where all symbols are the same as before and k_2 is the permeation rate constant. Adjuvant I ($k_2 = 0.42 \times 10^2$ min^{-1}) did not readily cross the rectal membrane, possibly due to its strong lipophobicity. Adjuvants II ($k_2 = 7.29 \times 10^2$ min^{-1}) and IV ($k_2 = 1.91 \times 10^2$ min^{-1}) which are more lipophilic, easily permeated the rectal membrane and promoted the absorption of inulin.

Thus, adjuvant enhancement of rectal absorption of insulin and inulin appears to depend on at least three factors: adjuvants must be effectively released from the suppository, be able to permeate the membrane, and be able to interact with the calcium and magnesium ions in the membrane.

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Analysis and Prediction of Partition Coefficients of *meta*- and *para*-Disubstituted Benzenes in Terms of Substituent Effects

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Abstract □ The hydrophobic substituent parameter for a system of *meta*- and *para*-disubstituted benzenes, XC_6H_4Y, defined as $\pi_{X/PhY} = \log P_{XC_6H_4Y} - \log P_{C_6H_5Y}$, where P is the octanol–water partition coefficient and X and Y are variable and fixed substituents, respectively, varies from one system to another, according to the variation in substituent effects on the hydrogen bonding association of substituents with solvents. Using parameters from monosubstituted benzenes, $\pi_{X/PhH}$ as the reference, the π_X values were analyzed by such relations as $\pi_{X/PhY} = a\pi_{X/PhH} + \rho_Y\sigma_X + \rho_X\sigma_Y$, where ρ_Y and ρ_X are susceptibilities of the relative hydrogen bonding association of substituents Y and X with two partitioning solvents to the electronic effect of X and Y, respectively. For substituents incapable of hydrogen bonding such as alkyl and halogen, the ρ value is 0. The parameter a is a constant $\simeq 1$. The relationship was applied in calculating log P values of disubstituted benzenes.

Keyphrases □ Partition coefficient—octanol-water, analysis and prediction, *meta*- and *para*-disubstituted benzenes in terms of substituent effects □ Disubstituted benzenes—*meta*- and *para*-, analysis and prediction of partition coefficient, substituent effects □ Structure–activity relationships—analysis and prediction of partition coefficient of *meta*- and *para*-disubstituted benzenes in terms of substituent effects

In recent years, log P values (P is the 1-octanol–water partition coefficient) have been widely used as a parameter of the hydrophobic property of organic compounds in structure–activity studies (1). Log P values of complex molecules often can be calculated from those of suitable reference molecules and π values, where π is defined as $\pi_X = \log P_X - \log P_H$ (P_X is the coefficient value of a derivative on which the substituent X is carried and P_H is the coefficient value of a reference).

As pointed out earlier, however, the π value varies from one solute system to another (2). It was suggested that the variation in π values of aromatic substituents in various disubstituted benzene systems should be rationalized in terms of electronic interactions between substituents when no significant steric interaction is involved (2). For *meta*- and *para*-X substituents in disubstituted benzene systems of the type XC_6H_4Y, it was proposed that the variation in π relative to the value obtained for the monosubstituted benzene system, XC_6H_4H, depends on electronic interaction between each of the X-substituents and the fixed function Y, and is formulated, in general, as:

$$\Delta\pi = \pi_{X/PhY} - \pi_{X/PhH} = \rho_Y\sigma_X + \rho_X\sigma_Y \quad \text{(Eq. 1)}$$

where ρ_Y and ρ_X are the susceptibility constants of substituents Y and X to the solubility-modifying effects of substituents X and Y, respectively.

Since interest in the use of log P values in quantitative structure–activity studies is growing rapidly, it is important to clarify the composition of π values from various solute systems. The present report examines how far relations such as Eq. 1 can be applied in predicting π values for calculation of log P values.

EXPERIMENTAL

Solute Systems—Seventeen sets of π values (a total of 360 values) were used for the study. They were calculated from log P values of 17 disubstituted benzene solute systems and the corresponding reference monosubstituted benzenes. The majority of the log P values were taken from earlier reports (2, 3).

Several were determined[1] according to the reported procedure (2). Other values, *e.g.*, those for substituted benzamides (4), formanilides (5), acetanilides (6), and pyridines (7), are from the literature.

General Procedure—It was assumed that the solubility-modifying effect of substituent X on Y, as well as that of Y on X, was due primarily to the variation in hydrogen bonding association of substituents with solvents, according to the variation in the electronic environment of substituents X and Y. In actual examination of the applicability of Eq. 1, analysis was performed according to equations where $\pi_{X/PhY}$ and $\pi_{X/PhH}$ were used as dependent and independent variables, respectively. Although it should be close to 1, the slope of the $\pi_{X/PhH}$ term is not necessarily equal to 1. To avoid giving the unsubstituted solute excessive weight, an intercept term, c, has been included which should be close to 0. Equation 2 is employed when the fixed substituent Y is capable of hydrogen bonding:

$$\pi_{X/PhY} = a\pi_{X/PhH} + \rho_Y\sigma_X + \rho_X\sigma_Y(meta) + \rho_X\sigma_Y(para) + c \quad \text{(Eq. 2)}$$

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Table I—Primary Correlations of $\pi_{X/PhY}$ Using Eqs. 2 and 4 [a]

Solute System	a	ρ_Y	σ^0_Y (*meta*)	σ^0_Y (*para*)	c	s [b]	r [c]	n [d]	Substituents Used for Correlation	Equation
Benzoic acids	0.964 (0.071)	0.499 (0.140)			−0.021 (0.048)	0.035	0.977	12	H, *m*-F, *m*-Cl, *m*-Br, *m*-I, *m*-CH_3, *m*-CF_3, *p*-F, *p*-Cl, *p*-Br, *p*-I, *p*-CH_3	5
Phenylacetic acids	1.038 (0.155)	0.317 [e] (0.304)			−0.057 (0.104)	0.076	0.987	12	H, *m*-F, *m*-Cl, *m*-Br, *m*-I, *m*-CH_3, *m*-CF_3, *p*-F, *p*-Cl, *p*-Br, *p*-I, *p*-CH_3	6
Phenoxyacetic acids	0.935 (0.051)	0.465 (0.118)			−0.007 (0.068)	0.065	0.993	24	H, *m*-F, *m*-Cl, *m*-Br, *m*-I, *m*-CH_3, *m*-C_2H_5, *m*-C_3H_7, *m*-*i*-C_3H_7, *m*-C_4H_9, *m*-*t*-C_4H_9, *m*-C_6H_5, *m*-CF_3, *m*-SF_5, *p*-F, *p*-Cl, *p*-Br, *p*-I, *p*-CH_3, *p*-*i*-C_3H_7, *p*-*s*-C_4H_9, 3,4-$(CH)_4$, 3,4-$(CH_2)_3$, 3,4-$(CH_2)_4$	7
Phenols	1.028 (0.108)	0.959 (0.202)			0.000 (0.081)	0.060	0.993	13	H, *m*-F, *m*-Cl, *m*-Br, *m*-I, *m*-CH_3, *m*-C_2H_5, *m*-CF_3, *p*-F, *p*-Cl, *p*-Br, *p*-I, *p*-CH_3	8
Benzamides	0.999 (0.077)	0.437 (0.181)			0.028 (0.085)	0.064	0.994	13	H, *m*-Br, *m*-Cl, *m*-F, *m*-CH_3, *p*-F, *p*-Cl, *p*-Br, *p*-I, *p*-CH_3, *p*-CF_3, *p*-*i*-C_3H_7, *p*-*t*-C_4H_9	9
Anilines	1.020 (0.055)	0.731 (0.082)			−0.005 (0.028)	0.015	0.999	7	H, *m*-F, *m*-Cl, *m*-CH_3, *p*-F, *p*-Cl, *p*-CH_3	10
Benzyl alcohols	0.937 (0.052)	0.486 (0.096)			0.023 (0.035)	0.046	0.998	11	H, *m*-Cl, *m*-CH_3, *m*-NO_2, *m*-OH, *m*-NH_2, *p*-Cl, *p*-CH_3, *p*-NO_2, *p*-OCH_3, *p*-OH	11
Formanilides	0.977 (0.053)	0.696 (0.068)			0.028 (0.027)	0.019	0.999	7	H, *p*-Cl, *p*-NO_2, *p*-CN, *p*-CH_3, *p*-OCH_3, *p*-$COCH_3$	12
Acetanilides	0.989 (0.058)	0.907 (0.159)			0.008 (0.060)	0.043	0.999	7	H, *p*-F, *p*-Br, *p*-I, *p*-OCH_3, *p*-NO_2, *p*-$CONH_2$	13
Benzonitriles	0.882 (0.135)		0.769 (0.264)	0.712 (0.244)	−0.095 (0.153)	0.083	0.987	11	H, *m*-OH, *m*-COOH, *m*-CH_2COOH, *m*-OCH_2COOH, *m*-$CONH_2$, *p*-OH, *p*-COOH, *p*-OCH_2COOH, *p*-$CONH_2$, *p*-NHCHO	14
Nitrobenzenes	0.920 (0.046)	−0.200 (0.109)	0.742 (0.128)	0.758 (0.132)	0.001 (0.047)	0.053	0.997	20	H, *m*-Cl, *m*-Br, *m*-CH_3, *m*-COOH, *m*-CH_2COOH, *m*-OCH_2COOH, *m*-CH_2OH, *m*-OH, *m*-NH_2, *m*-$CONH_2$, *p*-Cl, *p*-CH_3, *p*-COOH, *p*-CH_2COOH, *p*-OCH_2COOH, *p*-CH_2OH, *p*-OH, *p*-NH_2, *p*-$CONH_2$	15
Acetophenones	0.886 (0.111)	0.178 [f] (0.197)	0.388 (0.212)	0.352 (0.235)	0.044 (0.084)	0.068	0.994	12	H, *m*-OCH_2COOH, *m*-OH, *m*-NO_2, *p*-OCH_2COOH, *p*-OH, *p*-NO_2, *p*-NHCHO, *m*-NH_2, *p*-NH_2, *p*-CH_3, *p*-Cl	16
Anisoles	0.911 (0.077)	0.292 (0.130)	0.011 [g] (0.125)	−0.168 (0.124)	0.012 (0.082)	0.055	0.994	18	H, *m*-COOH, *m*-CH_2COOH, *m*-OCH_2COOH, *m*-OH, *m*-$CONH_2$, *m*-NH_2 *m*-NHCHO, *m*-NO_2, *p*-COOH, *p*-CH_2COOH, *p*-OCH_2COOH, *p*-OH, *p*-$CONH_2$, *p*-CH_2OH, *p*-NHCHO, *p*-$NHCOCH_3$, *p*-NO_2	17

[a] $\pi_{X/PhY} = a\pi_{X/PhH} + \rho_Y\sigma^0_X + \rho_X\sigma^0_Y(m) + \rho_X\sigma^0_Y(p) + c$; unless noted, all of the terms except for the intercept values are justified above the 99.5% level; figures in parentheses are the 95% confidence intervals. [b] Standard deviation. [c] Correlation coefficient. [d] Number of points used for correlations. [e] Justified at the 95% level. [f] Justified at the 93% level. [g] Justified at the 50% level.

For cases when Y is incapable of association:

$$\pi_{X/PhY} = a\pi_{X/PhH} + \rho_X\sigma_Y(meta) + \rho_X\sigma_Y(para) + c \quad \text{(Eq. 3)}$$

Since the effect of Y on X is accounted for either by $\sigma_Y(meta)$ or $\sigma_Y(para)$, depending on the position of X-substituents, the term $\rho_X\sigma_Y$ in Eq. 1 should be separated as in Eqs. 2 and 3. Each of the $\rho_X\sigma_Y$ terms is only applicable to each of the corresponding *meta*- and *para*-substituents. For nonhydrogen-bonding variable substituents X, the value of ρ_X should be taken as 0. For π values derived from a set of XC_6H_4Y compounds where a fixed substituent Y is capable of hydrogen-bonding while the variable X substituents are not, Eq. 2 can be simplified as:

$$\pi_{X/PhY} = a\pi_{X/PhH} + \rho_Y\sigma_X + c \quad \text{(Eq. 4)}$$

According to recent studies on the hydrogen-bonding effect on oil–water partitioning of substituted benzene derivatives, substituents such as hydrogen, halogen, alkyl, phenyl, trifluoromethyl (CF_3), and pentafluorothio (SF_5) are discriminated as nonhydrogen bonders (8).

Values of σ^0 were used throughout this study. Preliminary examinations showed that σ^0 works better than σ^- for π values from phenols and anilines. Even π values from benzoic acids and benzamides were better correlated by σ^0 than σ. Values for $\pi_{X/PhH}$ (1) and σ^0 (9) used for correlations were taken from the literature.

The values for a, ρ_Y, σ_Y (*meta*), σ_Y (*para*), and c were determined by regression analysis. If the correlation is complete, σ_Y (*meta*) and σ_Y (*para*) values determined as regression coefficients of ρ_X terms should be equal to the respective σ values of the fixed substituent Y.

Preliminary Analysis—To carry out analyses using Eqs. 2 and 3, ρ_X values for hydrogen bonding variable substituents were needed. In the first six cases in Table I, data for only nonhydrogen bonding X substituents were fit to an equation of the form of Eq. 4 to get an approximate value for ρ_Y for such Y substituents as carboxyl, carboxylmethyl (CH_2COOH), carboxylmethoxy (OCH_2COOH), hydroxy, carbamoyl ($CONH_2$), and amino. The assumption for the first approximation was that $\rho_X = 0$. In the next three cases in Table I, σ^0_Y values of functional groups such as *m*- and *p*-hydroxymethyl(CH_2OH), *p*-formylamido(NHCHO), and *p*-acetamido ($NHCOCH_3$) were essentially 0 (1, 9); hence, there was no electronic effect, for example, of hydroxymethyl on hydrogen bonding X substituents to affect π. Therefore, these three examples, including hydrogen bonding and nonhydrogen bonding substituents can be fit to the same type of equation as the first six. This provided the approximate ρ_Y values altogether for nine hydrogen bonding Y substituents.

For the benzonitriles, nitrobenzenes, acetophenones, and anisoles, few derivatives with nonhydrogen bonding X substituents have reported π values; therefore, in these examples, equations of the type derived for the

Table II—Final Correlation of $\pi_{X/PhY}$ Using Eqs. 2 and 3 [a]

Solute System	a	ρ_Y	$\sigma^0_Y(m)$	$\sigma^0_Y(p)$	c	s [a]	r [a]	n [a]	Substituents used for correlation [b]	Equation
Benzoic acids	1.001 (0.042)	0.435 (0.098)	0.352 (0.126)	0.427 (0.138)	−0.024 (0.046)	0.048	0.998	22	m-CN, p-CN, m-OCH_3, p-OCH_3, m-NO_2, p-NO_2, m-OH, p-OH, m-OCH_2COOH, p-NH_2	18
Phenylacetic acids	0.954 (0.057)	0.294 (0.143)			0.012 (0.059)	0.079	0.993	20	m-COOH, m-CN, m-OH, m-OCH_3, p-OCH_3, m-NO_2, p-NO_2, m-SO_2CH_3	19
Phenoxyacetic acids	0.913 (0.026)	0.416 (0.082)			0.035 (0.035)	0.076	0.996	44	m-$COCH_3$, p-$COCH_3$ m-CN, p-CN, m-OCH_3, p-OCH_3, m-OCF_3, m-NO_2, p-NO_2, m-$NHCOCH_3$, m-$NHCOC_6H_5$, m-SCH_3, m-SCF_3, m-SO_2CH_3, m-COOH, m-OH, p-OH, p-$N{=}NC_6H_5$, m-$NHCONH_2$, m-SO_2CF_3	20
Phenols	0.967 (0.040)	0.941 (0.105)		−0.151 [c] (0.138)	0.052 (0.040)	0.080	0.996	35	m-$COCH_3$, p-$COCH_3$, m-OCH_3, p-OCH_3, m-NO_2, p-NO_2, m-CN, p-CN, m-COOH, p-COOH, m-OH, p-OH, m-NH_2, p-NH_2, m-CH_2OH, p-CH_2OH, m-OCH_2COOH, p-OCH_2COOH, m-$CONH_2$, p-$CONH_2$, m-CH_2COOH, m-$N(CH_3)_2$	21
Benzamides	0.951 (0.056)	0.447 (0.132)	0.281 (0.174)	0.285 (0.170)	0.085 (0.062)	0.070	0.996	24	m-NO_2, p-NO_2, m-CN, p-CN, p-$NHCOCH_3$, m-OH, p-OH, m-NH_2, p-NH_2, m-OCH_3, p-OCH_3	22
Anilines	0.889 (0.100)	0.740 (0.219)	−0.255 [d] (0.259)	−0.566 (0.240)	0.069 (0.089)	0.087	0.994	18	m-NO_2, p-NO_2, m-OCH_3, m-OH, p-OH, m-$COCH_3$, p-$COCH_3$, p-COOH, m-CH_2OH, m-$CONH_2$, p-$CONH_2$	23
Benzonitriles	0.915 (0.087)		0.757 (0.142)	0.694 (0.132)	−0.048 (0.069)	0.059	0.990	15	m-NO_2, p-NO_2, m-$OCONHCH_3$, p-$OCONHCH_3$	24
Nitrobenzenes	0.913 (0.051)	−0.139 [e] (0.105)	0.751 (0.141)	0.751 (0.151)	0.018 (0.049)	0.063	0.993	28	m-$COCH_3$, p-$COCH_3$, m-CN, p-CN, m-OCH_3, p-OCH_3, m-NO_2, p-NO_2	25
Acetophenones	0.904 (0.092)	0.156 [c] (0.153)	0.410 (0.179)	0.376 (0.197)	0.050 (0.065)	0.058	0.995	13	p-OCH_3	26
Anisoles	0.924 (0.061)	0.272 (0.099)		−0.193 (0.084)	0.037 (0.058)	0.052	0.995	20	p-$COCH_3$, m-OCH_3	27
Toluenes	0.980 (0.034)				−0.054 [f] (0.029)	0.052	0.997	24	H, m-Cl, p-Cl, m-CH_3, p-CH_3, m-NO_2, p-NO_2, m-OCH_2COOH, p-OCH_2COOH, m-CH_2COOH, p-CH_2COOH, m-COOH, p-COOH, m-CH_2OH, p-CH_2OH, m-OH, p-OH, m-NH_2, p-NH_2, m-$CONH_2$, p-$CONH_2$, m-$OCONHCH_3$, p-$OCONHCH_3$, p-$COCH_3$	28
	0.998 (0.037)			−0.102 [c] (0.096)		0.061	0.998	24		28a
Chlorobenzenes	0.966 (0.058)		0.394 (0.137)	0.370 (0.138)	−0.088 [f] (0.043)	0.066	0.994	24	H, m-Cl, p-Cl, m-CH_3, p-CH_3, m-NO_2, p-NO_2, m-OH, p-OH, m-NH_2, p-NH_2, m-COOH, p-COOH, m-CH_2COOH, p-CH_2COOH, m-OCH_2COOH, p-OCH_2COOH, m-CH_2OH, p-CH_2OH, m-$CONH_2$, p-$CONH_2$, m-$OCONHCH_3$, p-$OCONHCH_3$, p-$COCH_3$	29
	0.975 (0.079)		0.269 (0.165)	0.240 [g] (0.166)		0.089	0.994	24		29a
Pyridines	0.800 (0.055)		0.430 (0.173)	0.604 (0.177)	0.169 [f] (0.048)	0.075	0.994	19	H, β-CH_3, β-Cl, β-Br, β-CN, γ-CH_3, γ-Br, γ-Cl, γ-C_6H_5, γ-CN, γ-C_3H_7, β-NO_2, β-$COCH_3$, γ-$COCH_3$, β-NH_2, γ-NH_2, β-$NHCOCH_3$, γ-$NHCOCH_3$, γ-OCH_3	30
	0.901 (0.064)	0.332 (0.138)	0.750 (0.195)	1.023 (0.194)		0.099	0.992	19		30a
Phenyl N-methylcarbamates	0.992 (0.049)	0.602 (0.140)	0.469 (0.297)	0.481 (0.318)	0.037 (0.066)	0.079	0.994	41	H, m-F, m-Cl, m-Br, m-I, m-CH_3, m-C_2H_5, m-C_3H_7, m-i-C_3H_7, m-t-C_4H_9, m-CF_3, p-F, p-Cl, p-Br, p-I, p-CH_3, p-C_2H_5, p-C_3H_7, p-i-C_3H_7, p-s-C_4H_9, p-t-C_4H_9, m-OCH_3, m-CN, m-NO_2, m-$COCH_3$, p-OCH_3, p-$COCH_3$, p-CN, p-NO_2, m-OC_2H_5, m-O-i-C_3H_7, m-OC_4H_9, m-CHO, m-$COOCH_3$, m-COC_2H_5, p-OC_2H_5, p-OC_4H_9, p-COC_2H_5, p-CHO, p-$COOCH_3$, p-O-i-C_3H_7	31

[a] $\pi_{X/PhY} = a\pi_{X/PhH} + \rho_Y\sigma^0_X + \rho_X\sigma^0_Y(m) + \rho_X\sigma^0_Y(p) + c$; see footnotes a–d in Table I. [b] Those already indicated in Table I are not listed. [c] Justified at the 95% level. [d] Justified at the 94% level. [e] Justified at the 97.5% level. [f] Justified above the 99.5% level. [g] Justified at the 99% level.

first nine data sets of Table I were not appropriate, so hydrogen bonding X substituents had to be included in these cases. The electronic effect of substituents from Y to X should be taken into account. The ρ_X value for each of the hydrogen bonding X substituents should be identical to the ρ_Y value for a solute system where the corresponding hydrogen bonding substituent was invariant. Values of ρ_Y, calculated for the nine

Table III—Susceptibility Constant of Relative Hydrogen Bonding Association with Solvents

Y-Substituent	ρ_Y	Y-Substituent	ρ_Y
Nonhydrogen bonder		Amphiprotic substituents	
CH_3	0	CH_2COOH	0.29(±0.14)
Cl	0	OCH_2COOH	0.42(±0.08)
		COOH	0.44(±0.10)
Hydrogen acceptor		$CONH_2$	0.45(±0.13)
NO_2	−0.14(±0.11)	CH_2OH	0.49(±0.10)
CN	0	$OCONHCH_3$	0.50(±0.14)
OCH_3	0.27(±0.10)	NHCHO	0.70(±0.07)
$COCH_3$	0.16(±0.15)	NH_2	0.74(±0.22)
—*N*=	0.33(±0.14)	$NHCOCH_3$	0.91(±0.16)
		OH	0.94(±0.11)

hydrogen bonding Y substituents, could be substituted for either of the ρ_X terms of Eq. 2 for these hydrogen bonding X substituents. The values of ρ_X for nonhydrogen bonding substituents was taken as 0. Performing the regression analysis yielded Eqs. 14–17 (Table I) with four new approximate ρ_Y values for hydrogen bonding Y substituents, nitro, cyano, acetyl, and methoxy. Values of σ_Y^0 were determined as regression coefficients of ρ_X terms. In the case of the benzonitriles, ρ_Y was essentially 0. The results of these primary correlations are shown as Eqs. 5–17 (Table I). The level of significance of all of the correlations in Table I was >99.5%, as determined by the *F* test.

Final Regression Analysis—The 13 primary ρ_Y values can now be substituted into Eq. 2 for the ρ_X values for hydrogen bonding X substituents. The regression analysis was performed by including nonhydrogen bonding as well as hydrogen bonding substituents. For π values from benzyl alcohol, formanilides, and acetanilides, it was unnecessary to refit, since σ_Y^0 is 0 in these examples, no matter what the ρ_X values were. The ρ_Y values for hydrogen bonding Y substituents determined for 10 series of π values were slightly different from the corresponding primary values; thus, this process was repeated by substituting newly derived ρ_Y values into Eq. 2 for ρ_X values until constant ρ_Y values were obtained. In the course of the calculations, ρ_X terms were found to be insignificant in the correlation equations for phenylacetic acids and phenoxyacetic acids; hence, it was possible to include hydrogen bonding X substituents for which the ρ_X values were not known in the final correlations.

Values of π_X from substituted toluenes and chlorobenzenes, where the fixed function is nonhydrogen bonding, were analyzed by means of Eq. 3 using self-consistent ρ_X values. Finally, π values from substituted phenyl *N*-methylcarbamates and pyridines were applied to Eq. 2. Since σ values of the substituent *N*-methylcarbamoyloxy ($OCONHCH_3$) were not available and, since there is some uncertainty for σ values of aza(—*N*=) function, π_X values of $OCONHCH_3$ and —*N*= as X substituents were not included in correlations, except for a few cases where the σ_X term was insignificant. In deriving Eq. 31 for those of phenyl-*N*-methylcarbamates, the ρ_X values of alkoxyl groups were approximated by that of the methoxyl group and those of acyl and carbomethoxyl groups by that of the acetyl group.

RESULTS

The results for 14 sets of π values are shown in Table II as Eqs. 18–31. All the correlations and the terms other than the intercepts are justified >99.5% by *F* and *t* tests, unless noted. Those for π values of benzyl alcohols, formanilides, and acetanilides are the same as the primary correlations, Eqs. 11–13 in Table I. Values of *a* and ρ_Y observed in Eqs. 18–23 of the correlations including hydrogen bonding substituents are practically identical with those in Eqs. 5–10 for only nonhydrogen bonding X substituents; this seems to support the assumptions made to formulate Eq. 1. The effect of X on Y and Y on X are mutually independent, and the effects are additive in determining the variation of π values.

As expected, the value of *a*, the slope of the $\pi_{X/PhH}$ term, and the *c* value (the intercept) are close to 1 and 0, respectively, in most of the equations in Tables I and II. For substituted pyridines, however, the value for *a* is considerably lower than 1 (0.80 ± 0.06) in Eq. 30. The ρ_X terms for toluenes (Eq. 28) and the σ_X^0 term for pyridines (Eq. 30) are insignificant. For substituted toluenes (Eq. 28), chlorobenzenes (Eq. 29), and pyridines (Eq. 30), the *c* value is significant, >99.5%. It was expected that the correlations without an intercept may reveal different features such as different and/or significant slope values of respective terms for these three sets from those of Eqs. 28–30; in fact, the deletion of the intercept seems to yield more reasonable results as shown in Eqs. 28*a*–30*a*, although the quality of correlations in terms of standard deviation becomes slightly poorer. In Eq. 28*a* for toluene π values, the slope of the ρ_X (*para*) term is now significant, coinciding with the authentic σ^0 (p-CH_3) value. In Eq. 30*a* for pyridine π values, the value of *a* comes close to 1, the σ_X^0 term becomes significant, and the σ_Y^0 values estimated for the β- and γ-aza (—*N*=) groups get closer to the values derived from hydrolytic rates of isonicotinic and nicotinic acid esters (10) and IR frequency studies of substituted pyridines (11). The following discussion will be made on the basis of final correlations: Eqs. 11–13 in Table I and Eqs. 18–27, 28*a*–30*a*, and 31 in Table II.

DISCUSSION

Intrinsic Hydrophobicity of Substituents—Although the values of *a* are close to 1, most of the values from 17 sets of π values are slightly <1; the average is 0.94 ± 0.03, which is attributable to the fact that the assumption leading to Eq. 1 is not entirely valid. After separating the effects due to hydrogen bond formation, the intrinsic hydrophobicity of substituents in disubstituted benzenes is lower than that in monosubstituted benzenes. When a substituent is introduced in the monosubstituted benzene ring, the extent of the iceberg formation could be slightly lower than that formed by the introduction into the unsubstituted benzene.

Susceptibility in Hydrogen Bonding Association of Fixed Substituents to Electronic Effect of Variable Substituents, ρ_Y Values—The ρ_Y values are summarized in Table III. The sign of the ρ_Y values can be explained by considering the relative hydrogen bonding effect of substituents with solvents. For hydrogen-accepting Y substituents, such as acetyl in acetophenones where the carbonyl oxygen works as a hydrogen acceptor, a type of solvation such as $>C{=}O \ldots HOR$ (I) is only possible where R=H or n-C_8H_{17} in each of the water and octanol phases. Water, being more acidic than 1-octanol, would effectively compete in this type of solvation; thus, the strongly electron-withdrawing substituents would not be favorable to the hydration at the basic group and raise the partition coefficient.

For amphiprotic substituents such as hydroxyl in substituted phenols, there are two types of hydrogen bonding, $XC_6H_4OH \ldots R{-}O{-}H$ (II) and $XC_6H_4H{-}O \ldots HOR$ (III). Octanol, being more basic and less acidic than water, would favor the association of type II, whereas water would more effectively undergo the type III association. The more electron-withdrawing the substituent X, the more the amount of type II solvation with octanol (and the less the ratio of type III hydration). This effect results in a higher partition coefficient; therefore, regardless of whether the Y group is hydrogen-accepting, -donating, or amphiprotic, the electron withdrawal of X substituents is expected to make the $\pi_{X/PhY}$ value higher than the $\pi_{X/PhH}$ value. The positive ρ values for most of the Y groups in Table III can be understood on this basis.

For amphiprotic functions, the ρ_Y value for the relative solvation effect seems to roughly depend on the distance between the ring and associable hydrogen. The higher ρ values are found for phenols, anilines, and anilides, while the lowest value is for phenylacetic acids. Almost identical ρ values are observed for carboxyl, carbamoyl, and hydroxymethyl functions where the location of the hydrogen is similar.

The ρ values for hydrogen-acceptor functions are lower than what might be anticipated from the location of the association sites; in particular, the value for the benzonitriles is insignificant. The low ρ value for the relative solvation effect at basic functions seems to reflect a difference in hydrogen-donating ability smaller than that in hydrogen-accepting ability between water and octanol; the type II solvation would be more susceptible to the substituent effect than types I and III. At the present time, no relevant rationalization can be found for the negative ρ value found for the nitro group.

Electronic Effect of Fixed Substituents on Hydrogen Bonding Association of Variable Substituents, σ_Y^0 Values—The regression coefficients of the ρ_X terms are compared with available authentic σ_Y^0 values in Table IV (12). The calculated σ_Y^0 values coincide with respective authentic values within the 95% confidence intervals. Although the sequence of magnitude of calculated σ_m^0 and σ_p^0 values for some pairs of *meta*- and *para*-substituents is reversed from that of the authentic values, the general agreement between calculated and authentic σ_Y^0 values seems good. The correlation between these values for 30 *meta*- and *para*-substituents is expressed by:

$$\sigma^0 \text{ (calculated)} = 1.058(\pm 0.091)\sigma^0 \text{ (authentic)} - 0.019(\pm 0.036) \quad \text{(Eq. 32)}$$

where *n* is 30, *r* is 0.971, and *s* is 0.081. The electronic effect of fixed substituents Y actually is represented by σ_Y^0 values and exhibited only toward hydrogen bondable variable substituents X. This is believed to

Table IV—Comparison of Calculated σ_Y^0 Values with Authentic σ_Y^0 Constants

Y-Substituent		σ_Y^0 (authentic)[a]	σ_Y^0 (calc.)	Y-Substituent		σ_Y^0 (authentic)[a]	σ_Y^0 (calc.)
COOH	*meta*	0.37	0.35(±0.13)	CN	*meta*	0.62	0.76(±0.14)
	para	0.46	0.43(±0.14)		*para*	0.69	0.69(±0.13)
CH_2COOH	*meta*	0.03	0	NO_2	*meta*	0.70	0.75(±0.14)
	para	−0.05	0		*para*	0.82	0.75(±0.15)
OCH_2COOH	*meta*	0.05	0	$COCH_3$	*meta*	0.34	0.41(±0.18)
	para	−0.21	0		*para*	0.46	0.38(±0.20)
OH	*meta*	0.04	0	OCH_3	*meta*	0.06	0
	para	−0.13	−0.15(±0.14)		*para*	−0.16	−0.19(±0.08)
$CONH_2$	*meta*	0.28	0.28(±0.17)	CH_3	*meta*	−0.07	0
	para	0.36	0.29(±0.07)		*para*	−0.12	−0.10(±0.10)
NH_2	*meta*	−0.14	−0.26(±0.26)	Cl	*meta*	0.37	0.27(±0.17)
	para	−0.38	−0.57(±0.24)		*para*	0.27	0.24(±0.17)
NHCHO	*para*	0	0	*—N=*	*β*	0.62[b]	0.75(±0.20)
					γ	0.93[b]	1.02(±0.19)
$NHCOCH_3$	*para*	0.03	0				
CH_2OH	*meta*	0	0				
	para	0.05	0				

[a] From Ref. 9. [b] Ref. 12.

support the fundamental assumption leading to the present procedure.

Prediction of Log *P* Values of Disubstituted Benzenes—The present work indicates that the variations in π values of *meta*- and *para*-aromatic substituents from one system to another are due primarily to variations in the extent of hydrogen bonding solvation of substituents. Practically no outliers from correlations are found using the present procedure. The substituent effects governing this variation, in general, are bidirectional. The π value of a certain substituent is modified not only by its own effect on a fixed function but also by a backward effect from the fixed function. These modifications depend on susceptibilities of substituents to relative hydrogen bond formation with solvents, and the susceptibility varies from one substituent to another. Thus, $\pi_{X/PhH}$ values could be used as fixed substituent constants in predicting log *P* values of aromatic compounds as a first approximation only when aromatic substituents are rather insensitive to and/or not influential on the relative hydrogen-bonding effect.

Had more ρ_X values been determined for hydrogen-bondable X substituents, a large number of log *P* values of disubstituted aromatic compounds could have been predicted more precisely according to the present procedure using relations such as:

$$\pi_{X/PhY} = 0.94\pi_{X/PhH} + \rho_Y\sigma_X^0 + \rho_X\sigma_Y^0 \ (\textit{meta} \text{ or } \textit{para}) \quad \text{(Eq. 33)}$$

Furthermore, had the present procedure been combined with the recently developed method to analyze the *ortho* effect (13), it would have been possible to calculate even the log *P* values of *ortho*-disubstituted benzenes.

The full account of this study, including theoretical considerations on the bidirectional Hammett relationship governing the $\Delta\pi$ values as well as the data and parameters used for correlations, will be published elsewhere (14).

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