Micelle/Water Partition Properties of Phenols Determined by Liquid Chromatographic Method. Proposal for Versatile Measure of Hydrophobicity

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Partition properties have been determined for 28 monosubstituted phenols in the sodium dodecylsulfate (SDS)/water system by micellar liquid chromatography (MLC), offering a useful and versatile method to estimate the hydrophobicity of compounds. The enthalpy and entropy terms of partition have also been determined from variable temperature experiments on MLC and are interpreted by such factors as molecular size and hydrogen-bond ability of the solute. The π constants (π, π_H and π_S) are determined from the experimental partition properties and applied to quantitative structure–activity relationships (QSAR) analysis, and their versatility supported.

Key words micelle/water partition coefficient; micellar liquid chromatography; quantitative structure–activity relationship; enthalpy; entropy; phenol

Hydrophobicity is an important property of drugs, being closely related to the process of transportation to the site of action. In the field of quantitative structure–activity relationships (QSAR), the most popular hydrophobic parameter is $\log P$, the decimal logarithm of oil/water partition coefficient, and the partition coefficients have usually been measured in the 1-octanol/water system. The measurement of such partition coefficients has not been widely accepted in the research and development of new drugs by synthetic method, however. This may be because the methods are tedious and time-consuming, and consume large amounts of synthesized materials. Chemical models of biomembrane, such as micelles or liposomes, have been studied as an organic phase in the biphasic solvent system. Micelles have the advantages of long stability and easy preparation. Several measurements of micelle/water partition coefficients, P_{mic}, have been reported; these were made by different analytical methods such as gas chromatography,[1] calorimetry,[2] NMR,[3] and so on. However, these methods also have some problems in practice,[3] and have therefore not been widely accepted.

In the present study, micelle/water partition coefficient as well as its thermochemical properties was measured by micellar liquid chromatography (MLC), and a versatile means of determining hydrophobicity is offered. MLC was first reported as a separation technique,[4] and was then applied to the quantitation of hydrophobicity.[5] However, only the retention factor, k', in the MLC has hitherto been used to indicate hydrophobicity,[5] and the partition coefficient, P_{mic}, has not been given any attention although it is derived from the analysis of micelle concentration dependence of k'. This is thus the first study that proposes P_{mic} obtained from MLC as a useful and versatile measure of hydrophobicity. The difference between k' and P_{mic} is clear as stated below, *i.e.*, k' includes not only P_{mic} but also the partition coefficient between the stationary phase and water, P_{stn}, as seen in Eq. 1 below. In MLC, the surfactant solutions above the critical micelle concentration (cmc) are used as a LC mobile phase, and P_{mic} is determined according to the following equation[4];

$$1/k' = \frac{(P_{mic}-1)V}{P_{stn}\phi} C_m + \frac{1}{P_{stn}\phi} \quad (1)$$

where C_m is the micelle concentration (*i.e.*, total surfactant concentration − cmc), V is the partial molar volume of the micellized surfactant, and ϕ is the chromatographic phase ratio.

We have recently been studying partition properties from the standpoint of thermodynamics.[6] The $\log P$ term corresponds to the Gibbs free energy change in partition (ΔG_p°), *i.e.*, $\Delta G_p^\circ = -\boldsymbol{R}T\ln P$, where "ln" means natural logarithm. The free energy change can be divided into the enthalpy change (ΔH_p°) and the entropy change (ΔS_p°). Therefore, the following equation holds:

$$\log P = \frac{-\Delta G_p^\circ}{2.303\boldsymbol{R}T} = \frac{-\Delta H_p^\circ}{2.303\boldsymbol{R}T} + \frac{\Delta S_p^\circ}{2.303\boldsymbol{R}} \quad (2)$$

where $\boldsymbol{R}$ is the gas constant, and T is the absolute temperature. We have defined the novel hydrophobic parameters, P_H, P_S, π_H and π_S[7] on the basis of this relationship. That is, the first term on the right-hand side of Eq. 2 is set to hydrophobic enthalpy parameter P_H and the second term to hydrophobic entropy parameter P_S. π_H and π_S are derived as equal to the group contribution to P_H and P_S, respectively: $\pi_H = P_H(X) - P_H(H)$ and $\pi_S = P_S(X) - P_S(H)$, where the difference is taken after replacing H atom by a group X in the aromatic system. These hydrophobic parameters have been determined for benzoic acids and fatty alcohols in the 1-octanol/water system, and been applied to QSAR analyses.[7]

In the present work, we determined the micelle/water partition coefficients of 28 monosubstituted phenols by the MLC method, and clarified the factors contributing to the enthalpy and entropy changes of partition. The hydrophobic parameters determined in the micelle/water system were then applied to QSAR analyses of phenols.

Experimental

LC System The Waters gradient liquid chromatographic system model 680 was used which consists of two 510 pumps, and a 484 UV detector (at 260 nm). The reversed-phase column used was Waters

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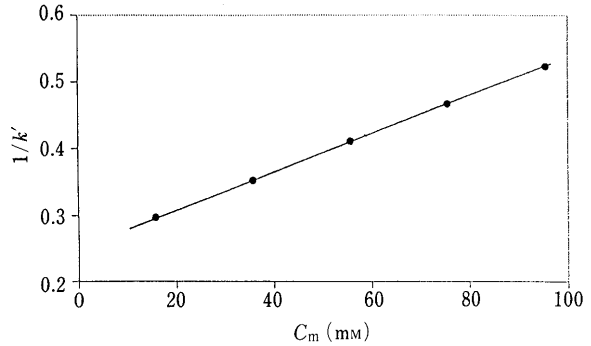

Fig. 1. The Plot of Eq. 1 for the Determination of P_{mic} by the Micellar Liquid Chromatographic Method

Sample, phenol; temperature, 22.4°C.

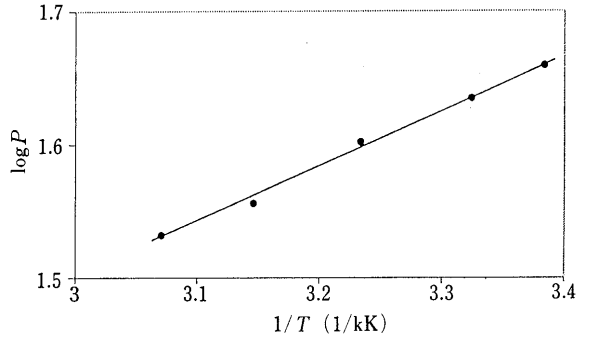

Fig. 2. The van't Hoff Plot for the Separation of the Gibbs Free Energy Term into the Enthalpy and Entropy Terms

Sample, phenol.

Novapak C-8 (3.9×75 mm). The guard column, Waters Guardpak Novapak C-8, was attached between the injector and the analytical column. The guard column and analytical column were kept at constant temperatures (±0.1 °C) in a circulating constant-temperature bath. The flow rate of 2.0 ml/min was used throughout this study.

Reagents Monosubstituted phenols obtained from Nacalai Tesque Inc. and Tokyo Kasei Kogyo Co., Ltd. were purified by recrystallization or distillation. Sodium dodecylsulfate (SDS) (≧99.0%) obtained from Nacalai Tesque Inc. was used without further purification.

Procedure Aqueous phase was the 0.001 M HCl–0.01 M NaCl solution to stabilize pH and cmc. The desired weight of SDS was dissolved in this solution. The cmc of SDS in this solution was determined to be 0.0044 M from the conductivity measurement. Sodium nitrate ($NaNO_3$) was used as an unretained compound to determine column dead time (t_0). The value of 249.7 ml/mol was used for the partial molar volume of the micellized SDS.[8] Partition coefficients in the SDS/water system, P_{SDS}, were measured at five temperatures between 20 and 55 °C, and calculated according to Eq. 1 (Fig. 1). The enthalpy and entropy changes were derived from van't Hoff plot (Eq. 2 and Fig. 2).

Results and Discussion

The correlation coefficients of the plot of Eq. 1 were above 0.999 in all cases, and all partition coefficients were obtained within the error of 1% on repeated runs. The correlation coefficients were also above 0.99 in the van't Hoff plot of Eq. 2. The resulting thermodynamic and hydrophobic parameters are all listed in Table I. Hydrophobic substituent constants (π, π_H, and π_S) determined in the SDS/water system were applied to QSAR analyses.

Factors Contributing to the Enthalpy and Entropy Changes of Partition For the thermodynamic study of partition, it is important to understand what kind of characters the enthalpy and entropy terms have. We found

TABLE I. Hydrophobic and Thermodynamic Parameters of Micelle/Water Partition for Monosubstituted Phenols[a]

No.	X	log P	ΔH_p°[b]	ΔS_p°[c]
1	H	1.65 (0.09)	−8.0 (0.4)	4.6 (1.2)
2	2-F	1.75 (0.05)	−8.6 (0.2)	4.7 (0.7)
3	4-F	1.80 (0.07)	−8.6 (0.3)	5.8 (0.9)
4	2-Cl	2.15 (0.07)	−10.1 (0.3)	7.2 (0.9)
5	3-Cl	2.30 (0.02)	−10.1 (0.1)	10.1 (0.3)
6	4-Cl	2.34 (0.03)	−10.7 (0.1)	8.9 (0.4)
7	3-Br	2.46 (0.13)	−10.7 (0.5)	11.1 (1.8)
8	4-Br	2.50 (0.10)	−11.3 (0.4)	9.6 (1.4)
9	2-I	2.58 (0.08)	−14.2 (0.3)	1.7 (1.0)
10	3-I	2.70 (0.17)	−13.1 (0.7)	7.8 (2.3)
11	4-I	2.76 (0.07)	−12.5 (0.3)	11.0 (1.0)
12	2-CH_3	2.05 (0.09)	−9.7 (0.4)	6.7 (1.2)
13	3-CH_3	2.05 (0.08)	−8.3 (0.3)	11.5 (1.0)
14	4-CH_3	2.09 (0.07)	−8.8 (0.3)	10.5 (0.9)
15	3-OCH_3	1.91 (0.06)	−12.0 (0.3)	−3.6 (0.8)
16	4-OCH_3	1.80 (0.09)	−11.2 (0.4)	−3.2 (1.2)
17	3-CHO	1.83 (0.18)	−12.1 (0.7)	−5.5 (2.4)
18	4-CHO	1.80 (0.03)	−12.9 (0.1)	−8.7 (0.4)
19	3-$COCH_3$	2.02 (0.16)	−12.1 (0.7)	−1.9 (2.2)
20	4-$COCH_3$	1.98 (0.06)	−14.5 (0.2)	−10.6 (0.8)
21	3-NO_2	2.01 (0.03)	−11.6 (0.1)	−0.3 (0.4)
22	4-NO_2	2.01 (0.12)	−12.8 (0.5)	−4.4 (1.5)
23	2-CN	2.03 (0.18)	−12.9 (0.7)	−4.4 (2.3)
24	3-CN	1.92 (0.13)	−11.4 (0.5)	−1.5 (1.8)
25	4-CN	1.89 (0.13)	−12.4 (0.6)	−5.4 (1.8)
26	3-$NHCOCH_3$	1.66 (0.04)	−13.6 (0.2)	−13.9 (0.6)
27	4-$NHCOCH_3$	1.48 (0.12)	−13.5 (0.5)	−17.0 (0.6)
28	4-$CONH_2$	1.47 (0.24)	−15.5 (1.0)	−23.7 (3.1)

a) log P is given at 25 °C. The values in parentheses are standard errors. b) In kJ·mol^{-1}. c) In J·K^{-1}·mol^{-1}.

that the enthalpy and entropy changes of partition (ΔH_p° and ΔS_p°) are expressed by four parameters, ΔV_w,[9] σ^-,[10] α, and β; ΔV_w is the van der Waals volume referenced to unsubstituted phenol and σ^- is the Hammett constant for phenols. α and β are hydrogen-bonding related parameters derived from $\sum\alpha$ and $\sum\beta$[11]: α and β are set equal to the group contributions to $\sum\alpha$ and $\sum\beta$, respectively, $\sum\alpha$ and $\sum\beta$ being defined as proton donor and proton acceptor scales from the data of hydrogen-bonding equilibrium constants.[11] Multiple regression analyses resulted in the following Eqs. 3 and 4, where the value in parenthesis denotes standard error:

$$\Delta H_p^{\circ} = -15.63(2.41)\Delta V_w - 2.08(0.56)\sigma^- + 1.05(0.67)\alpha - 0.86(0.38)\beta - 7.00(0.49) \quad (3)$$

$$r=0.92,\ \text{S.D.}=0.94,\ F=32.4$$

$$\Delta S_p^{\circ} = 11.74(7.41)\Delta V_w - 3.32(1.74)\sigma^- - 2.29(2.05)\alpha - 11.19(1.19)\beta - 6.30(1.50) \quad (4)$$

$$r=0.96,\ \text{S.D.}=8.39,\ F=65.3$$

For the enthalpy change (ΔH_p°), the molecular size (ΔV_w term) contributes almost half of the substituent dependence, the residual part coming from the other hydrogen-bonding related terms (σ^-, α, β), as revealed in the standard regression coefficients. That is, the following coefficients are obtained when analyzed after normalization of all parameters: −0.71 for ΔV_w, −0.35 for σ^-, 0.21 for α, and −0.30 for β. The molecular size may reflect the cavity term in the Scaled Particle theory,[12] in which each

TABLE II. Correlation Coefficients between the Two Parameters

	$\log P^{a)}$	$\Delta H_p^{\circ b)}$	$\Delta S_p^{\circ c)}$	ΔV_w	σ^-	α	β
$\log P$	1.000	0.063	0.298	−0.093	0.077	−0.182	−0.369
ΔH_p°	0.063	1.000	−0.673	−0.784	−0.495	−0.394	−0.677
ΔS_p°	0.298	−0.673	1.000	−0.511	−0.341	−0.644	−0.948
ΔV_w	−0.093	−0.784	−0.511	1.000	0.036	0.654	0.660
σ^-	0.077	−0.495	−0.341	0.036	1.00	−0.138	0.282
α	−0.182	−0.394	−0.644	0.654	−0.138	1.000	0.691
β	−0.369	−0.677	−0.948	0.660	0.282	0.691	1.000

a) This term is proportional to ΔG_p° as well as to π by definition, and hence the same correlation coefficients can be obtained when $\log P$ is replaced by ΔG_p° or π. *b*) This term is proportional to π_H by definition, and hence the same correlation coefficients are obtained when replaced by π_H. *c*) This term is proportional to π_S by definition, and hence the same correlation coefficients are obtained when replaced by π_S.

solute molecule is incorporated into solvent after making a cavity of sufficient size in the solvent, from which solvent molecules are excluded. A solute molecule can interact with solvent molecules when it is situated in the cavity. The cavity term expresses the energy of cavity formation and includes the volumes of solute and solvent molecules, surface tension, and so on. The molecular interaction term expresses the energy of solute–solvent interactions which include several kinds of interactions such as hydrogen bonding, electrostatic, charge-transfer, and van der Waals'.[13] The hydrogen-bonding ability terms may reflect the strength of the hydrogen-bond formed between solute and solvent.

For the entropy change (ΔS_p°), it is seen from the regression coefficients after normalization of parameters, *i.e.*, 0.13 for ΔV_w, −0.13 for σ^-, −0.11 for α, and −0.92 for β, that the hydrogen-bond ability term β, contributes by more than 70%. The minus sign before β in Eq. 4 means that when β is high and hydrogen-bond acceptor ability is increased, ΔS_p° is decreased, ΔG_p° is increased and P_{mic} is decreased. This result is interpreted as follows. When a phenol molecule is transferred from water to micelle, a definite number of water molecules will be released from the solvation sphere to the phenol molecule. But if the solute–solvent hydrogen-bonding is strengthened, fewer water molecules will be released (the phenol molecule will get into micelle accompanied by some water molecules around it near the micelle surface). That is, a smaller number of water molecules will be released for phenols with higher β value; this is in accordance with the decreased ΔS_p° for phenols with high β term. Here, ΔS_p° is viewed as reflecting the change in the degree of randomness resulting from the change in the degree of hydrogen-bonding. A similar effect is rather hard to observe with regard to α and ΔH_p° because the α value does not change much between the phenols treated here; it may be because the volumetric term ΔV_w induced much larger contributions to ΔH_p°, masking the effect of β to ΔH_p°.

Similar analyses with π_H and π_S give rise to Eqs. 5 and 6, which are consistent with Eqs. 3 and 4:

$$\pi_H = 2.18(0.34)\Delta V_w + 0.40(0.08)\sigma^- - 0.07(0.09)\alpha + 0.12(0.06)\beta - 0.06(0.07) \quad (5)$$
$$r = 0.93, \quad \text{S.D.} = 0.13, \quad F = 39.4$$

$$\pi_S = 0.71(0.42)\Delta V_w - 0.20(0.10)\sigma^- - 0.17(0.12)\alpha - 0.56(0.07)\beta + 0.07(0.08) \quad (6)$$
$$r = 0.95, \quad \text{S.D.} = 0.16, \quad F = 54.5$$

The same analysis with π, which is equal to $\pi_H + \pi_S$ by definition, gives rise to Eq. 7:

$$\pi = 2.90(0.32)\Delta V_w + 0.20(0.08)\sigma^- - 0.24(0.09)\alpha - 0.44(0.05)\beta + 0.01(0.06) \quad (7)$$
$$r = 0.94, \quad \text{S.D.} = 0.13, \quad F = 43.1$$

From Eqs. 5—7 it can be seen that ΔV_w and σ^- definitely contribute to π_H whereas β is important in π_S and that these three parameters as a whole contribute mainly to π. Although the α term (hydrogen donor ability) has only limited effect on π, π_H and π_S, the Hammett's σ^- constant exerts a compensating effect on π_H and π_S, leading to only slight impact on π. Such profiles of the π constants (π, π_H and π_S) indicate the advantage of separating π into π_H and π_S.

The correlation coefficients between all pairs of parameters treated here are shown in Table II. Quite a high degree of correlation is observed for ΔS_p° toward β, whereas ΔH_p° exhibits rather high correlation with ΔV_w. On the contrary, no discernible correlation is observable for $\log P$ toward any other parameters, indicating that $\log P$ possesses a dualistic nature that may appear in ΔH_p° and ΔS_p°. Of course, since it is usually observed that enthalpy–entropy compensation relation holds for chemical processes, separation of the free energy term ($\log P$) into the corresponding enthalpy (ΔH_p°) and entropy (ΔS_p°) terms would fall short of rigorous separation of the dualistic nature. But it can safely be said that the $\log P$ term includes volumetric as well as hydrogen-bonding features, the former being primarily reflected in ΔH_p° and the latter in ΔS_p°. The correlation coefficients are low ($|r| \leqq 0.691$) for any pair of ΔV_w, σ^-, α and β, in support of the following use of these as independent parameters.

Application to QSAR Analyses To test the applicability of the π constants derived above a few pieces of biological data are analyzed by regression equations. The biological activity data used are the bactericidal activities ($\log(1/C)$) against *Ps. aeruginosa*[14] and the sulfate conjugation catalyzed by phenol sulfotransferase from human liver ($\log(1/K_m)$),[15] where C is the killing concentration against *Ps. aeruginosa* at 40 min and K_m is the Michaelis constant of phenol sulfotransferase catalysis. The biologi-

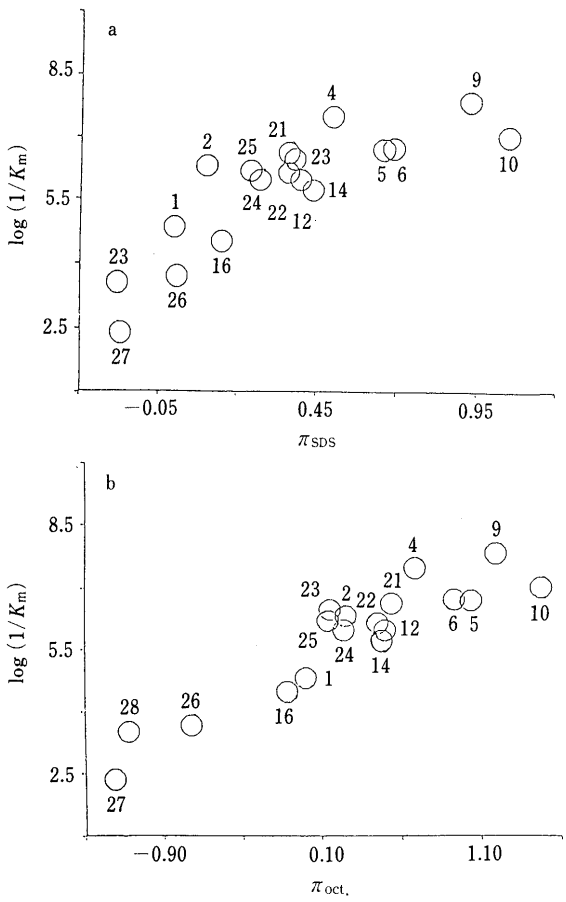

Fig. 3. The Plot of Biological Activity against π Constants

a: $\log(1/K_m)$ *vs* π_{SDS}. b: $\log(1/K_m)$ *vs* $\pi_{oct.}$ The numbering corresponds to that in Table I.

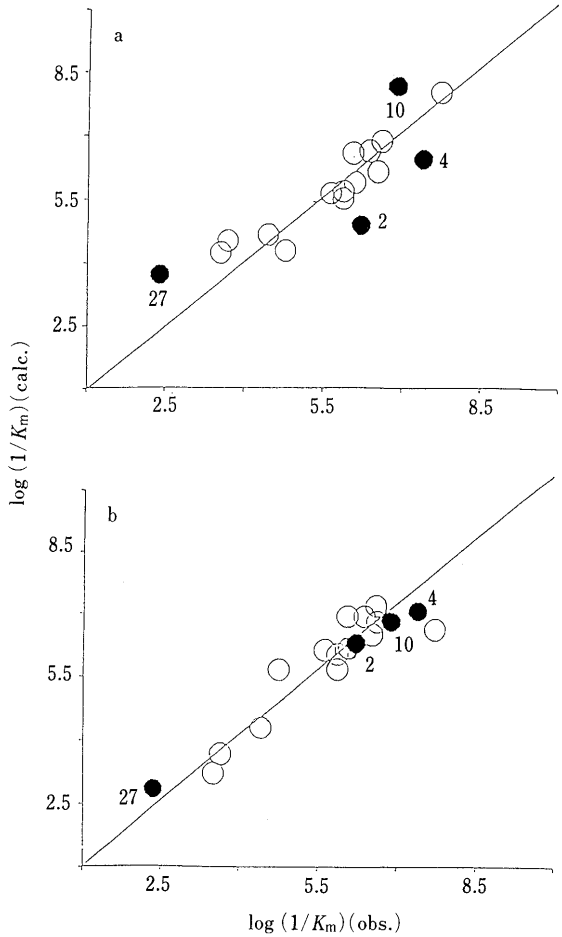

Fig. 4. Correlation Analyses of $\log(1/K_m)$

a: π_{SDS} and σ^- are used as independent parameters. b: $\pi_{S,SDS}$ and σ^- are used as independent parameters. The numbering corresponds to that in Table I. The closed circles are better located on a line in (b) than in (a).

TABLE III. Biological Activity Data and Parameters

No.	X	$\log(1/C)^{a)}$	$\log(1/K_m)^{b)}$	$\pi_{SDS}^{c)}$	$\pi_{H,SDS}^{c)}$	$\pi_{S,SDS}^{c)}$	$\pi_{oct.}^{d)}$	$\sigma^{-d)}$	$\Delta V_w^{e)}$	$\beta^{f)}$	$\alpha^{f)}$
1	H	1.08	4.78	0.00	0.00	0.00	0.00	0.00	0.000	0.0	0.0
2	2-F	1.11	6.24	0.10	0.09	0.01	0.25	0.29	0.046	0.0	0.0
3	4-F	1.53		0.15	0.09	0.06	0.31	0.06	0.046	0.0	0.0
4	2-Cl	1.28	7.41	0.50	0.36	0.14	0.69	0.50	0.165	0.0	0.0
5	3-Cl	1.70	6.62	0.66	0.37	0.29	1.04	0.37	0.165	0.0	0.0
6	4-Cl	1.75	6.64	0.69	0.47	0.22	0.93	0.27	0.165	0.0	0.0
7	3-Br	1.96		0.81	0.47	0.34	1.17	0.34	0.206	0.0	0.0
8	4-Br	1.98		0.85	0.58	0.27	1.13	0.27	0.206	0.0	0.0
9	2-I	1.51	7.76	0.93	1.08	−0.15	1.19	0.64	0.303	0.0	0.0
10	3-I	2.23	6.92	1.05	0.89	0.16	1.47	0.35	0.303	0.0	0.0
11	4-I	2.31		1.11	0.78	0.33	1.45	0.27	0.303	0.0	0.0
12	2-CH_3	1.70	5.90	0.40	0.29	0.11	0.50	−0.13	0.154	0.0	0.0
13	3-CH_3	1.60		0.41	0.05	0.36	0.51	−0.07	0.154	0.0	0.0
14	4-CH_3	1.60	5.66	0.44	0.13	0.31	0.48	−0.15	0.154	0,0	0.0
15	3-OCH_3	1.34		0.26	0.69	−0.43	0.12	0.12	0.235	0.7	0.0
16	4-OCH_3	1.79	4.44	0.15	0.56	−0.41	−0.12	−0.16	0.235	0.7	0.0
17	3-CHO			0.18	0.71	−0.53	−0.08	0.35	0.175	1.2	0.0
18	4-CHO			0.15	0.85	−0.70	−0.11	0.90	0.175	1.2	0.0
19	3-$COCH_3$			0.37	0.71	−0.34	−0.07	0.38	0.329	1.6	0.0
20	4-$COCH_3$			0.33	1.13	−0.80	−0.11	0.71	0.329	1.6	0.0
21	3-NO_2		6.55	0.36	0.62	−0.26	0.54	0.71	0.187	0.5	0.0
22	4-NO_2		6.08	0.36	0.83	−0.47	0.45	1.18	0.187	0.5	0.0
23	2-CN		6.40	0.38	0.85	−0.47	0.15	1.18	0.177	1.0	0.0
24	3-CN		5.90	0.27	0.59	−0.32	0.24	0.56	0.177	1.0	0.0
25	4-CN		6.12	0.24	0.77	−0.53	0.14	0.89	0.177	1.0	0.0
26	3-$NHCOCH_3$		3.65	0.01	0.98	−0.97	−0.73	0.21	0.436	2.1	1.6
27	4-$NHCOCH_3$		2.35	−0.17	0.96	−1.13	−1.21	0.00	0.436	2.1	1.6
28	4-$CONH_2$		3.51	−0.18	1.30	−1.48	−1.13	0.61	0.247	2.4	1.0

a) *C* is the killing concentration against *Ps. aeruginosa* at 40 min. See ref. 14. *b*) K_m is the Michaelis constant of phenol sulfotransferase catalysis. See ref. 15. *c*) $\pi_{H,SDS}$ and $\pi_{S,SDS}$ mean π_H and π_S values determined in the SDS/water system, respectively. *d*) See ref. 10. *e*) See ref. 9. *f*) See ref. 11.

TABLE IV. QSAR Analyses of Phenols

	Equations[a]	n[b]	R'[c]	S.D.[d]	F[e]
8	$\log(1/C)=0.80(0.17)\pi_{SDS}+1.23(0.11)$	16	0.76	0.23	22.0
9	$\log(1/C)=1.16(0.14)\pi_{SDS}-0.87(0.21)\sigma^{-}+1.20(0.07)$	16	0.90	0.23	32.7
10	$\log(1/C)=0.50(0.13)\pi_{oct.}+1.31(0.11)$	16	0.68	0.26	15.0
11	$\log(1/C)=0.83(0.12)\pi_{oct.}-1.03(0.25)\sigma^{-}+1.27(0.08)$	16	0.87	0.18	24.0
12	$\log(1/K_m)=3.50(0.58)\pi_{SDS}+4.52(0.28)$	18	0.82	0.82	36.1
13	$\log(1/K_m)=2.57(0.76)\pi_{H,SDS}+3.46(0.55)\pi_{S,SDS}+5.08(0.42)$	18	0.84	0.77	21.9
14	$\log(1/K_m)=-3.71(1.15)\pi_{SDS}^{2}+6.52(1.05)\pi_{SDS}+4.32(0.23)$	18	0.89	0.65	33.9
15	$\log(1/K_m)=3.31(0.54)\pi_{SDS}+0.90(0.44)\sigma^{-}+4.21(0.29)$	18	0.85	0.75	23.8
16	$\log(1/K_m)=2.47(0.25)\pi_{S,SDS}+2.04(0.31)\sigma^{-}+5.57(0.18)$	18	0.93	0.44	56.0
17	$\log(1/K_m)=1.80(0.19)\pi_{oct.}+5.23(0.15)$	18	0.91	0.58	87.7
18	$\log(1/K_m)=-0.37(0.21)\pi_{oct.}+1.85(0.18)\pi_{oct.}+5.43(0.18)$	18	0.95	0.44	81.5

a) The values in parentheses are standard errors. *b*) Number of data. *c*) Multiple correlation coefficient adjusted for the degree of freedom. *d*) Standard deviation. *e*) Variance ratio.

cal activity data and parameters for QSAR analyses are all summarized in Table III. It may be said in general that the biological activity data of phenols are correlated with hydrophobicity.[14b] The $\log(1/C)$ and $\log(1/K_m)$ data are also correlated with $\pi_{oct.}$, π constant in the 1-octanol/water system.[14,15] When the $\log(1/C)$ data are treated with different hydrophobic parameters (Table IV, Eqs. 8 and 10), π_{SDS} gives better results (lower S.D. and higher R' and F) than $\pi_{oct.}$ does; but if the Hammett's σ^{-} constant is included in the calculation (Table IV, Eqs. 9 and 11), $\pi_{oct.}$ gives slightly better results than π_{SDS} (lower S.D. and higher F, although R' is lower). As for the data of $\log(1/K_m)$ $\pi_{oct.}$ gives better fittings over π_{SDS} when linear and quadratic equations are considered with regard to the π constant (Table IV, Eqs. 12, 14, 17, and 18, and Fig. 3); but when the Hammett's σ^{-} constant is included, $\pi_{S,SDS}$, *i.e.*, the hydrophobic substituent entropy constant in the SDS/water system, gives better fittings than π_{SDS} does (Fig. 4). As stated above, $\pi_{S,SDS}$ reflects substituent dependence of ΔS_p°, which is highly correlated with the hydrogen-bond acceptor ability (β in Table II). This fact supports our separation of the free energy term into the corresponding enthalpy and entropy terms.

The biological activity data treated above are rather well explained by the traditional hydrophobic parameter π, and it may be difficult to notice any improvement with introduction of the new hydrophobic parameter defined in the micelle/water system (π_{SDS}). However, the newly introduced parameter dose not require tedious and time-consuming operation nor a large quantity of materials, and is thus expected to be broadly used in future medicinal chemistry.

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