mp 142–143.5 °C; UV max (95% EtOH) 243.5 nm (ε 13 820); IR (KBr) 1672 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.37 (3 H, s), 1.57 (3 H, s), 1.97 (3 H, s), 2.00 (3 H, s), 2.23 (1 H, d, J = 13 Hz), 2.73 (1 H, d, J = 13 Hz), 6.0–6.6 (2 H, br), 7.0–7.8 (5 H, m).

Biological Methods. The following test procedures have been described previously:[2] the 5-h pyloric-ligated rat test, the method for measuring inhibition of histamine-induced gastric acid secretion in the dog, the mouse mydriasis test for anticholinergic activity, and the procedure for assessment of H_2-receptor inhibitory activity in vitro.

The effect of **5b** on the response of guinea pig auricles to carbamylcholine was measured in vitro in a Krebs–Henseleit solution at 35 °C. The compound was dissolved in Me_2SO–H_2O and then added to the bath solution. The tissue was exposed to the drug for 5 min. At concentrations of 10^{-6} and 10^{-5} M the compound did not affect the dose-related carbamylcholine-induced decrease in spontaneous heart rate. At higher concentrations the drug precipitated from the bath solution.

In a similar manner the effect of **5b** on the response of guinea pig trachea to carbamylcholine was measured. At a concentration of 10^{-5} M the drug did not affect the dose-related carbamylcholine-induced constriction of the trachea.

References and Notes

(1) Presented at the Seventh Northeast Regional Meeting of the American Chemical Society, Albany, N.Y., 1976.
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(7) We are indebted to Dr. Bertram A. Spilker and his associates for these results.
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Hydrogen-Bonding Parameter and Its Significance in Quantitative Structure–Activity Studies

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When the relative hydrogen-bonding effect of drugs on phases involved in the binding at the site of biological action differs from that in the 1-octanol–H_2O partitioning phases used as the reference to estimate the hydrophobicity, a parameter (or parameters) which represents the "extra" hydrogen-bonding effect on the biological activity is required in the Hansch-type correlations. As a first approximation, the effect is analyzed in terms of the ratio of hydrogen-bonding association constants and the ratio of molarities of hydrogen-bonding species constituting the biological and organic phases. Sometimes, the association constants in both phases are so similar that they are not important in determining the extra hydrogen-bonding effect. The net result is that the effect is expressible by an indicator variable term the slope of which corresponds to the molarity ratio. The variable only applies to substituents having appreciable association capability in correlating a certain biological action exhibited by a series of congeners.

Quantitative analysis of structure–activity relationships of the Hansch-type assumes that the variation in a certain biological activity expressed as Δ log BR of a series of congeners can be analyzed in terms of variations in their free-energy-related physicochemical parameters, such as π or log P for hydrophobic, σ, σ*, or Δ log K_A for electronic, and E_s, E_s^c, or MV for steric and others.[1]

Although hydrogen bonding has long been recognized as being very important in biological reactions including drug actions, examples where the particular use of hydrogen-bonding parameters as an independent variable is necessary have scarcely been found so far. One of the reasons for such scarcity may stand on the fact that the hydrogen-bonding effect at a certain functional group in congeners is correlated with the electronic effect of substituents. Examples are found in analyses for the Hill reaction inhibition of herbicidal N-substituted phenylamides[2] and the bacteriostatic activity of kojic acid analogues[3] where hydrogen-bonding effects of such functional groupings as –NHCO– and –COC(OH)= on cellular components are anticipated. In fact, the free-energy-related hydrogen bond donating parameter, h_D, defined by Higuchi and co-workers[4] for a series of substituted phenols can be expressed by eq 1. A similar observation was made by Clotman and co-workers for the association equilibrium of substituted phenols with triethylamine.[5] Likewise, the hydrogen-accepting parameter, pK_{HB}, of substituted benzaldehydes has been expressed as eq 2 by Taft and associates.[6] σ^+ correlates better than σ since the site of association is partially electron deficient.

$$h_D = 1.562\ (\pm 0.169)\ \sigma + 0.096\ (\pm 0.064) \quad (1)$$
$$n = 22;\ r = 0.974;\ s = 0.115$$

$$pK_{HB} = -0.456\ (\pm 0.101)\ \sigma^+ + 0.782\ (\pm 0.092) \quad (2)$$
$$n = 5;\ r = 0.993;\ s = 0.061$$

Another line of reasoning may be that the parameter used for the hydrophobicity, log P or π, mostly estimated from the 1-octanol–H_2O partition coefficient, inherently includes the effect of hydrogen bonding. According to Hansch and co-workers, the nonspecific type of protein binding of miscellaneous molecules such as aromatic hydrocarbons, phenols, anilines, and aliphatic alcohols with bovine serum albumin (BSA)[7] and bovine hemoglobin (BHG)[8] is related only to their hydrophobicity defined by the octanol–H_2O partition coefficient. The binding equilibrium constant, log K (K is the reciprocal of the concentration of compound producing a 1:1 complex with protein), is linearly related to log P (octanol–H_2O) without any additional parameter, regardless of the number of hydrogen bonding sites of varying degrees of strength in the molecule as shown in eq 3 and 4. The effect of the relative hydrogen bonding on the octanol–H_2O partitioning is closely similar to that involved in the protein binding. Thus, the net difference in the hydrogen-bonding effect between the partitioning process and drug actions, whose

critical step occurs rather nonspecifically in the proteinous milieu, does not necessarily appear as an explanatory independent parameter in the Hansch-type correlations.

For BSA binding[7]

$$\log K = 0.751\ (\pm 0.07) \log P + 2.301\ (\pm 0.15) \quad (3)$$
$$n = 42;\ r = 0.960;\ s = 0.159$$

For BHG binding[8]

$$\log K = 0.713\ (\pm 0.11) \log P + 1.512\ (\pm 0.27) \quad (4)$$
$$n = 17;\ r = 0.950;\ s = 0.160$$
$$\log 1/p = 1.17\ (\pm 0.25) \log P\ (\text{oct-}H_2O) + 1.88\ (\pm 0.33)\ I - 2.11\ (\pm 0.39) \quad (5)$$
$$n = 30;\ r = 0.947;\ s = 0.438$$
$$\log 1/K_d = 1.55\ (\pm 0.26)\ \pi - 1.93\ (\pm 0.52)\ \sigma^0 + 1.53\ (\pm 0.36)\ HB + 2.46\ (\pm 0.28) \quad (6)$$
$$n = 21;\ r = 0.967;\ s = 0.247$$

However, examples such as eq 5 and 6 where hydrogen-bonding effects appear to be expressible by an indicator variable have been found quite recently. In eq 5 derived by Hansch and co-workers,[9] p is the effective anesthetic pressure of gaseous anesthetics and I is an indicator variable which takes a value of 1 when aliphatic anesthetics have an activated hydrogen atom attached directly to a carbon atom holding electronegative substituent(s), but otherwise 0. Equation 6 is derived from our acetylcholinesterase (AcChE) inhibition data of meta-substituted phenyl N-methylcarbamates.[10] K_d is the dissociation constant of the enzyme–inhibitor reversible complex and HB, an indicator variable, takes 1 only for hydrogen-acceptor substituents such as NO_2, CN, CHO, Ac, COEt, and $N(Me)_2$. σ^0 which is almost identical with σ for meta substituents except for alkoxy groups is used in conformity with correlations for ortho and para isomers where σ^0 works better than σ^-.[10]

It may be difficult to accept that the hydrogen-bonding capability of activated hydrogens in eq 5 and hydrogen accepting groups in eq 6 having "various" degrees of acidity and basicity can be represented by a discrete-type parameter. We attempted to clarify whether physicochemical significance can be rendered to this "hydrogen bonding" parameter. Although log P or π values from the octanol–H_2O partitioning system may take care of the nonspecific type of binding process with cellular components including both the hydrophobic and hydrogen-bonding interactions, the relative hydrogen-bonding capability of drugs between octanol and water phases may differ from those between phases involved in such biological actions as analyzed by eq 5 and 6. We examined relationships between log P values determined with various solvent systems differing in the relative hydrogen-bonding capability for series of congeners having substituents of varying degrees of hydrogen-bonding properties. This paper makes the point that the difference in hydrogen-bonding effect of certain classes of substituents between certain different partitioning systems is, in effect, expressible by the indicator variable as a first approximation. It also discusses the scope and limitation for the use of the indicator variable as well as implications in cases where such variables appear in structure–activity studies.

Experimental Section

Partition Coefficients. Partition coefficients with the $CHCl_3$–H_2O system were determined for monosubstituted benzenes and phenyl N-methylcarbamates having neutral and hydrogen-accepting groups. For substituted carbamates, 20–60 mg of each sample was shaken with 2–40 mL of $CHCl_3$ and 20–40 mL of H_2O at 25 ± 1 °C for 1 h. After separating two phases by centrifuging the whole for 20 min, the concentration in the water phase was measured spectrophotometrically as the corresponding phenols after alkaline hydrolysis according to the procedure described previously.[11] The concentration in the $CHCl_3$ phase was obtained by the difference. For monosubstituted benzenes, 50–400 mg of each sample was partitioned between 5 mL of $CHCl_3$ and 70 mL of H_2O by shaking for 1 h at 25 ± 1 °C. The concentrations in both phases were measured spectrophotometrically in this case. Determinations were performed at least at three different volume ratios or concentrations and the reproducibility was examined. Other partition coefficients used in this work were selected from literature.

The relationships between log P values from various solvent systems were examined by means of regression analysis. The calculations were performed with a FACOM 230/75 computer at the Data Processing Center of this University.

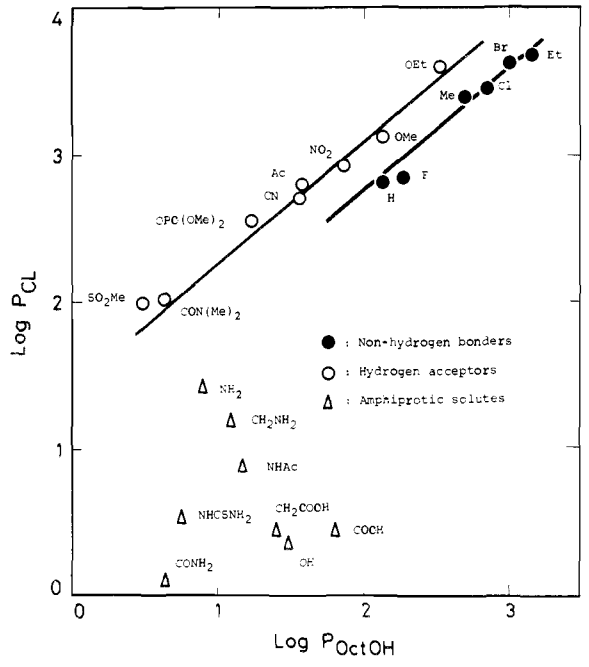

Figure 1. Plot of log P ($CHCl_3$–H_2O) vs. log P (octanol–H_2O) of monosubstituted benzenes.

Results

Figure 1 shows the relationship between log P values of monosubstituted benzenes from $CHCl_3$–H_2O and octanol–H_2O partitioning systems. The values for nonhydrogen bonders and hydrogen acceptors are related to each other by two parallel lines. Using the data in Table I, the relationship is formulated by eq 7 with HB as the hydrogen-bonding indicator variable. Hydrogen-acceptor substituents, such as alkoxy, NO_2, CN, Ac, $CON(Me)_2$, sulfonyl, and phosphoryl, seem to have almost equivalent effects to raise the log P ($CHCl_3$–H_2O) value relative to that predicted from those of nonhydrogen bonders regardless of differences in the basicity. On the contrary, the effect of acidic (amphiprotic) substituents is to cause negative deviations from the regression line for nonhydrogen bonders to varying extents.

$$\log P\ (CHCl_3\text{-}H_2O) = 0.801\ (\pm 0.087) \log P\ (\text{oct-}H_2O) + 0.367\ (\pm 0.142)\ HB + 1.157\ (\pm 0.244) \quad (7)$$
$$n = 14;\ r = 0.991;\ s = 0.081$$
$$\log P\ (\text{hex-}H_2O) = 0.804\ (\pm 0.338) \log P\ (\text{oct-}H_2O) + 0.718\ (\pm 0.881) \quad (8)$$
$$n = 5;\ r = 0.975;\ s = 0.079$$

Table I. Log P ($CHCl_3$-H_2O) and Log P (Octanol-H_2O) of Monosubstituted Benzenes

Substituents	Log P ($CHCl_3$-H_2O) Obsd[a]	Calcd[b]	$\lvert\Delta\rvert$	Log P (oct-H_2O)[c]	HB	pK_{HB}[d]
Nonhydrogen Bonders						
H	2.80	2.86	0.06	2.13	0	−0.36[o]
Me	3.41	3.31	0.10	2.69	0	−0.29[o]
Et	3.68[e]	3.68	0.00	3.15[k]	0	−0.34[o]
F	2.85	2.97	0.12	2.27	0	−1.12[p]
Cl	3.46[e]	3.43	0.03	2.84	0	−0.80[p]
Br	3.61	3.55	0.06	2.99	0	−0.84[p]
Hydrogen Acceptors						
OMe	3.12	3.21	0.09	2.11	1	0.02
OEt	3.62	3.53	0.09	2.51[l]	1	0.22[q]
Ac	2.79	2.79	0.00	1.58	1	1.13
NO_2	2.93	3.01	0.08	1.85	1	0.73
CN	2.71	2.77	0.06	1.56	1	0.79
$CON(Me)_2$	2.01	2.02	0.01	0.62[l]	1	2.22
$OPO(OMe)_2$	2.56	2.50	0.06	1.22[m]	1	2.21[r]
SO_2Me	2.00	1.90	0.10	0.47[n]	1	1.05[s]
Amphiprotic Substituents[f]						
NH_2	1.42[g]	1.88	0.46	0.90	0	
CH_2NH_2	1.18[h]	2.03	0.85	1.09[k]	0	
NHAc	0.88[g]	2.09	1.21	1.16	0	
$NHCSNH_2$	0.54[i]	1.74	1.20	0.73[l]	0	
$CONH_2$	0.11[i]	1.67	1.56	0.64	0	
OH	0.36[g]	2.33	1.97	1.46	0	
CH_2COOH	0.45[j]	2.29	1.84	1.41	0	
COOH	0.46[g]	2.64	2.18	1.81	0	

[a] Unless noted, data from this laboratory; the standard error (SE) is less than ±0.02. [b] By eq 7. [c] Unless noted, from T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964). [d] Unless noted, from ref 6. [e] SE ⩽ ±0.04. [f] Not included for the correlation. [g] C. Hogben, D. Tocco, and B. Brodie, *J. Pharmacol. Exp. Ther.*, **125**, 275 (1959). [h] H. Smith, *J. Phys. Chem.*, **25**, 204 (1921). [i] K. B. Sandell, *Monatsh. Chem.*, **89**, 36 (1958). [j] H. Smith and T. White, *J. Phys. Chem.*, **33**, 1953 (1929). [k] J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, **8**, 150 (1965). [l] Unpublished data by Hansch and co-workers, from the log P data file of the Pomona College Medicinal Chemistry Project. [m] K. Kamoshita and T. Fujita, unpublished data. [n] C. Hansch and S. Anderson, *J. Org. Chem.*, 32, 2583 (1967). [o] Estimated from the log K_f value with PhOH: Z. Yoshida and E. Osawa, *J. Am. Chem. Soc.*, **88**, 4019 (1966). [p] Estimated from the log K_f value with MeOH: P. J. Krueger and H. D. Mettee, *Can. J. Chem.*, 42, 288 (1964). [q] Estimated from the log K_f value with PhOH: T. Gramstad, *Spectrochim. Acta*, 19, 497 (1963). [r] Estimated from pK_{HB} values of $(PhO)_3PO$ and $(MeO)_3PO$ listed in ref 6 by interpolation. [s] Estimated from the log K_f value with PhOH: P. Biscarini, G. Galloni, and S. Gersetti, *Spectrochim. Acta*, 20, 267 (1964).

The situation for log P (hexane–H_2O) values is depicted in Figure 2 using the data in Table II. The regression line is drawn for nonhydrogen bonders for which eq 8 is obtained. As evident, the effect of hydrogen acceptor as well as amphiprotic substituents is not uniform lowering the log P (hexane–H_2O) value to various degrees.

$$\log P\,(CHCl_3\text{-}H_2O) = 0.949\ (\pm 0.111)\log P\,(\text{oct-}H_2O) + 0.303\ (\pm 0.137)\,HB - 0.231\ (\pm 0.121)\,\sigma + 0.731\ (\pm 0.239) \quad (9)$$

$$n = 24;\ r = 0.984;\ s = 0.096$$

For 24 ortho-, meta-, and para-substituted N-methylphenylcarbamates, eq 9 is derived from the data in Table III. Equation 9 seems to separate the effect of variable substituents on the relative hydrogen-bonding solvation

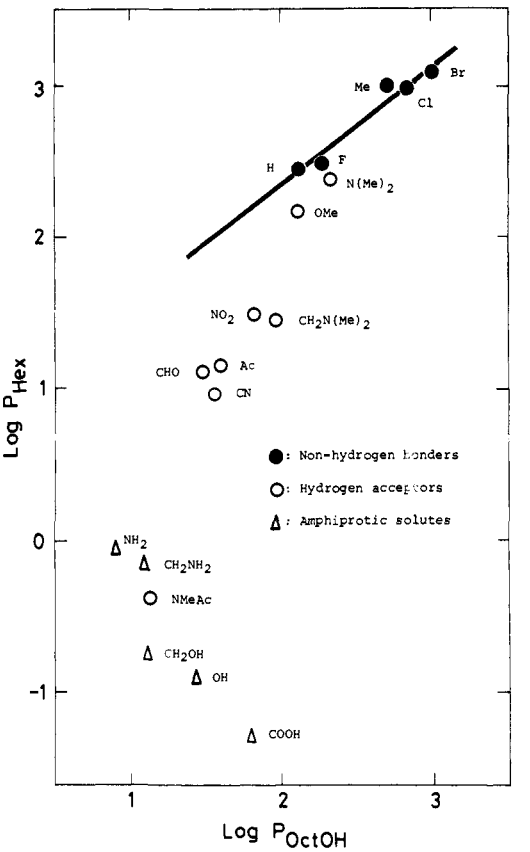

Figure 2. Plot of log P (hexane–H_2O) vs. log P (octanol–H_2O) of monosubstituted benzenes.

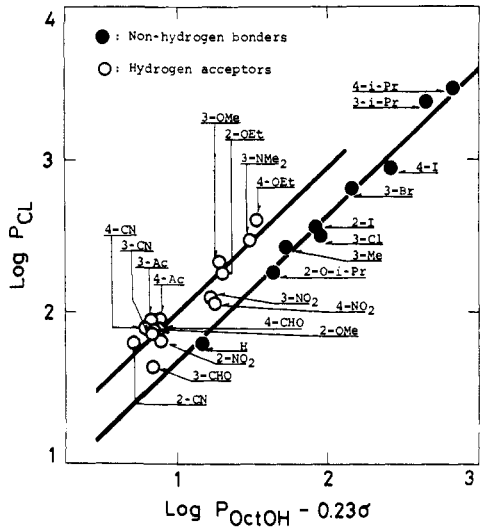

Figure 3. Plot of log P ($CHCl_3$–H_2O) vs. log P (octanol–H_2O) of substituted phenyl N-methylcarbamates.

at the side-chain carbamoyl groups, $-OC(=O)NHCH_3$ (expressed by −0.23 σ), and the hydrogen-accepting effect at the substituent site on the relative partitioning processes. For the electronic effect of ortho substituents, σ_p was used. The effect of ortho substituents has recently been shown[12] to be expressible by a linear combination of σ_p, the Swain–Lupton–Hansch F,[13] and Taft–Kutter–Hansch E_s constants.[14] The fact that eq 9 does not require F and E_s terms suggests that the proximity electronic (or field inductive) and steric effects of ortho substituents are not important in determining the relative solvation effect at the side chain. Figure 3 depicts the plot of log P ($CHCl_3$–H_2O) against the value of log P (octanol–H_2O) − 0.23 σ. The 2-O-*i*-Pr derivative does not require the in-

Table II. Log P (Hexane-H_2O) and Log P (Octanol-H_2O) of Monosubstituted Benzenes

Substituents	Log P (hexane-H_2O) Obsd[a]	Calcd[b]	$\|\Delta\|$	Log P (oct-H_2O)[c]	pK_{HB}[d]
	Nonhydrogen Bonders				
H	2.45	2.43	0.02	2.13	−0.36[o]
Me	2.99	2.88	0.11	2.69	−0.29[o]
F	2.48	2.54	0.06	2.27	−1.12[p]
Cl	2.98	3.00	0.02	2.84	−0.80[p]
Br	3.08	3.12	0.04	2.99	−0.84[p]
	Hydrogen Acceptors				
OMe	2.16[e,f]	2.41	0.25	2.11	0.02
$N(Me)_2$	2.38[h]	2.58	0.20	2.31	0.45[q]
NO_2	1.49	2.21	0.72	1.85	0.73
CN	0.96[e,f]	1.97	1.01	1.56	0.80
CHO	1.11[g]	1.91	0.80	1.48[f]	0.80
Ac	1.14[e-g]	1.99	0.85	1.58	1.13
$CH_2N(Me)_2$	1.44[e,i]	2.31	0.87	1.98[l]	1.56
NMeAc	−0.40[h]	1.62	2.02	1.12[m]	~2.0[r]
	Amphiprotic Substituents				
NH_2	−0.05	1.44	1.49	0.90	
CH_2NH_2	−0.15[e,j]	1.59	1.74	1.09[n]	
OH	−0.89	1.89	2.78	1.46	
CH_2OH	−0.76[k]	1.60	2.36	1.10	
COOH	−1.29	2.17	3.46	1.81	

[a] Unless noted, from T. Sekine, Y. Suzuki, and N. Ihara, *Bull. Chem. Soc.* Jpn., 46, 995 (1973). For eq 8, only the values of nonhydrogen bonders are used. [b] By eq 8. [c] Unless noted, from T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, 86, 5175 (1964). [d] Unless noted, from ref 6. [e] Estimated from the log P (heptane-H_2O) value assuming that the P value in terms of mole fractions instead of molarities is equivalent to that from the hexane-H_2O system. For relevancy of this assumption, see R. Aveyard and R. Mitchell, *Trans. Faraday Soc.*, 65, 2645 (1969); 66, 37 (1970). [f] Unpublished data by Hansch and co-workers, from the log P data file of the Pomona College Medicinal Chemistry Project. [g] K. Nasim, M. C. Meyer, and J. Austin, *J. Pharm. Sci.*, 61, 1775 (1972). [h] H. L. Schmidt, M. Moller, and N. Weber, *Biochem. Pharmacol.*, 22, 2989 (1973). [i] A. Chao and G. Miwa, *Drug Metab. Dispos.*, 2, 477 (1973). [j] G. Williams and F. G. Soper, *J. Chem. Soc.*, 2469 (1930). [k] A. C. McCulloch and B. H. Stock, *Aust. J. Pharm.*, 48, S14 (1966). [l] C. Takayama, T. Fujita, and M. Nakajima, unpublished data. [m] W. J. Dunn, unpublished data. [n] J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, 8, 150 (1965). [o] See footnote *o* in Table I. [p] See footnote *p* in Table I. [q] L. Joris, J. Mitsky, and R. W. Taft, *J. Am. Chem. Soc.*, 94, 3438 (1972). [r] Estimated from pK_{HB} values for N,N-disubstituted amides in ref 6.

dicator variable suggesting that the substituent is not basic enough, probably due to a steric congestion around the alkoxy lone pair electrons preventing the hydrogen bonding.

$$\log P\ (CHCl_3\text{-}H_2O) = 0.890\ (\pm 0.202) \log P\ (\text{oct-}H_2O) - 1.015\ (\pm 0.428)\ \sigma + 0.355\ (\pm 0.366)\ HB_1 - 1.051\ (\pm 0.308)\ HB_2 - 0.516\ (\pm 0.182) \quad (10)$$

$$n = 14;\ r = 0.988;\ s = 0.106$$

Equation 10 is derived from log P values in Table IV of meta- and para-substituted benzenesulfonamides determined by Kakeya and co-workers.[15] In this equation, two indicator variables, HB_1 for electron-accepting NO_2, CN, and acetyl and HB_2 for amphiprotic NH_2 and NHMe groups, are introduced. Since collinearity between HB_1 and σ in this set of congeners is somewhat high (the simple correlation coefficient = 0.786), and also since the data points contributing to the HB_2 term number only two, the data set might not really be adequate to what this type of analyses requires. However, the HB_1 term is justified at the 94% level of significance and the slope of this term, 0.36, is quite close to those in eq 7 and 9. The difference in relative hydrogen-bonding effect between $CHCl_3$–H_2O and octanol–H_2O systems seems to be nearly constant for hydrogen-acceptor aromatic substituents, in three series of congeners being represented as 0.34 ± 0.04 log unit. In eq 10, the OMe substituent is not classified as a hydrogen acceptor. A decrease in basicity of the oxygen lone pair electrons may be caused by an electron withdrawal from the strongly negative SO_2NH_2 group.

The above results seem to indicate that the indicator variable applies in certain cases to the hydrogen-bonding effect of substituents on relative partitioning processes.

Table III. Log P Values of Substituted Phenyl N-Methylcarbamates

Substituents	Log P ($CHCl_3$-H_2O) Obsd[a]	Calcd[b]	Log P (oct-H_2O)[c]	σ	HB
H	1.78	1.83	1.16	0	0
2-I	2.55	2.55	1.96	0.18	0
2-OMe	1.81	1.86	0.81	−0.27	1
2-OEt	2.25	2.27	1.24	−0.24	1
2-O-*i*-Pr	2.23[d]	2.28	1.52	−0.45	0
2-CN	1.80	1.70	0.86	0.66	1
2-NO_2	1.86	1.82	1.02	0.78	1
3-Me	2.41	2.36	1.70	−0.07	0
3-*i*-Pr	3.37[e]	3.24	2.63	−0.07	0
3-Cl	2.50	2.57	2.03	0.37	0
3-Br	2.81	2.78	2.25	0.39	0
3-OMe	2.33	2.24	1.30	0.12	1
3-NMe_2	2.46[d]	2.44	1.43	−0.21	1
3-CHO	1.63	1.83	0.92	0.35	1
3-Ac	1.93	1.80	0.90	0.38	1
3-CN	1.87	1.83	0.98	0.56	1
3-NO_2	2.09	2.19	1.39	0.71	1
4-*i*-Pr	3.47	3.42	2.80	−0.15	0
4-I	2.93	3.02	2.46	0.18	0
4-OEt	2.59	2.64	1.64	−0.24	1
4-CHO	1.89	1.88	0.99	0.42	1
4-Ac	1.95	1.88	1.01	0.50	1
4-CN	1.88	1.78	0.95	0.66	1
4-NO_2	2.05	2.24	1.46	0.78	1

[a] The standard error (SE) is less than ±0.02 unless noted. [b] By eq 9. [c] From ref 11. [d] SE is ±0.04. [e] SE is ±0.08.

Table IV. Log P Values of Substituted Benzenesulfonamides

Substituents	Log P ($CHCl_3$-H_2O) Obsd[a]	Calcd[b]	Log P (oct-H_2O)[a]	σ	HB_1	HB_2
H	−2.24	−0.24	0.31	0	0	0
3-Me	0.32	0.31	0.85	−0.07	0	0
3-Cl	0.26	0.26	1.29	0.37	0	0
3-NO_2	−0.36	−0.39	0.55	0.71	1	0
4-Me	0.33	0.39	0.82	−0.17	0	0
4-OMe	0.15	0.18	0.47	−0.27	0	0
4-Cl	0.14	0.00	0.84	0.23	0	0
4-Br	0.39	0.46	1.36	0.23	0	0
4-Ac	−0.36	−0.49	0.20	0.50	1	0
4-CN	−0.61	−0.63	0.23	0.66	1	0
4-NO_2	−0.60	−0.38	0.64	0.78	1	0
4-NH_2	−1.69	−1.64	−0.83	−0.66	0	1
4-NHMe	−0.59	−0.64	0.08	−0.84	0	1
3-CF_3-4-NO_2	0.19	0.15	1.73	1.21	1	0

[a] From ref 15. From the original set, 3,4-Cl_2 and 3-NO_2-4-Cl derivatives are deleted. According to the private communication from the original authors, log P values of these compounds may not be very accurate due to a lack of enough solubility. [b] By eq 10.

Discussion

In the partitioning phases considered above, except for *n*-hexane, compounds having hydrogen-accepting substituents (X) are believed to exist as hydrogen-bonding equilibrium mixtures. For monosubstituted benzenes, the situation is shown as eq 11–13, where K_X is the association constant for substituent X and oct, CL, and W denote the solvents. Total concentration of the molecule in each phase is given by $C^0_{oct}(1 + K_X^{oct}[oct])$, $C^0_{CL}(1 + K_X^{CL}[CL])$, and $C^0_W(1 + K_X^W[H_2O])$ where C^0 is the concentration of the unassociated molecule and [solvent] is the molarity of the solvent itself in that solvent phase. The partition coefficients for hydrogen-acceptor molecules are then expressed as in eq 14 and 15.

$$ArX + C_8H_{17}OH \overset{K_X^{oct}}{\rightleftharpoons} ArX\cdots HOC_8H_{17} \quad (11)$$

$$ArX + CHCl_3 \overset{K_X^{CL}}{\rightleftharpoons} ArX\cdots HCCl_3 \quad (12)$$

$$ArX + H_2O \overset{K_X^{W}}{\rightleftharpoons} ArX\cdots HOH \quad (13)$$

$$P_{oct} = C^0_{oct}(1 + K_X^{oct}[oct])/C^0_W(1 + K_X^W[H_2O]) \quad (14)$$

$$P_{CL} = C^0_{CL}(1 + K_X^{CL}[CL])/C^0_W(1 + K_X^W[H_2O]) \quad (15)$$

First, we intuitively assume that "true" partition coefficients for the unassociated solute, $P^0_{oct} = C^0_{oct}/C^0_W$ and $P^0_{CL} = C^0_{CL}/C^0_W$, are related to each other by eq 16. In eq 16, the intercept may consist of a correction for a more relevant thermodynamic expression of partition coefficients with a ratio of mole fractions rather than molarities and a term which takes care of differences in the solubility parameter of two organic phases based on the regular solution theory.[16]

$$\log P^0_{CL} = \log P^0_{oct} + \text{constant} \quad (16)$$

For nonhydrogen-bonding compounds, $P^0 = P$ so that eq 17 is assumed to hold. For hydrogen-acceptor solutes, eq 18 is derived by combining eq 14–16 and taking the logarithm. Equation 18 which is an expression of the ratio of partition coefficients from two systems does not require consideration of the association in the water phase. If conditions of $K_X[solv] \gg 1$ are satisfied, eq 18 is reduced to eq 19. If K_X is so low that $K_X[solv] \ll 1$, eq 18 coincides with eq 17.

$$\log P_{CL} = \log P_{oct} + \text{constant} \quad (17)$$

$$\log P_{CL} = \log P_{oct} + \log (1 + K_X^{CL}[CL])/(1 + K_X^{oct}[oct]) + \text{constant} \quad (18)$$

$$\log P_{CL} = \log P_{oct} + \log K_X^{CL}/K_X^{oct} + \log [CL]/[oct] + \text{constant} \quad (19)$$

For phenylcarbamates, we have to take care of the hydrogen-bonding equilibrium at the carbamyl function. In $CHCl_3$, behaving only as a hydrogen donor, the total concentration of carbamates having neutral substituents, C_{CL}, is formulated as eq 20, where K_{CO}^{CL} is for the association with the carbamyl–carbonyl group. In octanol, having an amphiprotic character, the contribution from doubly solvated species must be considered as shown in eq 21, where K_{NH}^{oct} is for the association at the carbamyl NH hydrogen which has a considerable acidic character.[17] We assume that each of the association constants giving monosolvated species is applicable to each of the corresponding processes giving doubly associated species. Thus, for those congeners having neutral substituents, eq 22 can be derived to relate log *P* values which reduces under conditions, $K_X^{solv}[solv] \gg 1$, to eq 23.

$$C_{CL} = C^0_{CL}(1 + K_{CO}^{CL}[CL]) \quad (20)$$

$$C_{oct} = C^0_{oct}(1 + K_{CO}^{oct}[oct] + K_{NH}^{oct}[oct] + K_{CO}^{oct}K_{NH}^{oct}[oct]^2) \quad (21)$$

$$\log P_{CL} = \log P_{oct} + \log (1 + K_{CO}^{CL}[CL])/(1 + K_{CO}^{oct}[oct] + K_{NH}^{oct}[oct] + K_{CO}^{oct}K_{NH}^{oct}[oct]^2) + \text{constant} \quad (22)$$

$$\log P_{CL} = \log P_{oct} + \log K_{CO}^{CL}/K_{NH}^{oct}K_{CO}^{oct} + \log [CL]/[oct]^2 + \text{constant} \quad (23)$$

$$\log P_{CL} = \log P_{oct} + \log K_{CO}^{CL}/K_{CO}^{oct}K_{NH}^{oct} + \log [CL]/[oct]^2 + \log K_X^{CL}/K_X^{oct} + \log [CL]/[oct] + \text{constant} \quad (24)$$

For those congeners having hydrogen-acceptor substituents, considering a contribution from the triply solvated species in the octanol phase, we obtain eq 24 under conditions similar to those in deriving eq 23. By replacing K_{CO}^{solv} with K_{SO}^{solv} which is the constant for the S=O group in the SO_2NH_2 side chain, log *P* values of substituted sulfonamides having neutral and basic substituents can also be related by eq 23 and 24, respectively.

In experimentally derived relationships such as eq 7, 9, and 10, the slope of the log P_{oct} term is 0.88 ± 0.08 being close to 1 which may justify the assumption leading to eq 16. In comparison of these equations with those "theoretically" derived, the indicator variable term is likely to correspond to the difference between eq 17 and 19 or between eq 23 and 24, log (K_X^{CL}/K_X^{oct}) + log ([CL]/[oct]). The molarity of the solvent is 12.4 M for $CHCl_3$ and 6.2 M for 1-octanol.[18a] Thus, the log of the solvent concentration ratio is 0.30, which is very close to the slope of the indicator variable term, 0.34 ± 0.04, for three series of correlations.

This means that the effect of the extra hydrogen-bond formation of the hydrogen-acceptor aromatic substituents on the relative partitioning process is determined mainly by the molarity ratio of organic solvents. The hydrogen bond strength of basic substituents may be almost equivalent in two organic phases so that the log of the ratio of *K* values is not very significant.

The $\rho\sigma$ term in eq 9 and 10 should correspond to log $(K_{CO}^{CL}/K_{CO}^{oct}K_{NH}^{oct})$ and log $(K_{SO}^{CL}/K_{SO}^{oct}K_{NH}^{oct})$, respectively. The hydrogen-bond strength of the carbonyl or sulfonyl function with hydrogen-donor solvents, $CHCl_3$ and octanol, may be so similar that log $(K_{CO}^{CL}/K_{CO}^{oct})$ and log $(K_{SO}^{CL}/K_{SO}^{oct})$ are perhaps ignored. Thus, the negative ρ values in eq 9 and 10 seem to be attributed mainly to the substituent effect on the solvation with 1-octanol at the side-chain acidic NH hydrogen. The lower the electron withdrawal of substituents, the lower the acidity of NH hydrogen-holding molecules in the octanol phase thus resulting in the higher partition coefficient with the $CHCl_3$–H_2O system, relatively.

Proceeding in a manner similar to that in deriving eq 18 and 19, we can obtain eq 25 and 26 for log P_{CL} of amphiprotic monosubstituted benzenes. For amphiprotic substituents (YH), Y denotes the hydrogen-accepting site such as –O–, –N=, C=O, and C=S, and H is the acidic hydrogen in these equations. In eq 26, the second term, log (K_Y^{CL}/K_Y^{oct}), may well be ignored as in eq 19 and 24.

$$\log P_{CL} = \log P_{oct} + \log (1 + K_Y^{CL}[CL])/(1 + K_Y^{oct}[oct] + K_H^{oct}[oct] + K_Y^{oct}K_H^{oct}[oct]^2) + \text{constant} \quad (25)$$

$$\log P_{CL} \simeq \log P_{oct} + \log K_Y^{CL}/K_Y^{oct} + \log 1/K_H^{oct} + \log [CL]/[oct]^2 + \text{constant} \quad (26)$$

For log P (hexane–H_2O) of monosubstituted benzenes having neutral, basic, and amphiprotic substituents, we can derive eq 27–29, respectively.

$$\log P_{hex} = \log P_{oct} + \text{constant} \quad (27)$$

$$\log P_{hex} = \log P_{oct} + \log 1/(1 + K_X^{oct}[oct]) + \text{constant} \simeq \log P_{oct} + \log 1/K_X^{oct} + \log 1/[oct] + \text{constant} \quad (28)$$

$$\log P_{hex} = \log P_{oct} + \log 1/(1 + K_Y^{oct}[oct] + K_H^{oct}[oct] + K_Y^{oct}K_H^{oct}[oct]^2) + \text{constant} \simeq \log P_{oct} + \log 1/K_Y^{oct}K_H^{oct} + \log 1/[oct]^2 + \text{constant} \quad (29)$$

In eq 26, 28, and 29, the hydrogen-bond formation constants only appearing as the denominator in respective terms are irreducible. Therefore, the effect of extra hydrogen bonding for these solvent–solute combinations is not represented by the indicator variable but by the negative deviations from eq 17 and 27 which vary according to the magnitude of K^{oct} values.

$$\log P_{CL} = \log P_{oct} + \log K_{SO}^{CL}/K_{NH}^{oct}K_{SO}^{oct} + \log [CL]/[oct]^2 + \log K_Y^{CL}/K_Y^{oct} + \log 1/K_H^{oct} + \log [CL]/[oct]^2 + \text{constant} \quad (30)$$

For benzenesulfonamides having amphiprotic substituents such as 4-NH_2 and 4-NHMe, eq 30 relates log P values from $CHCl_3$–H_2O and octanol–H_2O systems. The difference from eq 23 (replaced by K_{SO}^{solv}) is log (K_Y^{CL}/K_Y^{oct}) + log ($1/K_H^{oct}$) + log ([CL]/[oct]^2). Therefore, even though the term, log (K_Y^{CL}/K_Y^{oct}), is reducible, the hydrogen-bonding effect should vary according to the magnitude of K_H^{oct} for a wide variety of amphiprotic substituents. The fact that the effect comes out only as the indicator variable term, 1.05HB_2, in eq 10 means that the log K_H^{oct} value does not differ so much between 4-NH_2 and 4-NHMe substituents. Since the value of log ([CL]/[oct]^2) is –0.5, the log K_H^{oct} values are likely to be in the order of 0.5. In fact, the hydrogen-bond formation constants of aniline as the hydrogen donor with oxy compounds are about 1.5-fold those of *N*-methylaniline in cyclohexane.[18b] When this rather small difference (0.17 log unit) applies to the corresponding sulfonamide derivatives in the partitioning octanol solvent, it is not enough to discriminate between the 4-NH_2 and 4-NHMe substituents for which the averaged total effect amounts to 1.05 log unit.

According to Taft and his co-workers,[6] the hydrogen-bonding constant, K_f, of various bases with OH reference acids is expressed by eq 31 where pK_{HB} is a constant representing the hydrogen-accepting ability of organic bases defined as the logarithm of the association constant with 4-fluorophenol in CCl_4 and m and c are constants characteristic of the reference acid and experimental conditions. We have estimated the pK_{HB} value for some monosubstituted benzenes, whose K_f values with phenol or methanol are available in literature but not with 4-fluorophenol, using eq 31 and m and c values for these reference acids.[6]

$$\log K_f = m\text{p}K_{HB} + c \quad (31)$$

As shown in Tables I and II, nonhydrogen bonders and hydrogen acceptors seem to be classified according to their pK_{HB} value. For "nonhydrogen bonders", perhaps K_X[solv] $\ll$ 1 so that eq 18 and 28 reduce to eq 17 and 27, respectively. For hydrogen acceptors where K_X[solv] $\gg$ 1, the hydrogen-bonding effect on log P_{CL} is almost uniform in spite of the wide variety in basicity, a range of 150-fold K_{HB} units from anisole to *N*,*N*-dimethylbenzamide. For log P_{hex}, the effect of hydrogen bonding is such that the higher the pK_{HB} value, the larger the downward deviation, Δ, from eq 8.

The hydrogen-bond strength of hydrogen acceptors with $CHCl_3$ and octanol solvents was expected to be nearly equivalent to each other earlier in this paper. According to Taft and his associates,[6] the association constants of various bases with methanol and ethanol are correlated by eq 31 where m = 0.5 and c = –0.4 to –0.5 at 25 °C. For 1-octanol as the reference acid, a quite similar relationship is expected to hold under the same conditions. Gramstad and Vikane[19] derived eq 32 from the association constants, K_f, of $CHCl_3$ and phenol as hydrogen donors for a number (n = 16) of hydrogen acceptors including P=O, C=O, and S=O compounds at 25 °C in CCl_4. For phenol as the reference acid, m = 0.97 and c = –0.13 at 25 °C in eq 31.[6] Therefore, the log K_f (phenol) values are almost equivalent to corresponding pK_{HB} values. Thus, eq 32, where log K_f (phenol) was replaced by pK_{HB}, is quite similar to correlations for alkanols as the reference acid. Under conditions of partitioning experiments where organic solvents as the hydrogen donor were water-saturated, the m and c values could be even closer between two systems.

$$\log K_f (CHCl_3) = 0.40 \log K_f (\text{phenol}) - 0.85 \quad (32)$$

If we assume that eq 31 with m = 0.5 and c = –0.4 to –0.5 can be applied to the water-saturated octanol solvent as the reference acid, the log K_X^{oct} value for anisole is around –0.5 from which the K_X^{oct} value, ca. 0.3, is estimated. Since [CL] = 12.4 M and [oct] = 6.2 M, the conditions K_X^{solv}[solv] $\gg$ 1 cannot apply to anisole when $K_{anisole}^{oct} \simeq K_{anisole}^{CL}$. Nevertheless, the value of log [(1 + K_X^{CL}[CL])/(1 + K_X^{oct}[oct])] in eq 18 does not differ much from its reduced form, log ([CL]/[oct]). The values are 0.21 and 0.30, respectively, with the difference being 0.09 so that the hydrogen-bonding effect of this compound can be approximately represented as the common indicator term with other hydrogen acceptors. Anisole seems to be the compound which is located around the borderline differentiating compounds whose HB = 0 and 1. The assignment, HB = 1, for the aromatic OMe substituent is no longer warrantable in disubstituted benzenes having strongly electron-withdrawing substituents besides OMe. The K_{OMe}^{solv} values may be even lower, i.e., K_{OMe}^{solv}[solv] $\ll$ 1 in deriving eq 24, so that the indicator variable is not required for 4-methoxybenzenesulfonamide in eq 10.

The above arguments can be generalized as eq 33, where Δ log f(HB) = log [$f(HB)_{solv}/f(HB)_{oct}$]. The f(HB) term is formulated with solvent molarity and the association equilibrium constant, K_i, depending upon the situations as shown in eq 34–37, assuming that the K_i values are mutually independent in polysolvated molecules.

$$\log P_{solv} = \log P_{oct} + \Delta \log f(\text{HB}) + \text{constant} \quad (33)$$

For nonhydrogen bonders

$$f(\text{HB}) = 1 \quad (34)$$

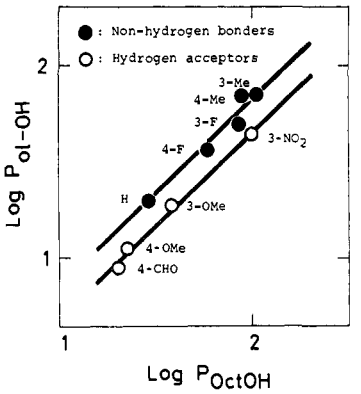

Figure 4. Plot of log P (oleyl alcohol–H_2O) vs. log P (octanol–H_2O) of substituted phenols.

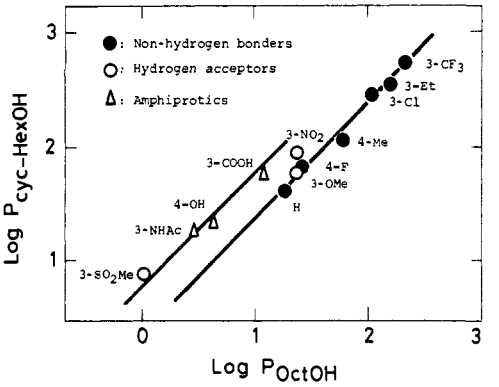

Figure 5. Plot of log P (cyclohexanol–H_2O) vs. log P (octanol–H_2O) of substituted phenoxyacetic acids.

In cases where a single association is conceivable

$$f(\mathrm{HB}) = 1 + K_1[\mathrm{solv}] \tag{35}$$

In cases where doubly solvated species participates

$$f(\mathrm{HB}) = 1 + K_1[\mathrm{solv}] + K_2[\mathrm{solv}] + K_1K_2[\mathrm{solv}]^2 \tag{36}$$

For compounds having three association sites

$$f(\mathrm{HB}) = 1 + \sum_{i=1}^{3} K_i[\mathrm{solv}] + \sum_{i \neq j} K_iK_j[\mathrm{solv}]^2 + K_1K_2K_3[\mathrm{solv}]^3 \tag{37}$$

Under conditions, $K_i[\mathrm{solv}] \ll 1$, $f(\mathrm{HB}) = 1$ so that $\Delta \log f(\mathrm{HB}) = 0$ in eq 33. When $K_i[\mathrm{solv}] \gg 1$, the value of $f(\mathrm{HB})$ is reduced only to the highest order term in eq 35–37, leading to eq 38 for $\Delta \log f(\mathrm{HB})$. In eq 38, n and m are the number of association sites involved in a solute molecule, in the solvent and octanol phases, respectively.

$$\Delta \log f(\mathrm{HB}) = \sum^{n} \log K_i^{\mathrm{solv}} - \sum^{m} \log K_i^{\mathrm{oct}} + n \log [\mathrm{solv}] - m \log [\mathrm{oct}] \tag{38}$$

If $n = m$ and $K_i^{\mathrm{solv}} \simeq K_i^{\mathrm{oct}}$ in a series of compounds, i.e., the equilibrium constants are almost equivalent between associations at each of the corresponding association sites in two organic phases, the relative hydrogen-bonding effect is determined by the solvent molarity ratio. This is the case for hydrogen-accepting monosubstituted benzenes in eq 7 where $n = m = 1$. If $n \neq m$ but $K_i^{\mathrm{solv}} \simeq K_i^{\mathrm{oct}}$ for the corresponding associations, the effect is governed not only by solvent molarity factors but also by the irreducible log K values. Equations 9 and 10 are examples where the Hammett σ constant can linearly correlate the variation in the irreducible log K which varies according to the effect of variable substituents on the constant hydrogen-donating side-chain group. Equations 26, 28, and 29 are the cases where $n \neq m$ and the irreducible log K term(s) are for the association at variable substituent sites. These are supposedly related with hydrogen-bonding parameters such as the Taft pK_{HB} for basic groups and its counterpart for acidic groups.

Thus, the indicator variable term for the extra hydrogen bonding applies to solvent–solute combinations where association patterns of substituents are equivalent to the patterns with the reference organic solvent with respect to the number of association sites as well as the strengths. With 1-octanol–H_2O as the reference, the effect on the log P ($CHCl_3$–H_2O) values can be parameterized as the indicator only for the basic substituents. The effect of hydrogen acceptors as well as donors on log P values from partition systems using water-immiscible aliphatic alcohols is expected to be related to indicators. The amphiprotic property of the OH group of aliphatic alcohols is not significantly different from that of 1-octanol.

Examples are indicated in Figure 4 for log P (oleyl alcohol–H_2O) of substituted phenols and in Figure 5 for log P (cyclohexanol–H_2O) of substituted phenoxyacetic acids listed in Tables V and VI, respectively. The hy-

Table V. Log P Values of Substituted Phenols

Substituents	Log P (ol-OH-H_2O)[a]	Log P (oct-H_2O)[b]	Substituents	Log P (ol-OH-H_2O)[a]	Log P (oct-H_2O)[b]
3-Br[c]	2.41	2.63	3-NO_2	1.64[d]	2.00
4-Br[c]	2.46	2.59	H	1.30	1.46
3-Cl[c]	2.16	2.50	3-CF_3[c]	2.72[e]	2.95
4-Cl[c]	2.24	2.39	4-CHO	0.96[d]	1.30[f]
3-F	1.69	1.93	3-Me	1.84	2.02
4-F	1.56	1.77	4-Me	1.84	1.94
3-I[c]	2.61	2.93	3-OMe	1.28	1.58
4-I[c]	2.80	2.91	4-OMe	1.04	1.34

[a] From the oleyl alcohol–H_2O system. Unless noted, from D. Burton, K. Clarke, and G. Gray, *J. Chem. Soc.*, 1315 (1964). The original data determined using an aqueous phase of pH 9.2 are corrected for the degree of dissociation using pK_A values listed in A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases", Methuen, London, 1962, p 130. [b] Unless noted, from T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, 86, 5175 (1964). [c] Not indicated in Figure 4. [d] K. Clarke and R. Cowen, *J. Chem. Soc.*, 168 (1963). Corrected for the degree of dissociation as footnote *a*. [e] J. Dearden and G. Weeks, *J. Pharm. Sci.*, 62, 843 (1973). [f] Estimated using a relationship, π/substd phenols (oct-H_2O) = 0.967 (±0.040) π/substd benzenes (oct-H_2O) + 0.946 (±0.109) σ^0 − 0.148 (±0.140) ρ_p + 0.051 (±0.042), $n = 34$, $s = 0.081$, $r = 0.996$, where ρ_p is the susceptibility in the relative solvation of para substituents with partitioning solvents to the electronic effect of the p-OH group. ρ_{CHO} is estimated as 0.30. From T. Fujita and C. Hansch, unpublished work.

Table VI. Log P Values of Substituted Phenoxyacetic Acids

Substituents	Log P (c-Hex-H_2O)[a]	Log P (oct-H_2O)[b]	Substituents	Log P (c-Hex-H_2O)[a]	Log P (oct-H_2O)[b]
3-Cl	2.46	2.02	3-COOH	1.75	1.11
4-F	1.82	1.41	4-Me	2.05	1.78
3-NO_2	1.93	1.37	3-OMe	1.80	1.38
H	1.61	1.26	3-SO_2Me	0.88	0.00
4-OH	1.32	0.65	3-NHAc	1.27	0.47
3-CF_3	2.72	2.33	3-Et	2.55	2.23

[a] From the cyclohexanol–H_2O system. T. Fujita and C. Hansch, unpublished data. [b] T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, 86, 5175 (1964).

Table VII. Log P (Olive Oil-H_2O) and Log P (Et_2O-H_2O) Values of Miscellaneous Compounds

Compd	Log P (oil-H_2O)[a]	Log P (Et_2O-H_2O)[a]	Compd	Log P (oil-H_2O)[a]	Log P (Et_2O-H_2O)[a]
	Amphiprotics			Hydrogen Acceptors	
EtOH	−1.52[b]	−0.50[c]	AcOEt	0.40	0.93
PrOH	−0.81[b]	−0.02[c]	Paraldehyde	0.28	0.95
BuOH	−0.20[b]	0.61[c]	Triacetin	−0.36	0.15
AmOH	0.36[b]	1.20[c]	Aminopyrine	−0.59	−0.20
HexOH	0.88[b]	1.80[c]	Antipyrine	−1.49	−1.14
MeCOOH	−1.30[d]	−0.34[e]	Caffeine	−1.48	−1.30
EtCOOH	−0.80[d]	0.22[e]	Urotropin	−3.68	−3.58
PrCOOH	−0.21[d]	0.70[e]	Acetone	−0.70[f]	−0.21[h]
BuCOOH	0.48[d]	1.26[e]	Et_2O	0.38[g]	1.00[h]
AmCOOH	0.83[d]	1.93[e]		Glycols	
$MeOCONH_2$	−1.60	−0.85	1,6-Hexanediol	−2.17	−0.92
$EtOCONH_2$	−1.13	−0.19	1,5-Pentanediol	−2.21	−1.26
$MeCONH_2$	−3.08	−2.60	1,3-Butanediol	−2.37	−1.38
$EtCONH_2$	−2.44	−1.89	2,3-Butanediol	−2.47	−1.54
$PrCONH_2$	−2.02	−1.24	1,2-Propanediol	−2.77	−1.74
i-$BuCONH_2$	−1.64	−0.77	1,4-Butanediol	−2.68	−1.72
Succinimide	−2.31	−1.51	Ethylene glycol	−3.31	−2.28

[a] Unless noted, from R. Collander, *Physiol. Plant.*, 7, 420 (1954), where more extensive log P values from these two partitioning systems are listed. Some of his values are believed to require reexaminations. Log P (Et_2O-H_2O) values by Collander for MeOH, EtOH, and PrOH are −0.85, −0.59, and 0.28, respectively. The differences between consecutive homologues seem irregular. In fact, the values recently determined by Matsui and Mochida (footnote *c*) are −1.15, −0.50, and −0.02, respectively. The log P (oil-H_2O) value determined by Collander for AcOMe is −0.36 which is also unexpectedly lower than the value extrapolated from the value for AcOEt, 0.40. The log P (Et_2O-H_2O) values for these two esters are 0.43 and 0.93, respectively. We did not include these irregular values in this table as well as in Figure 6. Even though all of his data are included, the general feature differentiating solute classes in Figure 6 is not changed in spite of the fact that the data points are more scattered. [b] B. A. Lindenberg, *J. Chim. Phys.*, 48, 350 (1951); *Soc. Biol. Strasbourg*, 116, 1405 (1934). [c] Y. Matsui and K. Mochida, private communication (1975). [d] M. Bodansky and V. Meigs, *J. Phys. Chem.*, 36, 814 (1932). [e] C. Hansch, A. Leo, and D. Nikaitani, *J. Org. Chem.*, 37, 3090 (1972). [f] A. Lindenberg, *Soc. Biol. Strasbourg*, 118, 1086 (1935). [g] K. Meyer and H. Hemmi, *Biochem. Z.*, 277, 39 (1935). [h] R. Collander, *Acta Chem. Scand.*, 3, 717 (1949).

drogen-acceptor substituents show a uniform effect on the log $P_{ol\text{-}OH}$ value of phenols, lowering ca. 0.2 log unit which nearly corresponds to the value of log ([ol-OH]/[oct]) $\simeq$ −0.30.[18a] Although some of the log $P_{ol\text{-}OH}$ values for nonhydrogen bonders not indicated in Figure 4 scatters to some extent, the effect seems to be real as long as the log P_{oct} value locates between 1.0 and 2.0. In Figure 5, the effect of the hydrogen acceptor as well as amphiprotic acidic substituents appears to be expressible by a common indicator term, ca. 0.4HB, and HB = 1. In fact, $n = m = 1$ for hydrogen acceptors and $n = m = 2$ for amphiprotic substituents without considering associations at the common oxyacetic acid side chain. Since log ([c-hex-OH]/[oct]) $\simeq$ 0.15,[18a] the indicator term is expected to be 0.15HB where HB = 0, 1, and 2 for neutral, basic, and amphiprotic substituents, respectively. The effect of hydrogen-accepting and amphiprotic groups should be indicated by separate lines which is not consistent with Figure 5. However, the fact that the effect of amphiprotic substituents of widely differing acidity is almost uniform amounting to ca. 0.4 log unit can be taken at least as being real. In Figure 5, the 3-OMe substituent locates closely to the line for nonhydrogen bonders. This is also unexpected since the oxyacetic acid side chain is not strongly electron withdrawing. (The Hammett σ of 3-OCH_2COOH is around 0.05–0.10.[13]) The expected effect of basic groups, 0.15 log unit, is rather low. If we use such solvent systems for which the log ([solv]/[oct]) value is more substantial, the difference in the effect between basic and amphiprotic groups will be clarified more definitely. The fact that eq 3 and 4 do not require additional terms for various molecules suggests that the conditions, $n \simeq m$ and [protein-OH] $\simeq$ [oct], are probably satisfied for the nonspecific protein binding.

When we compare log P values from two partitioning systems using hydrogen-accepting organic solvents such as ethers and carboxylic esters, the effect of amphiprotic acidic substituents can be expressed by the indicator term.

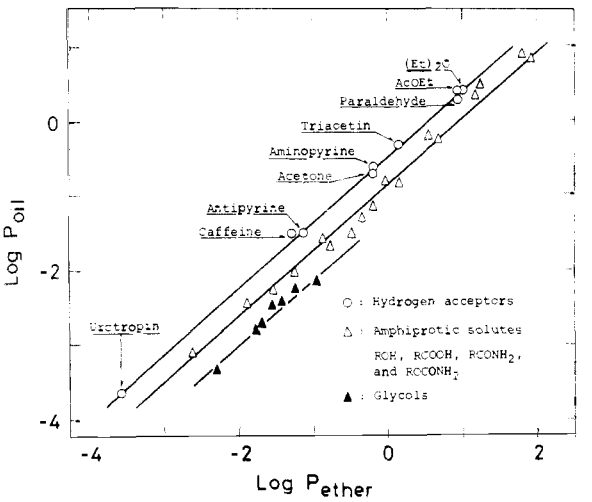

Figure 6. Plot of log P (olive oil-H_2O) vs. log P (Et_2O–H_2O) of various compounds.

Of course, the molarity of two organic solvents should differ moderately. The hydrogen-accepting scale of ethers and esters is not so different from each other that the ratio of K^{solv} values is reducible. The pK_{HB} value of aliphatic ethers locates around 1.0–1.1 and so does that of esters (1.01 for Et_2O, 1.05 for i-Pr_2O, 1.00 for AcOEt, and 1.02 for ethyl propionate[6]). The log P value of hydrogen acceptors, not requiring the indicator term, may be related in common with nonhydrogen bonders. An example is indicated in Figure 6 where the relationship between log P (olive oil-H_2O) and log P (Et_2O–H_2O) is compared for a variety of compounds having only hydrogen-accepting site(s), amphiprotic solutes of widely different acidities such as ROH, RCOOH, $RCONH_2$, and $ROCONH_2$, and aliphatic glycols having two amphiprotic OH groups using the data in Table VII. Three classes of solutes are nicely related with three parallel lines separated about 0.40 log

Table VIII. Solute Classes Whose Hydrogen-Bonding Effect on Relative Partitioning Process is Expressible by Indicator Variables

Class of solvent 1[a]	HB	Class of solvent 2[a]			
		N	A	B	AB
N	0	(N, A, B, AB)	(N, A)	(N, B)	(N)
A	0	(N, A)	(N, A)	(N)	(N)
	1		(B, AB)		(B)
B	0	(N, B)	(N)	(N, B)	(N)
	1			(A, AB)	(A)
AB	0	(N)	(N)	(N)	(N)
	1		(B)	(A)	(A, B)
	2				(AB)

[a] Organic solvents used for two partitioning systems to be compared.

unit from each other. Although the data for neutral compounds are lacking, the indicator term, –0.40 HB where HB = 0, 1, and 2 for basic, amphiprotic, and diamphiprotic compounds, respectively, seems to apply to the hydrogen-bonding effect. The effective molarity of olive oil is 1.04 × 3 M counting three ester functions in the molecule and assuming it as the pure triolein.[18a,20] Since [ether] ≃ 9.4,[18a] the log of the effective molarity ratio becomes log (3.1/9.4) = –0.48 which is about the magnitude of the effect shown in Figure 6.

The above results suggest that the effect of water molecules dissolved in organic phases is not significant on the relative hydrogen bonding in partitioning systems. In fact, the saturated water concentration in some organic solvents considered above is not so low as to be neglected. In particular, the percent mole fraction value of water in the water-saturated 1-octanol phase has been estimated as being about 25%.[20] In the water-saturated cyclohexanol, it should be even higher, since cyclohexanol dissolves water about three times more than 1-octanol.[22] Yet, partitioned organic molecules seem to prefer association with organic solvent molecules rather than with water. Once the organic molecules are partitioned into the organic phase, they may behave in a manner in which like attracts like. They may be surrounded by organic solvent molecules so that the association with dissolved water molecules may not be significant. In order to separate the effect of "dilution" by water molecules in water-saturated organic phases, the molarity values used here are the estimated values for the "pure" organic solvent in the water-saturated phase.[18a]

We can extend the above discussions to various classes of solvent–solute combinations. In Table VIII, classes of solute molecules whose hydrogen bonding effect is expressible as the indicator variable are indicated for various pairs of partitioning systems. The partitioning organic solvents as well as the partitioned solutes are classified into four categories: N, A, B, and AB. They denote, respectively, nonhydrogen bonders such as hydrocarbons, hydrogen donors such as $CHCl_3$ and $CHBr_3$, hydrogen acceptors having one of such groupings as C=O, N=O, P=O, S=O, C≡N, C=S, —O—, and –N=, and amphiprotic compounds such as ROH, RCOOH, $RCONH_2$, RSO_2NH_2, etc. The solute classes grouped together in parentheses are supposed to be related by a common indicator variable. The indicator variable term is necessary in correlations including more than one parenthesized groups of solute classes. Conditions are required so that hydrogen-accepting and/or -donating characters are nearly equivalent for each pair of combinations for A, B, and AB solvents. The solute classes not shown in each of the entries in Table VIII are not related by indicators.

The present work is believed to justify and refine observations made by Collander[21] and by Leo and Hansch[22]

Table IX. Log P Values and Anesthetic Activity of Gases

	Log P (H_2O-gas)[a]	Log P (oil-gas)[a]	Log P (oct-H_2O)[b]	Log $1/p$		
				Obsd[c]	Eq 41	Eq 50
He			0.28	–2.16		–2.26
Ne	–2.01	–1.65	0.28	–2.16	–2.00	–2.26
Ar	–1.55	–0.85	0.74	–1.18	–1.19	–1.24
Kr	–1.30	–0.35	0.89	–0.65	–0.67	–0.91
Xe	–1.07	0.25	1.28	0.02	–0.06	–0.04
N_2	–1.89	–1.17	0.67	–1.52	–1.51	–1.40
CH_4	–1.48	–0.56	1.09	–0.66	–0.89	–0.47
H_2	–1.76	–1.30	0.45	–2.16	–1.65	–1.89
N_2O	–0.37	0.18		–0.18	–0.13	
C_2H_4	–1.09	0.10		–0.15	–0.21	
c-C_3H_6	–0.68	1.06		0.80	0.77	
CF_4		–1.14[c]		–1.24	–1.48	
SF_6	–2.31	–0.59		–0.75	–0.92	
C_2F_6		–0.89[c]		–1.19	–1.23	
CF_2Cl_2	–1.29	0.69		0.40	0.39	
$CHCl_3$	0.59	2.42		2.08	2.16	
$(Et)_2O$	1.14	1.81		1.52	1.54	
Halothane	–0.09	2.35		2.11	2.09	
Methoxy-flurane	0.65	2.99		2.66	2.75	

[a] From P. Seeman, *Pharmacol. Rev.*, 24, 583 (1972), unless noted. [b] From ref 9; the values for eq 50 are listed only. [c] From ref 24.

that separate parallel correlations exist between log P_{solv} values from different partitioning systems for certain solvent–solute combinations which can be expressed by eq 39. Recently, Seiler has correlated log $P_{c\text{-}hex}$ values of compounds having various hydrogen-bonding groups with their log P_{oct} values by eq 40.[23] In eq 40, I_H is the additive increment assigned to each of the hydrogen-bonding groups, which corresponds to the log of the f(HB) function such as eq 35–37, where [solv] = [oct], according to the number of association sites in a molecule.

$$\log P_{solv} = a \log P_{ref\ solv} + \Sigma\ b_i HB_i + \text{constant} \quad (39)$$

$$\log P_{c\text{-}hex} + \Sigma I_H = \log P_{oct} + \text{constant} \quad (40)$$

Applications

On the basis of above discussions, we attempted to analyze the physicochemical significance of the indicator term in eq 5 and 6.

(1) **Activity of Gaseous Anesthetics.** Equation 5 correlates the activity of gaseous anesthetics originally determined and compiled by Miller and co-workers.[24] The set used to derive eq 5 includes various gases such as CHX_3, RCH=CH_2, CH≡CH, CH_3X, and CH_2X_2 besides those listed in Table IX. With 1-octanol–H_2O partition coefficients, the indicator variable is required for those having activated hydrogen. In the original work,[24] the same activity data were excellently correlated with the olive oil–gas partition coefficients without any additional term. For those whose log $P_{oil\text{-}gas}$ value is available, eq 41 was derived from the data in Table IX, showing that the anesthetic activity and oil–gas partitioning correspond to each other exactly in a 1 to 1 fashion. Therefore, we can replace the dependent variable, log $1/p$, in eq 5 with log $P_{oil\text{-}gas}$ as shown in a reduced form as eq 42.

$$\log 1/p = 1.024\ (\pm 0.061) \log P_{oil\text{-}gas} - 0.316\ (\pm 0.088) \quad (41)$$

$$n = 18;\ r = 0.994;\ s = 0.169$$

$$\log P_{oil\text{-}gas} = \log P_{oct\text{-}H_2O} + 1.9HB + \text{constant} \quad (42)$$

For molecules without an activated hydrogen atom, we

assume that no association occurs between molecule and solvent. Thus, $\log P_{\text{oil-gas}} = \log P^0_{\text{oil-gas}}$ and, applying eq 16, $\log P_{\text{oct-H}_2\text{O}} = \log P^0_{\text{oct-H}_2\text{O}} = \log P^0_{\text{oil-H}_2\text{O}} + c_1$, where c_1 is a constant. For those having activated hydrogen, eq 43 and 44 are derived. In these equations $\log P^0_{\text{oil-H}_2\text{O}}$ and $\log P^0_{\text{oil-gas}}$ should be related by eq 45. From the "nonliquid" partition coefficient data in Table IX, we can see that the value of $\log P^0_{\text{H}_2\text{O-gas}}$ for such unreactive gases as Ne, Ar, Kr, Xe, H_2, N_2, and CH_4 does not vary as much (-1.52 ± 0.36) as the value of $\log P^0_{\text{oil-gas}}$ (-0.82 ± 0.68). Thus, we first assume that $\log P^0_{\text{H}_2\text{O-gas}} \simeq$ constant leading to eq 46 where c_2 is a constant. By combining eq 43, 44, and 46, eq 47 is formulated, suggesting that the second term on the right side may correspond to the indicator variable term in eq 42.

$$\log P_{\text{oil-gas}} = \log P^0_{\text{oil-gas}} + \log (1 + K_{\text{CH}}^{\text{oil}}[\text{oil}]) \quad (43)$$

$$\log P_{\text{oct-H}_2\text{O}} = \log P^0_{\text{oct-H}_2\text{O}} + \log (1 + K_{\text{CH}}^{\text{oct}}[\text{oct}])/(1 + K_{\text{CH}}^{\text{W}}[\text{H}_2\text{O}]) = \log P^0_{\text{oil-H}_2\text{O}} + \log (1 + K_{\text{CH}}^{\text{oct}}[\text{oct}])/(1 + K_{\text{CH}}^{\text{W}}[\text{H}_2\text{O}]) + c_1 \quad (44)$$

$$\log P^0_{\text{oil-H}_2\text{O}} = \log P^0_{\text{oil-gas}} - \log P^0_{\text{H}_2\text{O-gas}} \quad (45)$$

$$\log P^0_{\text{oil-gas}} = \log P^0_{\text{oil-H}_2\text{O}} + c_2 \quad (46)$$

$$\log P_{\text{oil-gas}} = \log P_{\text{oct-H}_2\text{O}} + \log (1 + K_{\text{CH}}^{\text{W}}[\text{H}_2\text{O}])(1 + K_{\text{CH}}^{\text{oil}}[\text{oil}])/(1 + K_{\text{CH}}^{\text{oct}}[\text{oct}]) - c_1 + c_2 \quad (47)$$

Although the $K_{\text{CH}}^{\text{solv}}$ value should vary according to the structure of diverse compounds such as $CHCl_3$, C_2H_2, CH_3I, and $CF_3CHClBr$ included in eq 5, the variation does not seem to be very large. From the compilation of Joesten and Schaad of association constants for CHX_3, CH_2X_2, and RC≡CH as the hydrogen donor,[25] K_f values with oxy and oxo bases can be evaluated to locate around 0.3–0.6 and 0.5–0.8, respectively. Thus, the conditions, $K_{\text{CH}}^{\text{solv}}[\text{solv}] \gg 1$, are roughly satisfied for water (55.5 M) and 1-octanol (6.3 M). The extra term in eq 47 is reduced to $\log (K_{\text{CH}}^{\text{W}}/K_{\text{CH}}^{\text{oct}}) + \log ([\text{H}_2\text{O}]/[\text{oct}]) + \log (1 + K_{\text{CH}}^{\text{oil}}[\text{oil}])$ which becomes 1.40–1.50 when $K_{\text{CH}}^{\text{W}} \simeq K_{\text{CH}}^{\text{oct}}$, $K_{\text{CH}}^{\text{oil}} =$ 0.5–0.8, and [oil] = 1.04 × 3 M counting three carbonyl functions in the molecule.

The above discussion suggests that the indicator variable term in eq 5 is mostly attributed to the effect of the association in solvents, 1-octanol and water, which is not required to be considered for the correlation with $\log P_{\text{oil-gas}}$. If ethyl ether and methoxyflurane having an oxy base structure are excluded from the set used to derive eq 5, the slope of the indicator term will probably be reduced from 1.9 to 1.6–1.7.

The assumption, $\log P^0_{\text{H}_2\text{O-gas}} \simeq$ constant, is only a very crude approximation. For seven unreactive gases, the "nonliquid" partition coefficients in Table IX are indeed correlated by eq 48. Equations 45 and 48 lead to eq 49 suggesting that the susceptibility of $\log 1/p$ to $\log P_{\text{oct-H}_2\text{O}}$ should be about double of what eq 5 shows. In fact, if we pick up eight unreactive gases from the set used for eq 5, eq 50 is obtained which conforms to eq 49. By a procedure similar to that used in deriving eq 47, we can formulate eq 51 under conditions of $K_{\text{CH}}^{\text{solv}}[\text{solv}] \gg 1$ for those having only one hydrogen-donating site in the molecule. In this equation, the terms corresponding to the extra effect are asterisked.

$$\log P^0_{\text{oil-gas}} = 1.892\ (\pm 0.449) \log P^0_{\text{H}_2\text{O-gas}} + 2.186\ (\pm 0.723) \quad (48)$$

$$n = 7;\ r = 0.979;\ s = 0.142$$

$$\log P^0_{\text{oil-gas}} = 2.12 \log P^0_{\text{oil-H}_2\text{O}} - 2.46 = 2.12 \log P^0_{\text{oct-H}_2\text{O}} - 2.46 - 2.12c_1 \quad (49)$$

$$\log 1/p = 2.218\ (\pm 0.488) \log P_{\text{oct-H}_2\text{O}} - 2.883\ (\pm 0.385) \quad (50)$$

$$n = 8;\ r = 0.977;\ s = 0.193$$

$$\log P_{\text{oil-gas}} = 2.12 \log P_{\text{oct-H}_2\text{O}} + \log (1 + K_{\text{CH}}^{\text{oil}}[\text{oil}])^* + 2.12 \log (K_{\text{CH}}^{\text{W}}/K_{\text{CH}}^{\text{oct}})^* + 2.12 \log ([\text{H}_2\text{O}]/[\text{oct}])^* - 2.12c_1 - 2.46 \quad (51)$$

Thus, the somewhat large standard deviation, 0.438, of eq 5 compared with that of eq 41 may be due to the fact that the model used to derive eq 5 is not entirely relevant. Considering the number and nature of hydrogen-bondable sites in a molecule, the set of compounds in eq 5 could be subdivided into more than two subsets leading to a need of more than one indicator variable. In any case, the indicator variable appearing in correlations of anesthetic activity occurring under "nonaqueous" conditions is likely to arise from corrections required for the solvation effect involved in the "aqueous" partition coefficients.

(2) Binding of Substituted Phenyl *N*-Methylcarbamates with AcChE. The indicator variable term in eq 6 for AcChE inhibition of meta-substituted phenyl *N*-methylcarbamates, 1.53HB, is likely to be attributed to the effect of a hydrogen donor group located on the enzyme close to meta substituents in the enzyme–inhibitor complex formation. The effect corresponds to that of an acid, the concentration of which is about 30–40-fold that of the hydrogen donor, 1-octanol, in the bulk solution. The hydrogen donor group on the enzyme seems to be either an NH or OH acid. Since the $\log K_f$ value of such an NH acid as *N*-methylacetamide with carbonyl compounds (0.2–0.3) is about in the same order as that of alkanols (0–0.2),[25] the first term in the expression, $\log K_X^{\text{Enz}}/K_X^{\text{oct}} + \log [\text{Enz-H}]/[\text{oct}]$, which is supposed to correspond to the indicator variable, could be ignored.

Equation 52 correlates the $\log 1/K_d$ values for AcChE inhibition of the ortho-substituted phenyl *N*-methylcarbamates. In this equation, the σ^0 value is taken as being equivalent to that of corresponding para substituents. The signs of the ρ value in eq 6 and 52 are opposite.

$$\log 1/K_d = 1.30\ (\pm 0.33)\ \pi + 2.24\ (\pm 0.61)\ \sigma^0 + 1.68\ (\pm 0.46)\ \text{HB} - 2.56\ (\pm 0.29) \quad (52)$$

$$n = 15;\ r = 0.944;\ s = 0.223$$

We considered that a nucleophilic attack of enzymic active serine OH against the side-chain carbamyl–carbonyl carbon occurs with an assistance of concomitant protonation at the carbonyl oxygen for the meta derivatives, while without such catalytic assistance for the ortho isomers, leading to a common tetrahedral intermediate structure.[10] The slopes of π and HB terms in eq 6 and 52 are quite similar, indicating that the ortho and meta substituents perhaps fit a common hydrophobic region of the enzyme and that the ortho and meta basic substituents probably associate with a common enzymic hydrogen donor by a common mechanism.[10]

As described earlier, the indicator variable is required

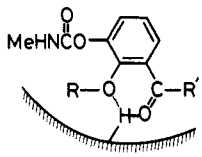

Figure 7. Stereospecificity in hydrogen bonding with enzymic hydrogen donor.

for 3-acyl, –CN, $-NO_2$, and NMe_2 derivatives in eq 6. 3-Alkoxy compounds are not classified as the hydrogen acceptor. On the contrary, eq 52 requires the indicator variable only of the 2-alkoxy- but not of 2-NO_2 and –CN compounds. The hydrogen-accepting ability of alkoxy substituents is much lower than the other basic groups as judged by pK_{HB} value of monosubstituted benzenes. Therefore, the enzymic hydrogen donor may be specifically oriented so that it can associate only with alkoxyl groups among ortho basic substituents. With this orientation, its association with meta basic substituents may be controlled not only by a close fitness to the oxo oxygen (depicted as Figure 7) but also by the magnitude of $K_X^{Enz\text{-}H}$. For *m*-alkoxy compounds the net effect is such that the ratio, $K_X^{Enz\text{-}H}[Enz\text{-}H]/K_X^{oct}[oct]$, becomes close to 1.

Since the orientation of the inhibitor molecule in the reversible complex formation with the enzyme is determined by the simultaneous attack of enzymic serine against the carbonyl carbon,[10] the association of the basic substituents with the enzymic donor group could be regarded as an "intramolecular" hydrogen-bond formation. The very stereospecific nature of the intramolecular association can be illustrated by a couple of examples. For the equilibrium observed in α,ω-diol monomethyl ethers, $HO(CH_2)_nOCH_3$, by Kuhn and Wires,[26] the intramolecular equilibrium constant, K_f(dimensionless), is 12.3 (n = 2), 1.5 (n = 3), and 0.67 (n = 4) in CCl_4 at 20 °C. The association is likely to be enforced specifically by a five-membered ring association structure in 2-methoxyethanol where the associating partners are located close enough to each other. The K_f values for 3- and 4-methoxyalkanol are similar in magnitude to the intermolecular K_f value (M^{-1}) between alkanol and ether which is around 0.8–1.5.[25] Since the enthalpy difference in the intramolecular association does not differ much from that of intermolecular association equilibria,[26] the larger the magnitude of K_f, the smaller the loss of the translational freedom of intramolecular reactants. The ratio, K_f(intramolecular)/K_f(intermolecular), having a dimension of molarity is supposed to imply the "effective concentration" of the hydroxyl group in the close neighborhood of the alkoxyl group in the intramolecular association equilibrium.[27] The "effective concentration" of the hydroxyl group in 2-methoxyethanol is 8- to 15-fold that for the intermolecular association. A similar magnitude of the "effective concentration" is found for intramolecular association of *cis*-5-hydroxy-2-methyl-1,3-dioxane whose K_f = 18.8 is about the same as that of 2-methoxyethanol considering the chance factor due to two alkoxy bases in the molecule.[28] These figures of the "effective concentration" for the intramolecular association are quite similar to those anticipated from eq 6 and 52 for the stereospecific association with the enzymic hydrogen donor.

The above analyses are thought to rationalize the use of the indicator variable for the hydrogen-bonding effect of substituents in certain cases of QSAR. The present procedure to render a physicochemical significance to the apparent hydrogen-bonding effect appearing as an indicator variable term is to analyze its magnitude in terms of the association equilibrium constants and molarities of hydrogen acceptors (or donors) in bioorganic and reference organic phases. Sometimes the association constants in two organic phases are so similar that they are not important in determining the magnitude of the indicator term. We hope that this procedure will contribute to a better understanding of indicator variables appearing in QSAR, especially in those by means of a multiple indicator variable approach currently developed by Hansch and co-workers.[29]

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