-H	1.0	−0.038	C=C (aromatic)	1.4	−0.086
N-N	1.4	−0.050	Branching for saturated bond except bonding with H		−0.05
N-O	1.4	−0.042			
N-S	1.6	−0.061			

[a] round value from Chemical Society of Japan (ed.), "Kagaku Benran," Maruzen Co., Tokyo, 1966, p. 1203

[b] negative value of geometrically calculated volume of overlapping part of two spheres

Example

V_W for bromopropane (C_3H_7Br) $= 0.206 \times 3$ (for 3C) $+ 0.056 \times 7$ (for 7H) $+ 0.244$ (for Br) $- 0.078 \times 2$ (for 2C-C) $- 0.043 \times 7$ (for 7C-H) $- 0.060$ (for C–Br) $= 0.737$ (10^2Å^3)

van der Waals Surface Area (A_W)——Spherical shapes were also assumed for all atoms. The values of van der Waals radii and bond lengths used in the calculation were the same as those in the case of V_W. The cut-off surface area due to sphere overlapping by covalent bonding between atoms was similarly corrected for polyatomic molecules.

Regression Analysis——Correlations and regression equations were calculated with JEOL digital computer, model JEC-7E.

Results and Discussion

Hydrophobicity of Apolar Molecules

a) **Comparison of V_W with A_W in the Correlation to log P**——The values of V_W and A_W with 60 apolar molecules (*e.g.* innert gases, hydrocarbons, and alkyl and aryl halides) have been calculated. The values are listed in Table III, together with log P which has been

TABLE III. Constants Relating to Hydrophobicity for 60 Apolar Molecules

No.	Name	log P		$V_W$$^{c)}$ 10^2Å^3	$V_W$$^{d)}$ 10^2Å^3	$A_W$$^{c)}$ 10^2Å^2	$D_1$$^{e)}$	$D_2$$^{f)}$
		Obsd.$^{a)}$	Calcd.$^{b)}$					
1	helium	0.28$^{g)}$	0.315	0.072	0.072	0.181	0	0
2	neon	0.28$^{g)}$	0.583	0.171	0.171	0.322	0	0
3	hydrogen	0.45$^{g)}$	0.342	0.082	0.082	0.200	0	0
4	nitrogen	0.67$^{g)}$	0.719	0.221	0.221	0.396	0	0
5	argon	0.74$^{g)}$	0.898	0.287	0.287	0.454	0	0
6	krypton	0.89$^{g)}$	1.028	0.335	0.335	0.503	0	0
7	methane	1.09$^{g)}$	0.819	0.258	0.258	0.443	0	0
8	ethylene	1.13$^{g)}$	1.123	0.370	0.370	0.582	0	0
9	carbon tetrafluoride	1.18$^{g)}$	1.218	0.442	0.342	0.699	2	0
10	xenon	1.28$^{g)}$	1.329	0.446	0.446	0.608	0	0
11	methyl iodide	1.69	1.521	0.517	0.517	0.742	0	0
12	thiophene	1.81	2.077	0.722	0.722	0.914	0	0
13	chloroform	1.97	1.867	0.663	0.613	0.959	1	0
14	ethyl iodide	2.00	1.938	0.671	0.671	0.942	0	0
15	1-bromopropane	2.10	2.117	0.737	0.737	1.054	0	0
16	benzene	2.13	2.283	0.798	0.798	1.014	0	0
17	fluorobenzene	2.27	2.407	0.844	0.844	1.078	0	0
18	1-fluoropentane	2.33	2.613	0.920	0.920	1.307	0	0
19	1-chlorobutane	2.39	2.437	0.855	0.855	1.215	0	0
20	1,5-hexadiene	2.45	2.678	0.944	0.944	1.321	0	0
21	pentane	2.50$^{h)}$	2.489	0.874	0.874	1.243	0	0
22	toluene	2.69	2.700	0.952	0.952	1.214	0	0
23	*o*-xylene	2.77	2.977	1.106	1.106	1.414	0	1
24	trifluoromethylbenzene	2.79	2.974	1.090	0.990	1.406	2	0
25	chlorobenzene	2.84	2.730	0.963	0.963	1.214	0	0
26	indene	2.92	3.139	1.114	1.114	1.310	0	0
27	styrene	2.95$^{i)}$	3.003	1.064	1.064	1.353	0	0
28	2-chloro-1-ethylbenzene	2.95	3.343	1.241	1.241	1.586	0	1
29	bromobenzene	2.99	2.841	1.004	1.004	1.257	0	0
30	2-bromo-1-ethylbenzene	3.09	3.441	1.277	1.277	1.625	0	1
31	benzothiophene	3.12	3.236	1.150	1.150	1.344	0	0
32	ethylbenzene	3.15	3.117	1.106	1.106	1.414	0	0
33	*p*-xylene	3.15	3.117	1.106	1.106	1.414	0	0
34	azulene	3.20	3.421	1.218	1.218	1.436	0	0
35	*m*-xylene	3.20	3.117	1.106	1.106	1.414	0	0
36	allylbenzene	3.23	3.421	1.218	1.218	1.553	0	0
37	iodobenzene	3.25	3.104	1.101	1.101	1.349	0	0
38	*m*-chlorotoluene	3.28	3.147	1.117	1.117	1.414	0	0
39	*p*-chlorotoluene	3.33	3.147	1.117	1.117	1.414	0	0
40	1-phenyl-1-propene	3.35	3.421	1.218	1.218	1.553	0	0
41	naphthalene	3.37	3.421	1.218	1.218	1.436	0	0
42	*o*-dichlorobenzene	3.38	3.177	1.128	1.128	1.414	0	0
43	*m*-dichlorobenzene	3.38	3.177	1.128	1.128	1.414	0	0
44	*p*-dichlorobenzene	3.39	3.177	1.128	1.128	1.414	0	0
45	*o*-chlorotoluene	3.42	3.147	1.117	1.117	1.414	0	0
46	γ-phenylpropyl chloride	3.55	3.760	1.395	1.395	1.786	0	1
47	isopropylbenzene	3.66	3.485	1.260	1.210	1.614	1	0
48	propylbenzene	3.68	3.535	1.260	1.260	1.614	0	0

No.	Name	log *P* Obsd.[a]	log *P* Calcd.[b]	V_W[c] $10^2Å^3$	V_W[d] $10^2Å^3$	A_W[c] $10^2Å^2$	D_1[e]	D_2[f]
49	γ-phenylpropyl bromide	3.72	3.858	1.431	1.431	1.825	0	1
50	2-thienylbenzene	3.74[i]	3.957	1.416	1.416	1.671	0	0
51	benzene hexachloride	3.78	3.519	1.734	1.434	2.232	6	0
52	γ-phenylpropyl iodide	3.90	4.096	1.519	1.519	1.913	0	1
53	biphenyl	4.09	4.163	1.492	1.492	1.785	0	0
54	*t*-butylbenzene	4.11	3.852	1.414	1.314	1.814	2	0
55	diphenylmethane	4.14	4.441	1.646	1.646	1.985	0	1
56	fluorene	4.18	4.299	1.542	1.542	1.742	0	0
57	anthracene	4.45	4.559	1.638	1.638	1.858	0	0
58	phenanthrene	4.46	4.559	1.638	1.638	1.858	0	0
59	*p*-di(trichloromethyl)benzene	4.62	5.112	1.916	1.716	2.446	4	0
60	bibenzyl	4.79	4.858	1.800	1.800	2.185	0	1

a) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971), unless otherwise noted.
b) using Eq. 6
c) uncorrected for branching
d) corrected for branching
e) dummy parameter for branching
f) dummy parameter for intramolecular hydrophobic bonding
g) C. Hansch, A. Vittoria, C. Silipo, and P.Y.C. Jow, *J. Med. Chem.*, **18**, 546 (1975).
h) ref. 9
i) C. Hansch, A. leo, S.H. Unger, K.H. Kim, D. Nikaitani, and E.J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).

generally utilized as an experimental measure of hydrophobicity. From the data, Eq. 1 and 2 have been formulated where the figures in parenthes are the 95 percent confidence intervals.

$$\log P = 2.51(\pm 0.13)V_W + 0.23(\pm 0.15) \qquad n=60,\ r=0.980,\ s=0.228 \qquad (1)$$

$$\log P = 2.17(\pm 0.15)A_W - 0.04(\pm 0.21) \qquad n=60,\ r=0.966,\ s=0.295 \qquad (2)$$

n is the number of data points used in deriving the equations, r is the correlation coefficient, and s is the standard deviation. V_W and A_W are given in units of 10^2 Å^3 and 10^2 Å^2, respectively, throughout the report. The regression equations are both highly significant. There was seemingly no distinct difference between V_W and A_W in correlation to log *P*. However, this might arise from a high correlation of V_W with A_W (r=0.992). Therefore, a *t*-test for the difference between the two correlation coefficients (*i.e.* r_{12} for log *P* *v.s.* V_W and r_{13} for log *P* *v.s.* A_W) has been made by using the following equation.[7]

$$t = \frac{(r_{12}-r_{13})\sqrt{(n-3)(1+r_{23})}}{\sqrt{2(1-r_{12}^2-r_{13}^2-r_{23}^2+2r_{12}r_{13}r_{23})}} = 4.26 \qquad (3)$$

Here, r_{23} is the correlation coefficient between V_W and A_W.

The *t*-value obtained is significant at the 0.1 percent level ($t_{0.001}=3.47$). Accordingly, the superiority of V_W over A_W in the correlation with log *P* is clear.

Thus, it can be concluded with apolar molecules that hydrophobicity is linearly related to van der Waals volume.

b) Effects of Branching and Intramolecular Hydrophobic Bonding on Hydrophobicity——For the purpose to estimate the effects of branching and intramolecular hydrophobic bonding, dummy parameters (D_1 and D_2) have been assumed. D_1 and D_2 indicate the number of branching and of hydrophobic bonding in a molecule, respectively (see Table III). The relation of V_W and the dummy parameters to log *P* has been formulated as Eq. 4. In the equation, the figures in parenthes after the parameters are the Student *t*-values which are

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[7] N.M. Downie and R.W. Heath, "Basic Statistical Methods," Harper & Row, New York, 1974, p. 228. The following data were used for the calculation: $n=60$, $r_{12}=0.9800$, $r_{13}=0.9662$, and $r_{23}=0.9920$.

$$\log P = 2.71(\pm 0.11)V_w(48.36) - 0.14(\pm 0.05)D_1(6.11)$$
$$- 0.37(\pm 0.14)D_2(5.27) + 0.12(\pm 0.11)$$
$$n=60,\ r=0.990,\ s=0.166 \qquad (4)$$

necessary for the test of statistical significance of the parameters in the multiple regression analysis. The *t*-values indicate that the effects of branching and intramolecular hydrophobic bonding are both highly significant ($p > 0.999$). Equation 4 can be rewritten as

$$\log P = 2.71(V_w - 0.05D_1 - 0.14D_2) + 0.12 \qquad (4')$$

Consequently, −0.05 (10^2 Å^3) and −0.14 (10^2 Å^3) have been tempolarily taken as the effects of branching and intramolecular hydrophobic bonding, respectively, although it is not warranted that all kinds of branching or intramolecular hydrophobic bonding have the same hydrophobic effect.

It is generally known that the boiling point of a branched isomer is lower than that of the unbranched molecule. The relation between boiling point at 1 atm and V_W of 20 unbranched alkanes having 1—20 carbon atoms has been formulated as Eq. 5.

$$V_w = 0.09(\pm 0.01)(Bp.10^{-2})^2(30.82) + 0.39(\pm 0.02)Bp.10^{-2}(49.08)$$
$$+ 0.69(\pm 0.02) \qquad n=20,\ r=0.9995,\ s=0.027 \qquad (5)$$

Using this equation, apparent V_W reduction due to branching has been calculated with 66 branched alkanes having 4—9 carbon atoms from their boiling points.[8] The average V_W reduction per branch has been 0.044 (standard deviation 0.016). This value agrees well wit hthe effect of branching estimated from the linearity of V_W to log *P*.

Consequently, the correction for branching (−0.05 per branch) will be applied hereafter to the calculation of V_W, because the validity of the correction is not limited to hydrophobic phenomena. On the other hand, the treatment of the effect of intramolecular hydrophobic bonding remains unclear. This effect will tentatively be included among a "hydrophilic effect" (V_H) described in the next section.

Thus, Eq. 4′ has been revised as Eq. 6, in which V_W includes the effect of branching and V_W

$$\log P = 2.71(V_w - V_H) + 0.12 \qquad (6)$$

is the correction for intramolecular hydrophobic bonding in the case of apolar molecules. For apolar molecules, since the V_H value is generally zero or relatively small, a good linear-relation is expected between V_W and log *P* (Fig. 1).

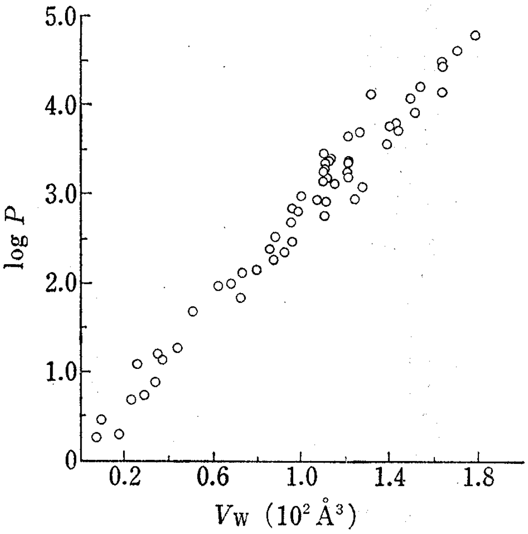

Fig. 1. Relation of V_W to log *P* for 60 Apolar Molecules

(V_W is corrected for branching.)

Hydrophobicity of Polar Molecules

For polar molecules, the relation between V_W and log *P* is not expected to be linear owing to solute-solvent and/or solute-solute interactions. Hence, in a similar manner as the case of parachor,[1b] "hydrophilic effect," V_H, has been evaluated from V_W and log *P* by utilizing Eq. 6, as follows.

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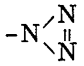
[8] R.R. Dreisbach, "Physical Properties of Chemical Compounds-II," American Chemical Society, Washington, 1959, p. 11.

$$V_{\mathrm{H}} = V_{\mathrm{w}} - (\log P - 0.12)/2.71 \qquad (7)$$

Thus, the values of V_{H} for a wide variety of hydrophilic groups or moieties have been estimated by using a number of homologous or single polar molecules of which the log P values are available. The obtained V_{H} values are listed in Table IV.

TABLE IV. Hydrophilic Effect

Group	Aliphatic			Aromatic		
	V_{H} 10^2Å^3	SD	Number of data[a]	V_{H} 10^2Å^3	SD	Number of data[a]
$-B(OH)_2$				0.59		1
$-C\equiv C-$	0.11		1	0.14		1
$-C\equiv N$	0.60	0.02	3	0.44		1
-CHO				0.47		1
$>C=O$	0.65	0.06	6	0.56	0.02	2
$-CO_2-$	0.56	0.07	14	0.41	0.04	4
$-CON<$	1.07	0.08	3	0.86	0.01	3
-CONHCO-	1.16		1	0.77		1
$-CONHCON<$	0.99	0.05	2			
-CONHCONHCO-	1.29	0.16	9			
-CONHCSNHCO-	0.92	0.04	3			
$-N<$ (*prim.* amines)	0.59	0.06	14	0.59	0.01	8
(*sec.* or *tert.* amines)				0.45	0.09	9
$-N=$				0.48	0.05	13
$>NCO_2-$	0.87		1	0.66		1
$>NCON<$				1.03	0.11	4
$>NCSN<$				1.10	0.03	2
$-N=N-$				0.30		1
$-NHNH_2$				0.59		1
				0.02		1
$\geqslant N \rightarrow O$				0.70		1
$-NO_2$	0.54	0.06	5	0.31	0.02	7
=NOH	0.64		1	0.49		1
-O-	0.48	0.07	4	0.29	0.03	3
-OH	0.54	0.07	17	0.32	0.04	14
-S-	0.23		1	0.18		1
-SH	0.10		1	0.09		1
$-SO_2-$				1.07	0.08	3
$-SO_2N<$				1.08	0.09	9
$-SO_2NHCO-$				1.09	0.11	6
Heteronuclei in a heteroaromatic ring						
$-\dot{N}=$				0.48	0.05	13
$-\underset{\mid}{\ddot{N}}-$				0.34	0.03	6
$-\ddot{O}-$				0.10		1
$-\dot{N}=,\ -\dot{N}=$				0.80	0.13	5
$-\dot{N}=,\ -\underset{\mid}{\ddot{N}}-$				0.54	0.07	6
$-\dot{N}=,\ -\ddot{O}-$				0.52	0.06	2
$-\dot{N}=,\ -\dot{N}=,\ -\underset{\mid}{\ddot{N}}-$				0.52		1
(For ring $-\ddot{S}-$, no correction is required)						
Intramolecular hydrophobic bonding					−0.14	

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[a] Number of log P dtaa used for calculation of V_{H}. The log P data were taken from A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).

As seen in Table IV, the standard deviation (SD) of V_H for each group is considerably small. This indicates that V_H value is nearly constant for homologous compounds bearing the same hydrophilic group, and therefore that the proposal of V_H constant is reasonable. The V_H values obtained are of cource almost proportional to hydrophilic group effect (E_W),[1b] and so V_H constant may also be ascribed mainly to the hydrogen bonding with water.

Application of V_W and V_H to Regression Analysis of Physicochemical and Pharmacological Data

For the test of V_W and V_H in the application to regression analysis as independent variables, the same data used for parachor[1b] have been utilized for convenience. No compound has been omitted from the calculation of correlations.

First, the data[9] of water-solubility of 156 different organic liquids including aliphatic and aromatic hydrocarbons, halides, alcohols, ketones, esters, ethers, *etc.* have been analysed (Eq. 8—10).

$$\log(1/S) = 2.91(\pm 0.78)V_W - 1.22(\pm 0.80) \qquad n=156,\ r=0.506,\ s=1.146 \qquad (8)$$

$$\log(1/S) = -3.54(\pm 0.55)V_H + 2.82(\pm 0.23) \qquad n=156,\ r=0.716,\ s=0.927 \qquad (9)$$

$$\log(1/S) = 3.73(\pm 0.26)V_W(28.25) - 4.10(\pm 0.22)V_H(36.06) - 0.72(\pm 0.26) \qquad n=156,\ r=0.960,\ s=0.373 \qquad (10)$$

Here, S is the water-solubility in molar concentration. In Eq. 10, V_H has almost the same regression coefficient as V_W but the sign is opposite. Therefore, a parameter V_L has been defined as

$$V_L = V_W - V_H \qquad (11)$$

The relation between $\log(1/S)$ and V_L is shown in Fig. 2. The correlation has been formulated as

$$\log(1/S) = 3.95(\pm 0.19)V_L - 0.98(\pm 0.14) \qquad n=156,\ r=0.958,\ s=0.380 \qquad (12)$$

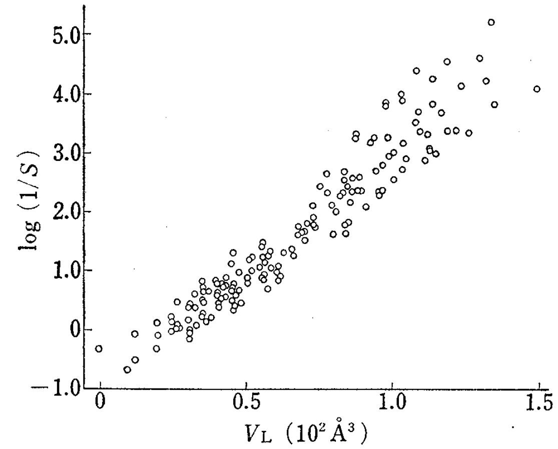

Fig. 2. Relation of V_L to Water-Solubility of 156 Organic Liquids

S: water-solubility in M

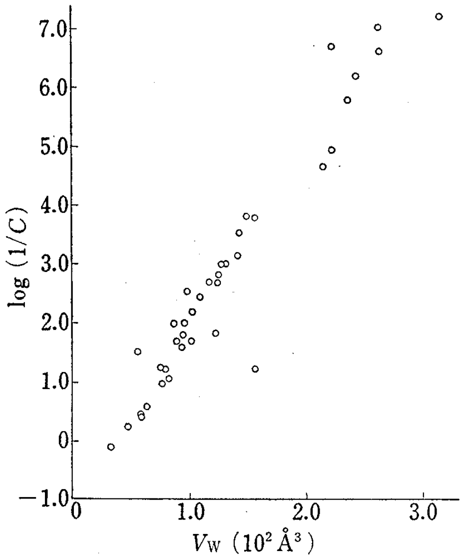

Fig. 3. Relation of V_W to Frog Muscle Narcosis of 39 Drugs

C: minimum concentration necessary for complete block of excitability

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[9] C. Hansch, J.E. Quinlan, and G.L. Lawrence, *J. Org. Chem.*, 33, 347 (1968).

From Eq. 7 and 11, V_L can be expressed as

$$V_L = (\log P - 0.12)/2.71 \tag{13}$$

Eq. 13 indicates the linear relation between V_L and log P. Therefore, it can be said from Eq. 12 that water-solubility is linearly related to hydrophobicity as already reported.⁹⁾ The correlation in Eq. 12 has been somewhat superior to that ($r=0.935$) reported by Hansch, *et al.*⁹⁾

Second, the data¹⁰⁾ of narcosis of frog muscle with a wide variety of 39 drugs (*e.g.* alcohols, acetone, ether, chloroform, aromatic and heterocyclic molecules, local anesthetics, *etc.*) have been submitted to regression analysis, and Eq. 14—17 have been formulated.

$$\log(1/C) = 2.82(\pm 0.26)V_W - 0.90(\pm 0.40) \qquad n=39,\ r=0.963,\ s=0.562 \tag{14}$$

$$\log(1/C) = 2.79(\pm 0.95)V_H + 0.63(\pm 0.90) \qquad n=39,\ r=0.700,\ s=1.490 \tag{15}$$

$$\log(1/C) = 3.65(\pm 1.05)V_L + 0.95(\pm 0.71) \qquad n=39,\ r=0.758,\ s=1.363 \tag{16}$$

$$\log(1/C) = 3.34(\pm 0.39)V_W(17.18) - 0.88(\pm 0.54)V_H(3.33) - 0.89(\pm 0.35) \qquad n=39,\ r=0.972,\ s=0.498 \tag{17}$$

In these equations, C is the minimum concentration necessary for complete block of excitability. These equations indicate that the most significant parameter is V_W ($p>0.999$) and not V_L, contrary to our expectation. This may be a very interesting finding, but the details will be discussed elsewhere. The relation between V_W and log $(1/C)$ is shown in Fig. 3.

It may be considered that non-specific behavior (including hydrophobicity) of molecules is mainly based on their size and polarity. In conclusion, van der Waals volume and hydrophilic effect proposed here are useful parameters for structure-activity analysis and especially design of drugs because these parameters can easily be calculated for a wide variety of molecules.

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10) D. Agin, L. Hersh, and D. Holtzman, *Proc. Natl. Acad. Sci. U.S.*, 53, 952 (1965).