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Quantitative Structure-Activity Studies. I. Parameters relating to Hydrophobicity[1]

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The logarithm of partition coefficient between octanol and water, log P, widely used in structure-activity studies as a hydrophobic parameter was factored into two intrinsic components, free molecular volume and hydrophilic effect of polar group. Among those additive parameters relating to molecular volume as parachor, molar refraction, diamagnetic susceptibility, molar attraction constant, and Exner's molar volume, Quayle's atomic parachor, Pr, showed the best correlation with observed log P for apolar compounds. The hydrophilic group effect, E_W, was estimated as a correction term in the evaluation of log P for polar compounds by using a linear relation of log P to Pr obtained for apolar molecules. The parameters Pr and E_W could be satisfactorily applied to the regression analysis of water-solubility of 156 organic liquids and frog muscle narcosis of 39 drugs. These artificial parameters have a great advantage in drug design because they can be evaluated for a wide variety of classes of compounds before the molecules are even synthesized.

Many diverse biochemical and pharmacological processes involved in drug action are dependent on the hydrophobicity of the drugs.[3] Parametrization of hydrophobicity is one of the most important aspects in the quantitative structure-activity studies. Hansch and his coworkers[4] have successfully employed the logarithm of partition coefficient between octanol and water, log P, as a measure of hydrophobicity in regression analysis of various *in vitro* and *in vivo* biological activities. However, experimental parameters such as log P suffer from disadvantage that, in general, the compounds studied must be available for the determination. An additive character of log P has been described with aliphatic molecules and several substitutes of simple aromatic nuclei,[4b,5] but the use of this additivity would be much restricted in actual practice of drug design because drug molecules are frequently complex heterocyclic systems. Recent publications[6] by Rogers and Cammarata report

1) Presented in part before the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1973.
2) Location: *Shirokane, Minato-ku, Tokyo, 108, Japan.*
3) C. Hansch and W.D. Dunn, *J. Pharm. Sci.*, **61**, 1 (1972).
4) *a*) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964); *b*) C. Hansch, "Drug Design," Vol. 1, ed. by E.J. Ariëns, Academic Press, New York, 1971, p. 271.
5) C. Hansch, A. Leo, and D. Nikaitani, *J. Org. Chem.*, **37**, 3090 (1972); A. Canas-Rodriguez and M.S. Tute, *Advan. Chem. Ser.*, **No. 114**, 41 (1972).
6) K.S. Rogers and A. Cammarata, *Biochim. Biophys. Acta*, **193**, 22 (1969); A. Cammarata and K.S. Rogers, *J. Med. Chem.*, **14**, 269 (1971).

that log P is correlated with two quantum-chemical indices, electrophilic superdelocalizability and electron net charge, both of which can be evaluated only by calculation. Unfortunately this attractive method is also much restricted in its use because the method is only applicable to aromatic molecules bearing neither of those substituents as nitro, azo, sulfonyl, amino, nor large aliphatic groups.

The present study has been undertaken to find out suitable parameters for hydrophobicity applicable to a wide variety of classes of organic compounds for use in drug design. For this purpose, the partition coefficient has been factored into two intrinsic components, free molecular volume and hydrophilic effect of polar group, which have been so parameterized that they can be estimated only by calculation. These parameters proposed here have been satisfactorily applied to regression analysis of water-solubility of 156 organic liquids[7] and frog muscle narcosis of 39 drugs,[8] both known to be dependent upon hydrophobicity of the molecules.

Method

Parachor (*Pr*)——Four kinds of Pr values, Pr_1, Pr_2, Pr_3, and Pr_4, were calculated using Sugden's,[9] Quayle's,[9] and Vogel's[10] atomic parachor constants and Vogel's[10] bond parachor constant, respectively. In Pr_2 and Pr_3, 38.0[11] was used for triple bond because of a better approximation to observed parachor values.[9] In Table V, VII, and VIII, Pr_2 with a correction for folding or intramolecular hydrophobic bonding was used as Pr, and the value of correction was assumed to be -40. The details were described in the text.

Molar Refraction (*MR*)——Three kinds of MR values, MR_1, MR_2, and MR_3, were calculated using Meloan and Kiser's[12] and Vogel's[10] atomic constants and Vogel's[10] bond constant, respectively.

Molar Diamagnetic Susceptibility (χ_M)——The $-\chi_M$ values in Table I were calculated using Pascal's constant compiled by Ferguson.[13]

Molar Attraction Constant (*F*)——The F values in Table I were calculated using the group constants determined by Small.[14]

Exner's Molar Volume (*MV*)——The MV values in Table I were calculated using the group constant determined by Exner.[15]

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

Results and Discussion

Hydrophobicity of Apolar Molecules

The difference of the standard potential of a solute, $\Delta\mu_s^\circ$, for the transfer from solvent 1 to solvent 2, both solutions being regular, is given by the Hildebrand-Scott solubility theory as[16]

$$\Delta\mu_s^\circ = V_s(\delta_1-\delta_2)(\delta_1+\delta_2-2\delta_s) \quad (1)$$

Here V_s is the molal volume, δ the solubility parameter, and subscripts 1, 2, and s refer to the solvents 1 and 2, and the solute. Accordingly, the partition coefficient of apolar solutes can be expressed as

7) C. Hansch, J.E. Quinlan, and G.L. Lawrence, *J. Org. Chem.*, **33**, 347 (1968).
8) D. Agin, L. Hersh, and D. Holtzman, *Proc. Natl. Acad. Sci. U.S.*, **53**, 952 (1965).
9) O.R. Quayle, *Chem. Rev.*, **53**, 484 (1953).
10) A.I. Vogel, W.T. Cresswell, G.H. Jeffery, and J. Leicester, *J. Chem. Soc.*, **1952**, 514.
11) S.A. Mumford and J.W.C. Phillips, *J. Chem. Soc.*, **1929**, 2112.
12) C.E. Meloan and R.W. Kiser, "Problems and Experiments in Instrumental Analysis," Charles E. Merrill Books, Columbus, 1963, p. 295.
13) L.N. Ferguson, "Modern Structural Theory of Organic Chemistry," Prentice-Hall, Englewoods Cliffs, 1952, p. 54.
14) P.A. Small. *J. Appl. Chem.* (London), **3**, 71 (1953).
15) O. Exner, *Collect. Czech. Chem. Commun.*, **32**, 1 (1967).
16) L.P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1970, p. 248.

$$\log P = V_s(\delta_a-\delta_o)(\delta_a+\delta_o-2\delta_s)/2.303\,RT \quad (2)$$

where subscripts a and o refer to aqueous and organic phases. In the case of apolar solutes, the value of solubility parameter does not vary greatly from substance to substance. Consequently, a linear relationship can be expected between free molecular volume and log P.

Thus, correlations of log P were examined to those additive parameters relating to molecular volume,[9–15,17–19] as parachor, molar refraction, diamagnetic susceptibility, molar attraction constant, and Exner's molar volume. These parameters were calculated for various hydrocarbons and halogenated hydrocarbons whose log P values observed were available.[7,20] The data are listed in Table I, along with a dummy parameter, D,[21] assumed for folding or intramolecular hydrophobic bonding,[20] and molecular weight, MW, for comparison. The regression equations (3—24) obtained are given in Table II and III. Table II indicates

TABLE I. Constants Relating to Hydrophobicity for 43 Apolar Molecules

No.	Empirical formula	Name	log P Obsd.[a]	log P Calcd.[b]	Pr_1	Pr_2	Pr_3	Pr_4	MR_1	MR_2	MR_3	$-\chi_M\times10^5$	F	MV	D	MW
1	$CHCl_3$	chloroform	1.97	1.96	184.8	182.7	189.9	190.1	21.43	21.14	21.21	6.923	778	70.56	0	119.4
2	CH_3I	methyl iodide	1.69	1.55	147.1	145.8	146.0	146.0	19.62	19.63	19.64	5.939	639	64.41	0	141.9
3	C_2H_5I	ethyl iodide	2.00	2.00	186.1	185.8	186.0	186.0	24.24	24.28	24.29	7.125	772	80.99	0	156.0
4	C_3H_7Br	1-bromopropane	2.10	2.20	202.1	203.5	204.5	204.5	23.82	23.72	23.71	6.911	820	90.83	0	123.0
5	C_4H_9Cl	1-chlorobutane	2.39	2.51	227.4	230.7	230.9	231.0	25.55	25.47	25.48	7.047	883	104.18	0	92.6
6	C_5H_8	1-pentyne	1.98	2.24	207.4	207.0	209.2	209.2	23.30	23.17	23.17	5.264	765	97.86	0	68.1
7	$C_5H_{11}F$	1-fluoropentane	2.33	2.63	238.2	241.6	241.8	241.8	25.20	25.09	25.06	7.373	870	112.91	0	90.1
8	C_5H_{12}	pentane	2.50	2.51	229.2	231.0	231.4	231.4	25.30	25.31	25.30	6.516	827	112.70	0	72.2
9	$C_6H_4Cl_2$	*m*-dichlorobenzene	3.38	3.11	281.5	284.5	285.9	285.2	36.37	35.93	35.85	8.936	1097	105.67	0	147.0
10	$C_6H_4Cl_2$	*o*-dichlorobenzene	3.38	3.11	281.5	284.5	285.9	285.2	36.37	35.93	35.85	8.936	1097	105.67	0	147.0
11	$C_6H_4Cl_2$	*p*-dichlorobenzene	3.39	3.11	281.5	284.5	285.9	285.2	36.37	35.93	35.85	8.936	1097	105.67	0	147.0
12	C_6H_5Br	bromobenzene	2.99	2.81	258.0	257.6	260.0	259.2	34.26	34.02	33.90	8.269	1075	100.84	0	157.0
13	C_6H_5Cl	chlorobenzene	2.84	2.67	244.3	244.8	246.4	245.7	31.37	31.12	31.02	7.219	1005	97.61	0	112.6
14	C_6H_5F	fluorobenzene	2.27	2.34	215.7	215.7	217.3	216.5	26.40	26.09	25.95	6.359	859	89.76	0	96.1
15	C_6H_5I	iodobenzene	3.25	3.06	281.0	279.9	281.5	280.7	39.30	39.23	39.12	9.669	1160	107.58	0	204.0
16	C_6H_6	benzene	2.13	2.22	207.1	205.1	206.9	206.1	26.37	26.31	26.18	5.502	825	89.55	0	78.1
17	C_6H_{10}	1,5-hexadiene	2.45	2.69	246.2	247.2	248.4	248.4	28.72	29.00	28.99	5.430	868	118.12	0	82.1
18	$C_7H_5F_3$	trifluoromethylbenzene	2.79	2.95	271.9	269.5	278.1	277.2	30.82	30.30	30.12	9.259	1009	106.76	0	146.1
19	C_7H_7Cl	*m*-chlorotoluene	3.28	3.12	283.3	284.8	286.4	285.7	36.12	35.77	35.67	8.405	1142	114.19	0	126.6
20	C_7H_7Cl	*o*-chlorotoluene	3.42	3.12	283.3	284.8	286.4	285.7	36.12	35.77	35.67	8.405	1142	114.19	0	126.6
21	C_7H_7Cl	*p*-chlorotoluene	3.33	3.12	283.3	284.8	286.4	285.7	36.12	35.77	35.67	8.405	1142	114.19	0	126.6
22	C_7H_8	toluene	2.69	2.67	246.1	245.1	246.9	246.1	31.12	30.96	30.83	6.688	949	106.13	0	92.1
23	C_8H_6	ethynylbenzene	2.53	2.85	263.3	261.1	264.7	259.6	33.74	33.47	33.35	6.622	1020	107.87	0	102.1
24	C_8H_9Br	2-bromo-1-ethylbenzene	3.09	3.26	336.0	337.6	340.0	339.2	43.63	43.32	43.19	10.641	1345	134.00	1	185.1
25	C_8H_9Cl	2-chloro-1-ethylbenzene	2.95	3.12	322.3	324.8	326.4	325.7	40.74	40.42	40.31	9.591	1275	130.77	1	140.6
26	C_8H_{10}	ethylbenzene	3.15	3.12	285.1	285.1	286.9	286.1	35.74	35.61	35.48	7.874	1082	122.71	0	106.2
27	C_8H_{10}	*m*-xylene	3.20	3.12	285.1	285.1	286.9	286.1	34.11	35.61	35.48	7.874	985	122.71	0	106.2
28	C_8H_{10}	*o*-xylene	2.77	2.67	285.1	285.1	286.9	286.1	34.11	35.61	35.48	7.874	985	122.71	1	106.2
29	C_8H_{10}	*p*-xylene	3.15	3.12	285.1	285.1	286.9	286.1	34.11	35.61	35.48	7.874	985	122.71	0	106.2
30	C_9H_8	indene	2.92	3.12	287.4	285.2	288.6	283.4	37.84	37.53	37.50	7.338	1148	103.91	0	116.2
31	C_9H_{10}	allylbenzene	3.23	3.44	313.1	313.2	315.4	314.6	39.76	39.78	39.65	7.924	1169	133.71	0	118.2
32	C_9H_{10}	1-phenyl-1-propene	3.35	3.44	313.1	313.2	315.4	314.6	40.04	39.78	39.65	7.924	1196	133.71	0	118.2
33	C_9H_{12}	isopropylbenzene	3.66	3.53	324.1	321.4	326.9	326.1	40.62	40.26	40.13	9.060	1191	139.29	0	120.2
34	C_9H_{12}	propylbenzene	3.68	3.57	324.1	325.1	326.9	326.1	40.35	40.26	40.13	9.060	1215	139.29	0	120.2
35	$C_{10}H_8$	azulene	3.20	3.39	309.3	308.5	315.7	324.3	42.01	41.85	42.98	9.156	1161	108.10	0	128.2
36	$C_{10}H_8$	naphthalene	3.37	3.42	313.0	311.1	313.9	324.3	42.00	41.74	42.98	9.156	1236	122.22	0	128.2
37	$C_{10}H_{14}$	*t*-butylbenzene	4.11	3.94	363.1	357.7	366.9	366.1	44.98	44.91	44.78	10.246	1284	155.87	0	134.2
38	$C_{12}H_{10}$	biphenyl	4.09	4.18	380.0	379.2	382.4	390.0	50.80	50.56	51.70	10.418	1470	149.30	0	154.2
39	$C_{13}H_{10}$	fluorene	4.18	4.32	393.3	391.2	395.6	401.6	53.46	52.96	54.30	11.018	1559	136.08	0	166.2
40	$C_{13}H_{12}$	diphenylmethane	4.14	4.18	419.0	419.2	422.4	420.8	55.42	55.21	54.96	11.604	1603	165.88	1	168.2
41	$C_{14}H_{10}$	anthracene	4.45	4.61	418.9	417.1	420.9	442.5	57.64	57.18	59.77	12.810	1729	149.78	0	178.2
42	$C_{14}H_{10}$	phenanthrene	4.46	4.61	418.9	417.1	420.9	442.5	57.63	57.18	59.77	12.810	1729	149.78	0	178.2
43	$C_{14}H_{14}$	bibenzyl	4.79	4.64	463.4	459.2	462.4	460.8	60.04	59.86	59.61	12.790	1736	182.46	1	182.3

a) ref. 7, 20 b) calculated using Eq. 25

17) J.C. McGowan, *J. Appl. Chem.* (London), **1**, 1205 (1951); *idem, ibid.*, **2**, 323 (1952); *idem, ibid.*, **4**, 41 (1954).
18) A. Leo, C. Hansch, and C. Church, *J. Med. Chem.*, **12**, 766 (1969).
19) P.N. Craig, *J. Med. Chem.*, **14**, 680 (1971); W.P. Purcell, G.E. Bass, and J.M. Clayton, "Strategy of Drug Design," John Wiley & Sons, New York, 1973, p.1, 38.
20) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
21) $D=1$ in the presence of intramolecular hydrophobic bonding, and otherwise $D=0$.

that all the parameters relating to molecular volume are linearly related to log P with high significance and especially Quayle's atomic parachor (Pr_2) shows the best fit. Consequently, Quayle's atomic parachor was selected as a parameter for free molecular volume for the further studies. However, a choice of other parameters than Quayle's parachor may not be much unfavorable because these parameters highly intercorrelate as shown in Table IV. It must

Table II. Regression Equations for log P of 43 Apolar Compounds

$\log P = aX + b \quad n = 43$

X	a	b	$r^{a)}$	$s^{b)}$	Eq.
$Pr_1 \cdot 10^{-2}$	1.03±0.10	0.13±0.32	0.954	0.224	(3)
$Pr_2 \cdot 10^{-2}$	1.04±0.10	0.11±0.32	0.955	0.224	(4)
$Pr_3 \cdot 10^{-2}$	1.03±0.10	0.11±0.32	0.954	0.224	(5)
$Pr_4 \cdot 10^{-2}$	0.99±0.10	0.22±0.31	0.953	0.227	(6)
$MR_1 \cdot 10^{-1}$	0.70±0.07	0.55±0.28	0.951	0.232	(7)
$MR_2 \cdot 10^{-1}$	0.70±0.07	0.53±0.28	0.951	0.232	(8)
$MR_3 \cdot 10^{-1}$	0.67±0.07	0.62±0.29	0.946	0.242	(9)
$F \cdot 10^{-2}$	0.26±0.03	0.21±0.36	0.938	0.260	(10)
$-x_M \cdot 10^{-5}$	0.35±0.05	0.16±0.49	0.897	0.331	(11)
$MV \cdot 10^{-1}$	0.27±0.05	−0.04±0.61	0.872	0.367	(12)
$MW \cdot 10^{-2}$	1.39±0.58	1.32±0.78	0.604	0.599	(13)

a) correlation coefficient *b*) standard error of the estimate

Table III. Regression Equations for log P of 43 Apolar Compounds

$\log P = aX + bD + c \quad n = 43$

X	a	b	c	$r^{a)}$	$s^{b)}$	Eq.
$Pr_1 \cdot 10^{-2}$	1.12±0.09	−0.46±0.19	−0.07±0.25	0.972	0.180	(14)
$Pr_2 \cdot 10^{-2}$	1.13±0.09	−0.47±0.19	−0.11±0.25	0.973	0.176	(15)
$Pr_3 \cdot 10^{-2}$	1.11±0.09	−0.46±0.19	−0.09±0.26	0.971	0.180	(16)
$Pr_4 \cdot 10^{-2}$	1.05±0.09	−0.38±0.21	0.07±0.27	0.965	0.199	(17)
$MR_1 \cdot 10^{-1}$	0.74±0.07	−0.34±0.22	0.44±0.25	0.961	0.211	(18)
$MR_2 \cdot 10^{-1}$	0.75±0.07	−0.37±0.21	0.41±0.25	0.963	0.206	(19)
$MR_3 \cdot 10^{-1}$	0.71±0.07	−0.29±0.23	0.54±0.27	0.954	0.228	(20)
$F \cdot 10^{-2}$	0.27±0.03	−0.34±0.25	0.08±0.33	0.948	0.242	(21)
$-x_M \cdot 10^{-5}$	0.37±0.06	−0.35±0.33	0.00±0.47	0.908	0.318	(22)
$MV \cdot 10^{-1}$	0.30±0.05	−0.49±0.37	−0.34±0.57	0.893	0.342	(23)
$MW \cdot 10^{-2}$	1.36±0.62	0.08±0.61[c)]	1.34±0.79	0.605	0.606	(24)

a) multiple correlation coefficient *b*) standard error of the estimate *c*) not significant at the 95% confidence level

Table IV. Intercorrelation of the Parameters

	Pr_1	Pr_2	Pr_3	Pr_4	MR_1	MR_2	MR_3	F	$-x_M$	MV	MW
Pr_1	1.000										
Pr_2	0.999	1.000									
Pr_3	0.999	0.999	1.000								
Pr_4	0.999	0.997	0.998	1.000							
MR_1	0.984	0.982	0.982	0.985	1.000						
MR_2	0.985	0.984	0.983	0.986	0.999	1.000					
MR_3	0.980	0.979	0.979	0.984	0·998	0.999	1.000				
F	0.975	0.975	0.974	0.979	0.989	0.984	0.985	1.000			
$-x_M$	0.912	0.912	0.914	0.921	0.922	0.918	0.920	0.939	1.000		
MV	0.936	0.937	0.934	0.923	0.874	0.882	0.869	0.858	0.776	1.000	
MW	0.587	0.586	0.586	0.592	0.664	0.655	0.655	0.683	0.813	0.385	1.000

be noted that there is a pioneer work by McGowan who has reported a rather high correlation between physical toxicity and Vogel's bond parachor of a variety of chemicals.

Because Table III indicates the dummy parameter (D) being highly significant, a correction for folding or intramolecular hydrophobic bonding should be favored in the calculation of the parameters. Here, the value for the correction of parachor was estimated from Eq. 15 (Table III), which can be rewritten as

$$\log P = 1.13(Pr_2 - 41.6D) \times 10^{-2} - 0.11 \qquad (15')$$

Because of the diversity of intramolecular hydrophobic bonding, a round value of -40 was employed for the correction.

Thus, Pr_2 values were substracted by 40 if $D=1$ in Table I, and were subjected to regression analysis with log P. The correlation of the corrected Quayle's parachor, Pr, with log P for the 43 apolar molecules is given as

$$\log P = 1.13(\pm 0.08)Pr \cdot 10^{-2} - 0.10(\pm 0.25)$$
$$n=43 \quad r=0.973 \quad s=0.174 \qquad (25)$$

where the figures in parenthes are the 95% confidence intervals, n is the number of compounds submitted to the regression analysis, r the correlation coefficient, and s the standard error of the estimate. The significance of the correlation was very high as well as that for Eq. 15 (Table III).

Hydrophobicity of Polar Molecules

In the case of polar molecules, a simple linear relation between log P and parachor can not be expected because Eq. 2 does not hold for a non-regular solution including solute-solvent and/or solute-solute interactions. As a typical example, the data for a variety of alcohols are listed in Table V. The plot of log P calculated using Eq. 25 against observed log P is shown in Fig. 1. The points for monofunctional alcohols fall close to a straight line of the

Table V. Constants Relating to Hydrophobicity for 21 Alcohols

No.	Empirical formula	Name	log P			Pr	E_W
			Obsd[a]	Calcd[b]	Calcd[c]		
1	CH_4O	methanol	−0.66	0.86	−0.54	85.3	1.4
2	$C_2H_3OF_3$	2,2,2-trifluoroethanol	0.41	1.59	0.17	149.7	1.4
3	C_2H_6O	ethanol	−0.32	1.32	−0.08	125.3	1.4
4	$C_2H_6O_2$	ethylene glycol	−1.93	1.48	−1.32	139.6	2.8
5	C_3H_6O	allyl alcohol	0.17	1.63	0.23	153.4	1.4
6	C_3H_8O	propanol	0.34	1.77	0.37	165.3	1.4
7	$C_4H_{10}O$	butanol	0.83	2.22	0.82	205.3	1.4
8	$C_4H_{10}O$	*sec*-butanol	0.61	2.18	0.68	201.6	1.5
9	$C_4H_{10}O$	*tert*-butanol	0.37	2.14	0.44	197.9	1.7
10	$C_4H_{10}O_2$	2,3-butanediol	−0.92	2.30	−0.70	212.2	3.0
11	$C_5H_{12}O$	pentanol	1.16	2.67	1.27	245.3	1.4
12	$C_5H_{12}O$	2,2-dimethyl-1-propanol	1.36	2.59	1.19	237.9	1.4
13	$C_5H_{12}O$	2-ethyl-2-propanol	0.89	2.59	0.89	237.9	1.7
14	$C_6H_{12}O$	cyclohexanol	1.23	2.74	1.24	251.4	1.5
15	$C_6H_{14}O$	hexanol	2.03	3.12	1.72	285.3	1.4
16	C_7H_7OCl	*m*-chlorobenzyl alcohol	1.94	3.28	1.88	299.1	1.4
17	C_7H_7OCl	*p*-chlorobenzyl alcohol	1.96	3.28	1.88	299.1	1.4
18	C_7H_8O	benzyl alcohol	1.10	2.83	1.43	259.4	1.4
19	$C_8H_{10}O$	*m*-methylbenzyl alcohol	1.60	3.28	1.88	299.4	1.4
20	$C_8H_{10}O$	*p*-methylbenzyl alcohol	1.58	3.28	1.88	299.4	1.4
21	$C_8H_{12}O$	1-ethynylcyclohexanol	1.73	3.33	1.63	303.7	1.7

a) ref. 20 b) calculated using Eq. 25 c) [Calcd[b]]$-E_W$

expected 45° slope but the intercept gives a value of about 1.5. In the case of diols, *i.e.* ethylene glycol and 2,3-butanediol, the intercept is estimated to be about 3 by extrapolation. The findings suggest that there is another factor, almost constant per hydroxy group, involved in the partition of alcohols. The factor was evaluated as 1.4, 1.5, and 1.7, for aliphatic *prim*-, *sec*-, and *tert*-OH, respectively, as a correction for the intercept being zero (Fig. 1).

In a similar manner as the aliphatic hydroxy group, the factor was evaluated for a wide variety of hydrophilic groups containing nitrogen and/or oxygen atoms, as "hydrophilic

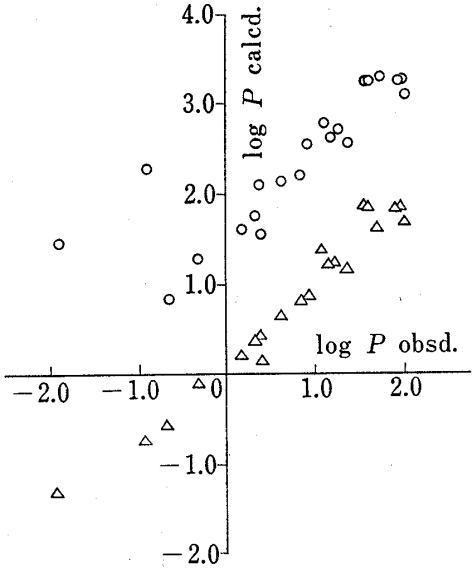

Fig. 1. Plots of Observed log P against Calculated log P for Alcohols

○: calculated using Eq. 25
△: corrected by E_W

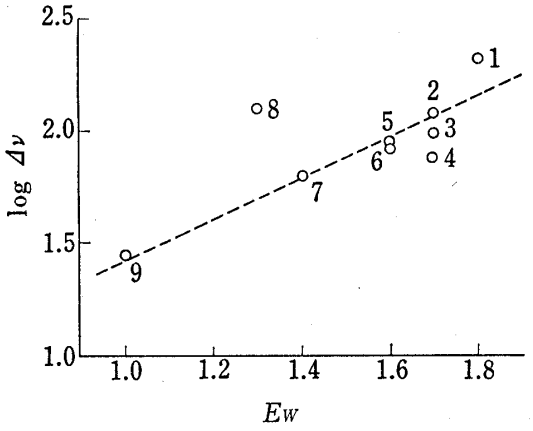

Fig. 2. Relation of Gordy's Hydrogen Bonding Strength to E_W

1. tributylamine, 2. cyclohexanone, 3. acetone, 4. methyl ethyl ketone, 5. amyl acetate, 6. ethyl acetate, 7. aceto nitrile, 8. diethyl ether, 9. nitrobenzene

TABLE VI. Hydrophilic Group Effect

Group		E_W Aromatic	E_W Aliphatic
-N<	amines	1.6	1.6 (*prim.*) 1.7 (*sec.*) 1.8 (*tert.*)
	pyrrole type	0.9*a*	—
=N-		1.3*a*	—
-C≡N		1.2	1.4
-O-	ethers	0.8	1.3
	hydroxy	0.8	1.4 (*prim.*) 1.5 (*sec.*) 1.7 (*tert.*)
	furan type	0.5*a*	—
-C=O	ketones	1.6	1.7
	aldehydes	1.2	1.3
$-CO_2-$	carboxy	1.3	1.6
-CON<	amides	2.4	2.7
$-SO_2-$	sulfonyl	3.1	3.5
$-SO_2N<$	sulfamoyl	3.5	
$-NO_2$	nitro	1.0	1.5
>NCON<	ureas	2.7	
$>NCO_2-$	urethans	2.4	2.7

a a correction for N and/or O atoms adjacent or located in one aromatic ring: ×0.7 for 2 atoms and ×0.4 for 3 atoms.

TABLE VII. Data on Water-Solubility of 156 Organic Liquids

No.	Compounds	P_f	E_W	log $(1/S)^{a)}$ Obsd[b)]	log $(1/S)^{a)}$ Calcd[c)]
1	butanol	205.3	1.4	−0.026	−0.045
2	2-methyl-1-propanol	201.6	1.4	−0.098	−0.100
3	2-butanol	201.6	1.5	−0.285	−0.251
4	pentanol	245.3	1.4	0.592	0.556
5	3-methyl-1-butanol	241.6	1.4	0.507	0.500
6	methylbutanol	241.6	1.4	0.460	0.500
7	2-pentanol	241.6	1.5	0.276	0.349
8	3-pentanol	241.6	1.5	0.211	0.349
9	3-methyl-2-butanol	237.9	1.5	0.176	0.294
10	2-methyl-2-butanol	237.9	1.7	−0.147	−0.009
11	2,2-dimethylpropanol	237.9	1.4	0.386	0.445
12	hexanol	285.3	1.4	1.212	1.156
13	2-hexanol	281.6	1.5	0.867	0.949
14	3-hexanol	281.6	1.5	0.795	0.949
15	3-methyl-3-pentanol	277.9	1.7	0.361	0.592
16	2-methyl-2-pentanol	277.9	1.7	0.485	0.592
17	2-methyl-3-pentanol	277.9	1.5	0.697	0.894
18	3-methyl-2-pentanol	277.9	1.5	0.713	0.894
19	4-methyl-2-pentanol	277.9	1.5	0.787	0.894
20	2,3-dimethyl-2-butanol	274.2	1.7	0.370	0.536
21	3,3-dimethyl-1-butanol	277.9	1.4	1.125	1.045
22	3,3-dimethyl-2-butanol	274.2	1.5	0.613	0.838
23	heptanol	325.3	1.4	1.809	1.756
24	2-methyl-2-hexanol	317.9	1.7	1.074	1.192
25	3-methyl-3-hexanol	317.9	1.7	0.984	1.192
26	3-ethyl-3-pentanol	317.9	1.7	0.832	1.192
27	2,3-dimethyl-2-pentanol	314.2	1.7	0.871	1.136
28	2,3-dimethyl-3-pentanol	314.2	1.7	0.843	1.136
29	2,4-dimethyl-2-pentanol	314.2	1.7	0.932	1.136
30	2,4-dimethyl-3-pentanol	314.2	1.5	1.217	1.438
31	2,2-dimethyl-3-pentanol	314.2	1.5	1.148	1.438
32	octanol	365.3	1.4	2.346	2.356
33	2,2,3-trimethyl-3-pentanol	350.5	1.7	1.273	1.681
34	cyclohexanol	255.1	1.5	0.417	0.552
35	4-penten-1-ol	233.4	1.4	0.154	0.377
36	3-penten-2-ol	229.7	1.5	−0.055	0.171
37	1-penten-3-ol	229.7	1.5	−0.015	0.171
38	1-hexen-3-ol	269.7	1.5	0.588	0.771
39	2-hexen-4-ol	269.7	1.5	0.403	0.771
40	2-methyl-4-penten-3-ol	266.0	1.5	0.502	0.715
41	benzyl alcohol	259.4	1.4	0.454	0.767
42	2-butanone	198.9	1.7	−0.678	−0.594
43	2-pentanone	238.9	1.7	0.169	0.007
44	3-pentanone	238.9	1.7	0.232	0.007
45	3-methyl-2-butanone	235.2	1.7	0.124	−0.049
46	2-hexanone	278.9	1.7	0.779	0.607
47	3-hexanone	278.9	1.7	0.827	0.607
48	3-methyl-2-pentanone	275.2	1.7	0.671	0.551
49	4-methyl-2-pentanone	275.2	1.7	0.711	0.551
50	4-methyl-3-pentanone	275.2	1.7	0.812	0.551
51	2-heptanone	318.9	1.7	1.422	1.207
52	4-heptanone	318.9	1.7	1.444	1.207
53	2,4-dimethyl-3-pentanone	311.5	1.7	1.299	1.096
54	5-nonanone	398.9	1.7	2.575	2.407
55	ethyl formate	174.8	1.6	−0.076	−0.804
56	propyl formate	214.8	1.6	0.491	−0.204

No.	Compounds	Pr	E_W	log $(1/S)^{a)}$ Obsd[b]	log $(1/S)^{a)}$ Calcd[c]
57	methyl acetate	174.8	1.6	−0.517	−0.804
58	ethyl acetate	214.8	1.6	0.040	−0.204
59	propyl acetate	254.8	1.6	0.733	0.396
60	isopropyl acetate	251.1	1.6	0.519	0.341
61	butyl acetate	294.8	1.6	0.693	0.996
62	isobutyl acetate	291.1	1.6	1.237	0.941
63	methyl propionate	214.8	1.6	0.094	−0.204
64	methyl butyrate	254.8	1.6	0.779	0.396
65	ethyl butyrate	294.8	1.6	1.275	0.996
66	propyl butyrate	334.8	1.6	1.907	1.596
67	ethyl valerate	334.8	1.6	1.767	1.596
68	ethyl hexanoate	374.8	1.6	2.356	2.196
69	ethyl heptanoate	414.8	1.6	2.737	2.796
70	ethyl octanoate	454.8	1.6	3.387	3.396
71	ethyl nonanoate	494.8	1.6	3.796	3.996
72	ethyl decanoate	534.8	1.6	4.097	4.596
73	diethyl ether	210.8	1.3	0.063	0.189
74	methyl butyl ether	250.8	1.3	0.992	0.789
75	methyl isobutyl ether	247.1	1.3	0.899	0.734
76	methyl *sec*-butyl ether	247.1	1.3	0.734	0.734
77	methyl *t*-butyl ether	243.4	1.3	0.210	0.678
78	ethyl propyl ether	250.8	1.3	0.665	0.789
79	ethyl isopropyl ether	247.1	1.3	0.554	0.734
80	dipropyl ether	290.8	1.3	1.317	1.389
81	propyl isopropyl ether	287.1	1.3	1.335	1.334
82	methyl propyl ether	210.8	1.3	0.372	0.189
83	methyl isopropyl ether	207.1	1.3	0.028	0.134
84	cyclopropyl ether	232.3	1.3	0.638	0.512
85	chloroethane	150.7	0	1.051	1.251
86	chloropropane	190.7	0	1.527	1.851
87	2-chloropropane	187.0	0	1.358	1.795
88	chlorobutane	230.7	0	2.143	2.451
89	isobutyl chloride	227.0	0	2.000	2.395
90	1,3-dichloropropane	230.4	0	1.614	2.446
91	chloroform	182.7	0	0.920	1.731
92	bromoethane	163.5	0	1.055	1.443
93	bromopropane	203.5	0	1.733	2.043
94	2-bromopropane	199.8	0	1.631	1.987
95	bromobutane	243.5	0	2.366	2.643
96	isobutyl bromide	239.8	0	2.432	2.587
97	isoamyl bromide	279.8	0	2.886	3.187
98	1,3-dibromopropane	256.0	0	2.081	2.830
99	iodomethane	145.8	0	1.000	1.177
100	iodoethane	185.8	0	1.600	1.777
101	iodopropane	225.8	0	2.290	2.377
102	iodobutane	265.8	0	2.960	2.977
103	diiodomethane	220.6	0	2.340	2.299
104	$(ClCH_2CH_2)_2S$	279.5	0	2.370	3.183
105	1-pentyne	207.0	0	1.640	2.095
106	1-hexyne	247.0	0	2.360	2.695
107	1-heptyne	287.0	0	3.010	3.295
108	1-octyne	327.0	0	3.660	3.895
109	1-nonyne	367.0	0	4.240	4.495
110	1,8-nonadiyne	303.0	0	2.980	3.535
111	1,6-heptadiyne	223.0	0	1.750	2.335
112	1-pentene	219.1	0	2.670	2.277
113	2-pentene	219.1	0	2.540	2.277
114	1-hexene	259.1	0	3.230	2.877

No.	Compounds	Pr	E_W	log $(1/S)^{a)}$ Obsd[b)]	log $(1/S)^{a)}$ Calcd[c)]
115	2-heptene	299.1	0	3.820	3.477
116	1-octene	339.1	0	4.620	4.077
117	4-methyl-1-pentene	255.4	0	3.240	2.821
118	1,6-heptadiene	287.2	0	3.340	3.298
119	1,5-hexadiene	247.2	0	2.690	2.698
120	1,4-pentadiene	207.2	0	2.080	2.098
121	cyclopentene	191.1	0	2.100	1.857
122	cyclohexene	228.9	0	2.580	2.424
123	cycloheptene	272.1	0	3.160	3.072
124	benzene	205.1	0	1.637	2.067
125	toluene	245.1	0	2.292	2.667
126	ethylbenzene	285.1	0	2.880	3.267
127	propylbenzene	325.1	0	3.302	3.867
128	fluorobenzene	215.7	0	1.796	2.226
129	chlorobenzene	244.8	0	2.363	2.662
130	bromobenzene	257.6	0	2.547	2.854
131	nitrobenzene	261.9	1.0	1.777	1.409
132	1,2,4-trimethylbenzene	285.1	0	3.320	3.267
133	*o*-xylene	245.1	0	2.780	2.667
134	isopropylbenzene	321.4	0	3.380	3.811
135	*m*-nitrotoluene	301.9	1.0	2.439	3.519
136	*o*-dichlorobenzene	284.5	0	3.006	3.258
137	*m*-dichlorobenzene	284.5	0	3.077	3.258
138	ethyl benzoate	348.9	1.3	2.280	2.261
139	aniline	232.1	1.6	0.410	0.056
140	propionitrile	162.6	1.4	−0.280	−0.685
141	pentane	231.0	0	3.270	2.455
142	isopentane	227.3	0	3.180	2.400
143	2-methylpentane	267.3	0	3.790	3.000
144	3-methylpentane	267.3	0	3.830	3.000
145	hexane	271.0	0	3.960	3.055
146	heptane	311.0	0	4.530	3.655
147	2,4-dimethylpentane	303.6	0	4.390	3.544
148	2,2-dimethylpentane	303.6	0	3.670	3.544
149	octane	351.0	0	5.240	4.255
150	cyclopentane	203.0	0	2.650	2.035
151	cyclohexane	240.8	0	3.180	2.602
152	methylcyclopentane	243.0	0	3.300	2.635
153	cycloheptane	284.0	0	3.510	3.250
154	methylcyclohexane	280.8	0	3.850	3.202
155	cyclooctane	320.0	0	4.150	3.790
156	1,2-dimethylcyclohexane	320.8	0	4.270	3.802

a) S is the water-solubility in molal concentration. *b*) ref. 7 *c*) calculated using Eq. 26

group effect," E_W. The values of E_W thus obtained are listed in Table VI. Fig. 2 shows the relation of Gordy's hydrogen bonding strength,[22] $\Delta\nu$, to E_W for several polar compounds. The approximate linearity may indicate that hydrophilic group effect is mainly ascribed to the hydrogen bonding with water.

Test for Parachor and Hydrophilic Group Effect

The first test for Pr and E_W is an analysis of the data[7] on aqueous solubility. Recently, Hansch and his coworkers[7] have studied water-solubility of 156 different organic liquids

22) J.D. Crowley, G.S. Teague, and J.W. Lowe, *J. Paint Technology*, **38**, 269 (1966).

and indicated that hydrophobicity governs the phenomenon. The data are listed in Table VII along with calculated Pr and E_W. The regression equation obtained was

$$\log(1/S) = 1.50(\pm 0.10)\, Pr \cdot 10^{-2}(0.999) - 1.51(\pm 0.08) E_W(0.999) - 1.01(\pm 1.31)$$
$$n=156 \quad r=0.962 \quad s=0.366 \qquad (26)$$

where the figures in parentheses after the parameters are the confidence level by the t-test. The correlation was highly significant, and not inferior to that of Eq. 27 reported by Hansch, *et al.*[7]

$$\log(1/S) = 1.34(\pm 0.07) \log P - 0.98(\pm 0.15)$$
$$n=156 \quad r=0.935 \quad s=0.472 \qquad (27)$$

TABLE VIII. Data on Frog Muscle Narcosis of 39 Drugs

No.	Compound	Pr	E_W	log (1/c)[a] Obsd[b]	log (1/c)[a] Calcd[c]
1	methanol	85.3	1.4	−0.09	−0.17
2	ethanol	125.3	1.4	0.25	0.32
3	acetone	158.9	1.7	0.40	0.64
4	isopropanol	161.6	1.5	0.45	0.74
5	propanol	165.3	1.4	0.60	0.81
6	urethan	201.8	2.7	1.00	0.87
7	ethyl ether	210.8	1.3	1.07	1.40
8	butanol	205.3	1.4	1.22	1.31
9	antipyrine	391.7	4.0	1.22	2.82
10	pyridine	207.1	1.3	1.23	1.36
11	chloroform	182.7	0.0	1.50	1.45
12	hydroquinone	233.7	1.6	1.60	1.59
13	aniline	232.1	1.6	1.70	1.57
14	benzyl alcohol	259.4	1.4	1.70	1.97
15	acetanilide	323.0	2.4	1.83	2.45
16	pentanol	245.3	1.4	1.80	1.80
17	toluene	245.1	0.0	2.00	2.21
18	phenol	219.4	0.8	2.00	1.66
19	benzimidazole	268.2	1.54	2.19	2.04
20	hexanol	285.3	1.4	2.44	2.29
21	nitrobenzene	261.9	1.0	2.53	2.12
22	quinoline	304.1	1.3	2.70	2.55
23	8-hydroxyquinoline	318.4	2.1	2.70	2.49
24	heptanol	325.3	1.4	2.80	2.78
25	2-naphthol	325.4	0.8	3.00	2.96
26	methyl anthranilate	335.9	2.9	3.00	2.46
27	octanol	365.3	1.4	3.16	3.27
28	thymol	375.7	0.8	3.52	3.58
29	*o*-phenanthroline	403.1	2.6	3.80	3.38
30	ephedrine	402.0	3.2	3.80	3.18
31	procaine	552.7	4.7	4.67	4.59
32	xylocaine	592.3	4.2	4.96	5.23
33	diphenhydramine	628.3	3.1	5.80	6.00
34	tetracaine	648.2	4.7	5.90	5.76
35	phenyltoloxamine	628.3	2.6	6.20	6.15
36	quinine	723.3	5.4	6.60	6.48
37	eserine	610.4	5.8	6.66	4.97
38	caramiphen	702.8	3.4	7.00	6.82
39	dibucaine	831.1	6.3	7.20	7.53

a) *c* is the minimum concentration necessary for complete block of excitability.
b) ref. 8
c) calculated using Eq. 29

The second test, that of narcosis of frog muscle,[8] deals with a wide variety of 39 drugs including complex heterocyclic molecules. The data are listed in Table VIII. All the compounds were submitted to regression analysis, and highly significant correlation was obtained.

$$\log(1/c) = 1.25(\pm 0.14)\, Pr\cdot 10^{-2}(0.999) - 0.28(\pm 0.18) E_{\mathrm{W}}(0.997) - 0.89(\pm 0.32)$$
$$n=39 \quad r=0.976 \quad s=0.462 \qquad (28)$$

Since two of the 39 drugs, antipyrine and eserine, somewhat deviated from the relation of Eq. 28, the rest 37 drugs were also analysed.

$$\log(1/c) = 1.23(\pm 0.09)\, Pr\cdot 10^{-2}(0.999) - 0.30(\pm 0.11) E_{\mathrm{W}}(0.999) - 0.80(\pm 0.19)$$
$$n=37 \quad r=0.992 \quad s=0.267 \qquad (29)$$

The significance of the correlation obtained was very high.

For comparison, the equation calculated for 23 compounds of the 39 drugs by Hansch, *et al.*[18] was cited here.

$$\log(1/c) = 0.90(\pm 0.10) \log P + 0.66(\pm 0.15)$$
$$n=23 \quad r=0.972 \quad s=0.242 \qquad (30)$$

From these findings it may be concluded that parachor and hydrophilic group effect proposed here are useful parameters relating to hydrophobicity in regression analysis. Especially, these artificial parameters have a great advantage in drug design because they can be evaluated for a wide variety of molecules before the compounds are even synthesized.

Acknowledgement The author is indebted to Miss N. Nakamura for her assistance in the calculation.