Hydrogen-Bonding Abilities for Phenols Assessed by Quantitative Analyses of Their Partition Coefficients Derived from Different Partitioning Systems

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We recently proposed a new hydrogen-accepting scale, S_{HA}, on the basis of the heat of formation calculated by the conductor-like screening model (COSMO) method. In this work, the same approach was applied to a series of compounds with a common hydrogen-donor group. Thus the S_{HA} values for monosubstituted phenols were calculated and used for correlating their $\log P_{oct}$ values (P_{oct}: 1-octanol/water partition coefficient) with $\log P_{CL}$ (P_{CL}: chloroform/water partition coefficient) and $\log P_{E}$ (P_{E}: butyl ether/water partition coefficient). It was demonstrated that the S_{HA} parameter works effectively, providing excellent correlations whose physicochemical meanings are well rationalized in terms of hydrogen-bonding characteristics of the substituents.

Key words hydrophobicity; partition coefficient; hydrogen-accepting parameter; phenol; conductor-like screening model (COSMO)

In proportion to the rapid advance of computational chemistry for rational drug design, the development of convenient methods for predicting various physicochemical parameters is getting more and more important. Among many parameters that are expected to correlate with bio-activity, the hydrophobicity of molecule, usually expressed by $\log P_{oct}$ (P_{oct}: 1-octanol/water partition coefficient), is one of the most important parameters used for quantitative structure–activity relationship (QSAR) studies.[1,2] We have so far studied systematically $\log P_{oct}$ values for heteroaromatic compounds and found it very important to estimate correctly the contribution of hydrogen-bonding effects involved in $\log P_{oct}$ values for reliable prediction of $\log P_{oct}$.[3—6] Many efforts have been devoted to developing appropriate parameters to describe the hydrogen-bonding abilities. Among them, the indicator variable HB[7] and Abraham's hydrogen-bond acidity and basicity scales[8,9] are most frequently used. Although the HB parameter is easy to use and the performance is good,[7] this scale is not "pre-established". Also although the Abraham's scales are "pre-established", appropriate experimental data are needed to derive these parameters. To overcome these problems, we have recently defined a new hydrogen-bond-accepting parameter, S_{HA}, for monosubstituted (di)azines with hydrogen-accepting substituents, $Ar_N\text{-}X$,[5] on the basis of the heat of formation calculated in various dielectronic environments by semi-empirical MO calculations with the conductor-like screening model (COSMO) method.[10] We verified it's availability by correlating $\log P_{oct}$ with the $\log P$ values derived from the chloroform/water partitioning system, $\log P_{CL}$, and also with the chromatographic retention factor, $\log k$, which reflects the partitioning of compounds between stationary and mobile phases. The S_{HA} parameter worked effectively to express the hydrogen-bond effects involved in the relationship between two different partitioning systems, providing Eq. 1 as the general formula.[5,6,11]

$$\log P_{CL}(\log k) = a \log P_{oct} + \rho\sigma + s S_{HA} + \text{const.} \qquad (1)$$

The $\rho\sigma$ (σ: Hammett's type electronic substituent constant) and $s S_{HA}$ terms act as correction terms for hydrogen-bonding effects; the $\rho\sigma$ term describes electronic effects of the substituent X on the change in hydrogen-bonding ability of the ring N-atom(s) and the $s S_{HA}$ term expresses the hydrogen-bonding ability of the X-substituent. The "a" value, the coefficient of the $\log P_{oct}$ term, should be close to 1, provided the hydrophobic and hydrogen-bonding contributions are satisfactorily separated by Eq. 1.[7]

Definition of the hydrogen-donating parameter is much more difficult because a hydrogen-donating site(s) is usually present as a part of amphiprotic moieties, that is, it(they) coexists with hydrogen-accepting site(s) as shown by the following examples: $-O\underline{H}$, $-N\underline{H}R(\underline{H})$, $-CO_2\underline{H}$, $-CON\underline{H}R(\underline{H})$, $-SO_3\underline{H}$ and $-SON\underline{H}R(\underline{H})$. Under such circumstances, application of the same approach used for the definition of S_{HA} to these amphiprotic substituents should result in indices involving the overall effects of hydrogen-donating and accepting properties. As a preparatory process to separate the results into the hydrogen-donating and -accepting contributions, we first tried to study a series of compounds having a common hydrogen-donating (amphiprotic) group. For this purpose, we measured, in this work, $\log P$ values for a series of monosubstituted phenols, $P_{OH}\text{-}X$, with non-hydrogen-donating substituents, in three partitioning systems of different hydrogen-bonding properties, $\log P_{oct}$, $\log P_{CL}$ and $\log P_{E}$ (P_{E}: butyl ether/water partition coefficient), and analyzed the relationship between $\log P_{oct}$ and $\log P_{CL}$ (or $\log P_{E}$) in terms of Eq. 1 to examine how well the results represent the hydrogen-bonding behavior of the amphiprotic fixed substituent OH, and hydrogen-accepting substituents X.

Experimental

Measurements for $\log P$ The compounds, $P_{OH}\text{-}X$, used in this work are listed in Table 1. All the substituents X are nonhydrogen-bonders or hydrogen-acceptors. Most of $\log P_{oct}$ values were taken from the literature.[12] The values for P_{CL} and P_{E} were measured at 25 °C by the conventional shake-flask method as described previously for measurements of P_{oct}.[13] After partitioning of a sample between water and chloroform (butyl ether), the concentrations of the solute were measured in both water and organic phases by RP-HPLC. A Shimadzu LC9A liquid chromatograph, equipped with an auto injector (IS-25, Kyoto Chromato), and a photodiode array detector (SPD-M10AVP, Shimadzu), was used. The measurements were undertaken at least at two different initial concentrations to ascertain that neither dissociation nor association of solutes affect the values of $\log P$. For most of compounds,

log *P* values were reproducible within the range of ±0.03. However, the log *P* values for some *ortho* substituted phenols such as *o*-OR, *o*-Ac and *o*-CO₂R phenols, were unstable and much larger than those for the corresponding *p*-substituted derivatives regardless of the partitioning system, suggesting the influence of the intra-molecular hydrogen-bonding. These compounds were excluded in this study. The results are summarized in Table 1 together with the physicochemical parameters used for analyses.

S_{HA} **Parameters**　The procedure for calculating the S_{HA} parameter was previously described in detail for (di)azines.[5] The same method was utilized to calculate S_{HA} for $\mathbf{P_{OH}}$-**X**. Calculations were done by an ANCHOR II modeling system[14] and CACHe Work System Pro (v. 5.04) (Fujitsu)[15] by using the COSMO method which calculates the heat of formation in the medium of the dielectric constant ε. The main principle for calculations of S_{HA} is as follows. First, the minimum energy conformation of each compound ($\mathbf{P_{OH}}$-**X**) in the gaseous state was established using the AM1 method.[16] With this conformation, the heat of formation, ΔH_f, of each compound was calculated with and without the "eps" command of the COSMO module, denoted as $\Delta H_f(\varepsilon)$ and $\Delta H_f(g)$, respectively. The difference between $\Delta H_f(g)$ and $\Delta H_f(\varepsilon)$, $\delta = \Delta H_f(g) - \Delta H_f(\varepsilon)$, should be larger as the molecule is stabilized by solvation with the more polar solvent. The S_{HA} value for $\mathbf{P_{OH}}$-**X** is defined as $S_{HA} = \delta(X)/\delta(H)$ where $\delta(X)$ and $\delta(H)$ represent the δ values for a X-substituted phenol and phenol itself, respectively. The S_{HA} thus obtained are given in Table 1.

Results

First, the relationship between $\log P_{CL}$ and $\log P_{oct}$ for *m*- and *p*-substituted phenols was analyzed by the regression analyses. The direct correlation was poor as shown by Eq. 2, indicating that significant hydrogen-bonding contributions are involved.

$$\log P_{CL} = 0.848 \log P_{oct} - 0.814 \tag{2}$$
$$n = 23, r = 0.776, s = 0.297, F = 31.8$$

In this equation and throughout this paper, *n* is the number of compounds used for calculations, *r* is the correlation coefficient and *s* is the standard deviation. *F* is the value of the *F*-ratio between the variances of the observed and calculated values. To correct for the hydrogen-bonding effects, we introduced the correction terms according to Eq. 1; the regression analysis using the parameters in Table 1 yielded an improved correlation as shown by Eq. 3.

$$\log P_{CL} = 1.050 \log P_{oct} - 1.172\sigma^\circ + 0.754 S_{HA} - 1.968 \tag{3}$$
$$n = 23, r = 0.974, s = 0.113, F = 115$$

As an electronic parameter, we used σ°[17] because it gave the best fit among various Hammett-type electronic parameters. In fact, Fujita demonstrated in analyses of partition coefficients for disubstituted benzenes that σ° worked better than σ^- for phenols and anilines.[12] Likewise, the analysis for $\log P_E$ by adding the same correction terms improved the single correlation (Eq. 4) to yield Eq. 5.

$$\log P_E = 1.252 \log P_{oct} - 1.074 \tag{4}$$
$$n = 23, r = 0.953, s = 0.171, F = 208$$

$$\log P_E = 1.188 \log P_{oct} - 0.280\sigma^\circ - 0.298 S_{HA} - 0.488 \tag{5}$$
$$n = 23, r = 0.990, s = 0.084, F = 311$$

In Eqs. 3 and 5, the coefficients of $\log P_{oct}$, 1.050 and 1.188, respectively, are close to 1, suggesting that the hydrophobic contribution is well separated by this treatment.[7]

Analyses for all the compounds including the *ortho* derivatives by Eq. 1 led to a poorer correlation where the *ortho* derivatives showed large deviations from the regression line. To solve this problem, we applied the procedure proposed by Fujita and coworkers[12,18] who analyzed the *ortho* substituent effects by adding the terms for proximity effects composed

Table 1. Log *P* Values for Different Partitioning Systems and Physicochemical Parameters for Monosubstituted Phenols

Substituent	$\log P_{oct}$	$\log P_{CL}$	$\log P_E$	S_{HA}	σ°	σ_I	E_s
H	1.46	0.38	1.03	1.00	0.00	0	0
m-F	1.93	0.38	1.52	1.04	0.35	0	0
m-Cl	2.50	0.93	2.10	1.03	0.37	0	0
m-Br	2.63	1.13	2.28	1.12	0.38	0	0
m-Me	2.02	0.96	1.52	1.01	−0.07	0	0
m-Et	2.40	1.57	2.04	1.00	−0.07	0	0
m-OMe	1.58	0.69	1.02	1.37	0.06	0	0
m-OEt	1.98	1.21	1.50	1.35	0.06	0	0
m-Ac	1.39	0.43	0.54	1.78	0.34	0	0
m-CN	1.68	0.29	0.92	1.39	0.62	0	0
m-CO₂Me	1.85	1.03	1.21	1.87	0.36	0	0
m-CO₂Et	2.40	1.68	1.78	1.83	0.36	0	0
p-F	1.77	0.38	1.29	1.06	0.17	0	0
p-Cl	2.39	1.00	1.96	1.04	0.27	0	0
p-Br	2.59	1.13	2.14	1.13	0.26	0	0
p-Me	1.94	1.03	1.48	1.00	−0.12	0	0
p-Et	2.41	1.47	2.04	0.99	−0.13	0	0
p-OMe	1.34	0.57	0.77	1.40	−0.16	0	0
p-OEt	1.78	1.06	1.24	1.38	−0.16	0	0
p-Ac	1.35	0.13	0.31	1.81	0.46	0	0
p-CN	1.60	0.08	0.67	1.44	0.69	0	0
p-CO₂Me	1.97	0.89	1.12	1.89	0.46	0	0
p-CO₂Et	2.42	1.35	1.65	1.83	0.46	0	0
o-F	1.64	0.79	1.37	1.13	0.17	0.54	−0.46
o-Cl	2.15	1.59	1.83	1.10	0.27	0.47	−0.97
o-Br	2.35	1.84	1.97	1.19	0.26	0.47	−1.16
o-Me	1.97	1.16	1.66	0.92	−0.12	−0.01	−1.24
o-Et	2.47	1.76	2.23	0.90	−0.13	−0.01	−1.31
o-CN	1.59	0.23	0.64	1.49	0.69	0.57	−0.51

Table 2. Developments of the Correlation Equation for $\log P_{CL}$ of Monosubstituted Phenols

Coefficient					Const.	n	r	s	F
a	ρ	s	e	ρ_I					
1.077	-1.037	$0.554^{a)}$			-1.698	29	0.898	0.238	34.5
1.042	-1.042	0.723	-0.429		-1.931	29	0.957	0.160	65.4
1.149	-1.315	0.740		1.001	-2.094	29	0.957	0.160	65.2
1.100	-1.215	0.779	$-0.272^{b)}$	$0.632^{c)}$	-2.095	29	0.972	0.132	78.8

$\log P_{CL} = a \log P_{oct} + \rho\sigma° + sS_{HA} + eE_s + \rho_I\sigma_I + const.$ *a—c*) The terms are justified above the 99.9% level unless otherwise noted: *a*) justified at the 99.5% level, *b*) justified at the 99.8% level, *c*) justified at the 99.7% level.

of steric effects, expressed by the E_s parameter,[19] and the field (inductive) effects by the Swain–Lupton's F parameter.[20] By replacing the F parameter with σ_I[21] which was developed later by Charton as a parameter for the field-inductive effect, we tried the following model for the whole set of data with *o*-, *m*- and *p*-derivatives.

$$\log P_{CL} = a \log P_{oct} + \rho\sigma° + s\,S_{HA} + e\,E_s(ortho) + \rho_I\sigma_I(ortho) + const. \quad (6)$$

In this equation, $\sigma°_{ortho}$ values are supposed to be equivalent with $\sigma°_{para}$,[18] and the E_s and σ_I terms are applied only to the *ortho* substituents. The analysis of $\log P_{CL}$ for all the compounds in Table 1 by using Eq. 6 yielded an excellent correlation as shown by Eq. 7.

$$\log P_{CL}$$
$$= 1.100 \log P_{oct} - 1.215\sigma° + 0.779S_{HA} - 0.272E_s + 0.632\sigma_I - 2.095 \quad (7)$$
$$n = 29, \ r = 0.972, \ s = 0.132, \ F = 78.8$$

Table 2 shows that both of the E_s and σ_I terms are needed to improve the correlation. It should be noted that the quality of Eq. 7 is similar to Eq. 3 judging from the fact that the corresponding coefficients are close to each other.

On the other hand, the same treatment for analysis of $\log P_E$ provided Eq. 8 as the most reasonable correlation, where the correction terms for *ortho* effects were statistically insignificant. Again, the coefficients of all the terms in Eq. 8 are in accord with those in Eq. 5.

$$\log P_E = 1.179 \log P_{oct} - 0.290\sigma° - 0.344S_{HA} - 0.392 \quad (8)$$
$$n = 29, \ r = 0.985, \ s = 0.102, \ F = 265$$

As shown in Fig. 1, Eqs. 7 and 8 are able to predict nicely the values for $\log P_{CL}$ and $\log P_E$, respectively.

Discussion

Inspection of Table 1 shows that the $\log P$ value for each compound decreases in the order $\log P_{oct} > \log P_E > \log P_{CL}$. This is in sharp contrast to the tendency for monosubstsitutaed (di)azines (**Ar$_N$-X**) with non-amphiprotic X-substituents, where the order $\log P_{CL} > \log P_{oct}$ is observed though the order $\log P_{oct} > \log P_E$ remains unchanged.[6] This discrepancy could be explained by considering the difference in hydrogen-bond capabilities of the solvents. Since each phenol molecule (solute) has an amphiprotic OH group, octanol is able to form hydrogen-bonds at OH and OH sites (types A and B) of the phenol. On the other hand, chloroform and butyl ether undergo the hydrogen-bond formation only at OH (type B) and OH (type A), respectively, as shown below. Such a situation would operate to raise $\log P_{oct}$ relative to $\log P_{CL}$ and $\log P_E$.
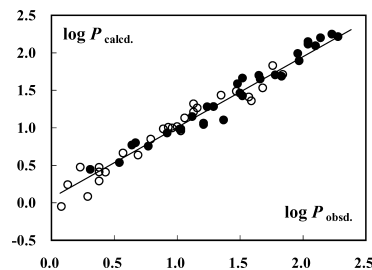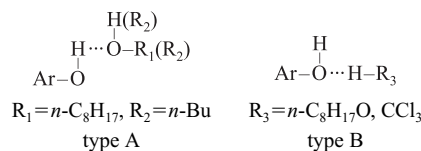

Fig. 1. Relationship between $\log P_{obsd.}$ and $\log P_{calcd.}$ calculated by Eqs. 7 ($\log P_{CL}$) and 8 ($\log P_E$)

Open circles: $\log P_{CL}$. Closed circles: $\log P_E$. The line is drawn with unit gradient.

$$
\begin{array}{cc}
\text{H(R}_2\text{)} & \\
\text{H}\cdots\text{O–R}_1\text{(R}_2\text{)} & \text{H} \\
| & \text{Ar–O}\cdots\text{H–R}_3 \\
\text{Ar–O} & \\
\text{R}_1 = n\text{-C}_8\text{H}_{17}, \text{R}_2 = n\text{-Bu} & \text{R}_3 = n\text{-C}_8\text{H}_{17}\text{O, CCl}_3 \\
\text{type A} & \text{type B}
\end{array}
$$

The order $\log P_E > \log P_{CL}$ seems to indicate that hydrogen-bonding with the phenolic hydrogen (type A) is more important than that with the phenolic oxgen (type B). Only chloroform is unable to form the type-A hydrogen-bonding, which is expected to lower the $\log P_{CL}$ value relative to $\log P_{oct}$ and $\log P_E$.

It is of interest to compare the corresponding coefficients of each term in Eqs. 3 and 5. The ρ value, which expresses the electronic substituent (X) effect on the change in hydrogen-bond ability of the fixed (phenolic) OH substituent, is more negative in Eq. 3 than in Eq. 5. Introduction of an electron-withdrawing X-substituent to phenol raises the acidity of phenolic OH, which would enhance the hydrogen-bonding association with octanol. Therefore, it would be more favored for the phenol to be partitioned into octanol relative to chloroform. The greater the electron-withdrawal of the X-substituent, the higher the $\log P_{oct}$ relative to the $\log P_{CL}$, leading to the negative ρ value. In Eq. 5, the ρ value should correspond to the difference between the type-A hydrogen-bonding with OctOH and that with butyl ether, and hence its contribution is expected to be smaller than in Eq. 3.

The coefficients of the S_{HA} term are opposite in sign in Eqs. 3 and 5. The negative coefficient in Eq. 5 means that a hydrogen-accepting substituent X can undergo hydrogen-bonding with octanol, Oct–OH, but not with butyl ether, which would raise the $\log P_{oct}$ relative to the $\log P_E$. On the other hand, the coefficient in Eq. 3 should reflect the difference in hydrogen-bonding effects between X and the two solvents, X$\cdots$HCCl$_3$ and X$\cdots$HO–Oct. The positive coefficient, 0.754, could be rationalized in analogy with the case studied

by Fujita and coworkers[7] who analyzed the relationship between $\log P_{oct}$ and $\log P_{CL}$ for monosubstituted benzenes, PhX, where X is a nonhydrogen-bonding or hydrogen-accepting substituent, by using the indicator variable HB where $HB=0$ for nonhydrogen-bonders and $HB=1$ for hydrogen-acceptors, and derived Eq. 9 as the first approximation.

$$\log P_{CL} = a \log P_{oct} + h\,HB + \text{const.} \qquad (9)$$

By comparing this equation with that theoretically derived, they showed that the coefficient "a" should be close to 1 and "h" is likely to correspond to the log of the solvent molarity ratio, $\log([CL]/[oct])=0.3$. In Eq. 3, the contribution of the $0.754 S_{HA}$ term for X with hydrogen-acceptor site is close to 0.3 (for X with two hydrogen-accepting sites like C(=$\underline{O}$)$\underline{O}$R, the contribution is approximately doubled), indicating that the S_{HA} parameter expresses well the hydrogen-accepting effect of the X-substituent.

In Eq. 8, the correction terms for the *ortho* effects were insignificant. It is not unexpected that the σ_I term is negligible considering that the electronic contribution itself is smaller in Eq. 5 than Eq. 3. As to steric effects, solvents are less accessible to the phenolic oxygen, Ar–$\underline{O}$H, than the phenolic hydrogen, Ar–O$\underline{H}$, because of steric hindrance caused by the *ortho* substituents. Considering that hydrogen-bonding of the type A is more important than type B and that butyl ether undergoes only the type A hydrogen-bonding, the relationship between $\log P_E$ and $\log P_{oct}$ is expected to be little influenced by *ortho* substitution, though a larger number of data is desirable for more precise analyses.

In this study, we applied the S_{HA} parameter to analyses of the relationship between $\log P_{oct}$ for monosubstituted phenols and the $\log P$ derived from other partitioning systems of different hydrogen-bonding characteristics, and demonstrated that this parameter works effectively to provide the relationship where the physicochemical meanings of correlations are well rationalized in terms of hydrogen-bonding behavior of the amphiprotic OH substituent. These results are thought to be useful for extending our research to development of a new hydrogen-donor parameter.

References and Notes
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