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Hydrophobicity Parameters Determined by Reversed-Phase Liquid Chromatography. V.[1] Relationship between the Capacity Factor and the Octanol–Water Partition Coefficient for Simple Heteroaromatic Compounds and Their Ester Derivatives

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The log k' (k': capacity factor) values of various heteroaromatic compounds were measured by reversed-phase high performance liquid chromatography (RPLC) using a Capcell pack C_{18} column and methanol–water eluents, and the relationship with the log P values (P: 1-octanol–water partition coefficient) was examined as a function of the mobile phase composition. Furans having nonhydrogen-bonding or weakly hydrogen-accepting substituents exhibited a good linear relationship at 50% MeOH concentration. Amphiprotic substituents, CONHR, showed an acceleration effect (less retained than nonhydrogen-bonders and hydrogen-acceptors under the condition of equivalent log P), as is often observed in heterocyclic systems. The relationship was more complicated at other methanol contents, due to different retention behavior demonstrated by the ester-type substituents, CO_2R and $CONR_2$ (ester effect). To gain more insight into this ester effect, the retention behavior of ester derivatives of various heteroaromatics such as furan, benzofuran, N-Me pyrrole and indole was also studied. The factors affecting the log P–log k' relationship were discussed, and the optimum RPLC condition for predicting the log P value was described.

Keywords RPLC; capacity factor; partition coefficient; hydrophobicity; hydrogen-bond; mobile phase composition; linear correlation; heteroaromatic compound; ester effect

The logarithm of 1-octanol–water partition coefficient (log P) is a conventionally used hydrophobicity parameter.[2] Though the standard method of measuring log P values is the shake-flask method, the logarithm of the capacity factor (log k') obtained from reversed-phase high performance liquid chromatography (RPLC) has often been used as an alternative method for predicting log P, partly because of the facility of measurements.[3–6] Most RPLC methods use C18-modified stationary phases and MeOH–water mixtures as the mobile phase.[3,5,6] Many recent investigators have reported that the log k_W values (the log k' values at 100% water obtained by extrapolation of the plot of log k' against volume fraction of methanol in MeOH–water eluents) correlate better with their log P than log k' in mixed eluents.[3,6] In our opinion, the log k_W parameter seems to predict quite well the log P values of compounds which have no or only one hydrogen-bonding site. For example, many successful examples are seen in some monosubstituted benzenes with substituents such as alkyls, halogens, OR and CN whose log k_W values mimic the log P values.

Recently, in our continuous studies on the estimation of heterocyclic hydrophobicity parameters, we have shown that the log k_W approach fails in predicting log P values for the solutes containing mutually interacting multi-hydrogen-bondable functional groups.[1,7] The relationship between log P and log k' for mono- and disubstituted pyrazines became more complicated with the decrease in MeOH content in the eluents and hence, the log k_W values correlated very poorly with the log P values. It was also found that the substituents of types, CO_2R and $CONMe_2$, gave higher log k' values relative to other substituents under the conditions of equivalent log P (ester effect). Interestingly, a fairly good log P–log k' linearity was observed around a 50% MeOH concentration, including the above-mentioned ester groups, although amphiprotic substituents (or hydrogen donors) behaved differently.

Our interest was directed toward examining whether these features were characteristic of the pyrazine series or common for other heterocyclic systems. To clarify this problem, we examined in this study the relationship between log P and log k' for monosubstituted furans at different mobile phase compositions. The ester effect was also studied by comparing the retention behavior of ester derivatives having various aromatic rings.

Experimental

Compounds The compounds used in this study are given in Tables I and II. Most of the parent compounds were commercially available. The preparation of diazine derivatives was described previously.[8] The ester derivatives, $ArCO_2R$, were prepared, if not commercially available, by an acid catalyzed esterification of an appropriate carboxylic acid. The amide derivatives, CONHR and $CONMe_2$, were synthesized by treating the corresponding esters with appropriate amines, RNH_2 and Me_2NH, respectively.

Partition Coefficients 1-Octanol–water log P values were measured at 25 °C by the conventional shake-flask method.[8]

RPLC Procedure The apparatus and the procedure used were the same as previously described except that Shimadzu LC9A and SPD-6AV UV detectors were used.[7] Commercial Capcell pak C_{18}[9] (4.6 mm × 5, 15 and 25 cm, Shiseido) was used without further treatment. Commercial high performance liquid chromatography (HPLC) grade methanol and water were used. As an aqueous phase, a 0.01 M phosphate buffer (pH 7.4) was used. The MeOH–buffer eluents were prepared by volume. Appropriate quantities of samples were dissolved in methanol and 1—2 μl was injected at 25 °C. The flow-rate was 0.3—2.0 ml/min. The capacity factor, k', was determined from the retention time of the sample, t_R, by $k' = (t_R - t_0)/t_0$, where the t_0 value is the retention time of methanol.

Results and Discussion

The log k' values of various furans were measured in the range of 0—70% methanol concentrations (M0—M70). The results are summarized in Table I together with the log P values. The log k_W values derived from the linear extrapolation using the data for M30—M70 are also given. The plots of log k' against log P at M15, M30, M50 and M70 are shown in Fig. 1.

The substituents of the furan derivatives examined are classified into three groups (i) H, alkyl, halogen and H-acceptors like OMe and Ac, (ii) ester and amido groups of the type, CO_2R, and $CONMe_2$, hereafter designated as "ester groups" and (iii) amphiprotic substituents of the type,

Table I. logk' Values and Related Parameters for Substituted Furans

	Substituent	logk'						log$k_W$$^{b)}$	log$P$	HB_{AM}
		M0$^{a)}$	M5$^{a)}$	M15$^{a)}$	M30$^{a)}$	M50$^{a)}$	M70$^{a)}$			
1	H	1.006	0.952	0.828	0.632	0.291	−0.141	1.23	1.34$^{c)}$	0.0
2	2-Me	1.593	1.536	1.369	1.094	0.648	0.124	1.83	1.85$^{c)}$	0.0
3	2-Et		2.118	1.913	1.559	1.002	0.370	2.46	2.40$^{c)}$	0.0
4	2-OMe	1.495	1.342	1.127	0.823	0.374	−0.132	1.55	1.44$^{c)}$	0.0
5	2-Ac	1.337	1.043	0.644	0.228	−0.237	−0.673	0.90	0.52	0.0
6	2-CO_2Me	1.725	1.429	1.039	0.611	0.087	−0.417	1.38	1.01	0.0
7	2-CO_2Et	2.293	1.956	1.530	1.021	0.395	−0.195	1.93	1.52	0.0
8	2-Br-5-CO_2Me		2.166	1.765	1.274	0.621	−0.014	2.26	1.84	0.0
9	2-$CONMe_2$	1.694	1.303	0.776	0.259	−0.280	−0.743	1.00	0.41	0.0
10	3-CO_2Me	1.802	1.529	1.209	0.796	0.260	−0.269	1.59	1.28	0.0
11	3-CO_2Et	2.384	2.101	1.712	1.214	0.573	−0.047	2.16	1.78$^{c)}$	0.0
12	3-$CONMe_2$	1.536	1.169	0.665	0.172	−0.351	−0.809	0.90	0.24$^{c)}$	0.0
13	2-$CONH_2$	0.634	0.379	0.013	−0.359	−0.806	−1.296	0.35	−0.11	1.0
14	2-CONHMe	1.032	0.712	0.304	−0.121	−0.576	−1.013	0.54	0.23	1.0
15	2-CONHEt	1.468	1.119	0.657	0.181	−0.324	−0.788	0.90	0.61	1.0
16	3-$CONH_2$	0.576	0.351	0.031	−0.299	−0.717	−1.198	0.39	0.09	1.0
17	3-CONHMe	0.946	0.657	0.269	−0.105	−0.525	−0.962	0.54	0.34	1.0
18	3-CONHEt	1.330	1.009	0.582	0.164	−0.295	−0.752	0.85	0.72	1.0

a) Mobile phase composition; the figure represents the volume % of MeOH. Aqueous phase: phosphate buffer (pH 7.4). *b)* Calculated by linear extrapolation using the data for 30—70% MeOH.[14] *c)* Taken from ref. 13.

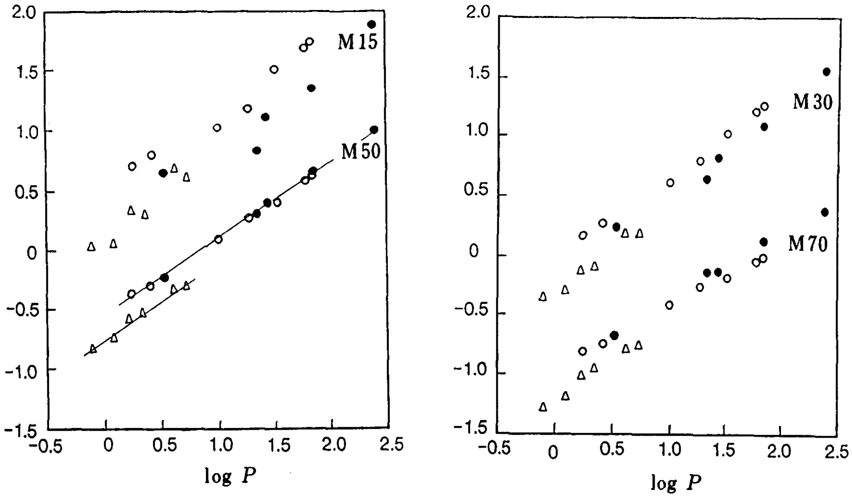

Fig. 1. Relationship between log$P$ and logk' for Furans

Closed circle: group i (compounds 1—5 in Table I). Open circle: group ii (compounds 6—12 in Table I). Triangle: group iii (compounds 13—18 in Table I).

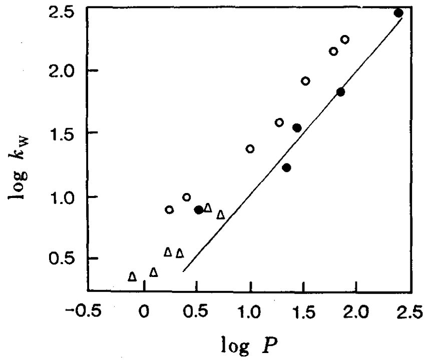

Fig. 2. Plot of logk_W against log$P$ for Furans

For symbols see the figure caption of Fig. 1. The linear line has the slope of unity.

CONHR (R=H or alkyl). It is clearly seen in Fig. 1 that groups i and ii (depicted by closed and open circles, respectively) present the best linear relationship at M50.

The amphiprotic group (depicted by triangles) gives another linear line parallel to the one above-mentioned but with a smaller intercept (amphiprotic effect). The relationship for M50 was excellently formulated by Eq. 1,

$$\log k'_{M50} = \underset{(0.020)}{0.635} \log P - \underset{(0.030)}{0.195} HB_{AM} - \underset{(0.029)}{0.544} \qquad (1)$$

$$n=18, \quad r=0.999, \quad s=0.022, \quad F=5137.5$$

where, HB_{AM} is an indicator variable which takes 1 for the compounds with CONHR, and 0 for the others. In Eq. 1 and throughout this work, n is the number of compounds used for calculations, r is the correlation coefficients, s is the standard deviation and F is the values of the F-ratio between regression and residual variances. The figures in parentheses are the 95% confidence intervals of the coefficients.

The downward deviations for CONHR indicate that these amide moieties act as H-donors as in the case of phenols.[5,10]

A similar feature was also observed in the plot of $\log k'$ against $\log P$ for substituted pyrazines[7]; the amphiprotic substituents such as NHR (R = H or alkyl), NHAc and $CONH_2$ exhibited negative deviations from the regression line for nonhydrogen-bonding and ordinary H-accepting substituents. This trend is common to heteroaromatic compounds and can be rationalized, as previously described,[7] by considering that the electron-withdrawing heteroaromatic rings increase the H-donating ability of the amphiprotic substituents. Such H-donating substituents would undergo hydrogen-bonding more effectively with more basic octanol than with the less basic stationary-phase; in other words, the amphiprotics appear to be more hydrophobic in the octanol–water system than in the stationary phase–mobile phase system. Monosubstituted benzenes present a single linear line at M50, including the above amphiprotic substituents,[11] supporting the notion that the ring-heteroatom is responsible for the amphiprotic effect.

As the methanol concentration in the mobile phases was decreased, the ester groups showed higher $\log k'$ values relative to the other substituents, and the linear relationship did not exist. The plots at M5 and M0 were even more scattered. One possibility for the complexity of the relationship at these mobile phase compositions is that the retention mechanism changes as the eluent approaches pure water because a modification of the stationary-phase structure itself may occur.[3] The situation was inversed at 70% MeOH; the $\log k'$ values for ester groups were somewhat smaller than those for group i. This means that the change in the hydrogen-bond effect of ester groups (group ii) is more sensitive to the change in mobile-phase composition.

Under such circumstances, it is not surprising that the observed $\log k_W$ correlates very poorly with $\log P$. Inspection of Table I and Fig. 2 shows that the extrapolated $\log k_W$ values are close to the $\log P$ values for H, alkyl and methoxy substituents, but much larger than the $\log P$ values for the other substituents. This suggests that the $\log k_W$ approach is effective in predicting the $\log P$ values of furans having nonhydrogen-bonding or very weak hydrogen-accepting substituents, but tends to overestimate $\log P$ values for those with strongly hydrogen-accepting substituents (for example, the case of 2-acetyl furan). In the case of the esters, the $\log k_W$ values were about 0.4 larger than the $\log P$ values.

On the other hand, the amphiprotic effect (acceleration effect) expressed by the HB_{AM} term seems to be reduced with a decrease in the MeOH concentration and slightly exceeded by the retardation effect ascribed to the ester groups (note that the CONHR group should also exert the ester effect).

To explore the origin of the above-mentioned ester effect, various aromatic compounds which have a CO_2Me substituent were studied. The results are summarized in Table II. The relationship between $\log P$ and $\log k'$ are plotted in Fig. 3. Here again, the esters, the parent compounds and the derivatives with non-hydrogen bonding substituents such as alkyls and halogens present a good linear relationship at 50% MeOH, though diazines (pyrazines, pyrimidines and pyridazines) and the other aromatics fall on two separate lines, plots A and B, respectively. Among the compounds studied, only two, indole and 3-CO_2Me-indole, are negative deviants, presenting an amphiprotic effect because the hydrogen

TABLE II. $\log k'$ Values and Related Parameters for Heteroaromatic Compounds and Ester Derivatives

Compound	Group	$\log k'$				$\log k_W$[b]	$\log P$	HB_{CO}
		M30[a]	M50[a]	M70[a]	M80[a]			
Pyrazine	A	−0.257	−0.584	−0.822	−0.967	0.15	−0.26[c]	0.0
2-CO_2Me-pyrazine	A	−0.055	−0.495	−0.840	−0.969	0.52	−0.23[c]	1.0
2-Me-5-CO_2Me-pyrazine	A	0.260	−0.248	−0.685		0.85	0.17[c]	1.0
2-Me-6-CO_2Me-pyrazine	A	0.235	−0.265	−0.700		0.93	0.10[c]	1.0
2-Cl-5-CO_2Me-pyrazine	A	0.456	−0.001	−0.414		1.10	0.47[c]	1.0
2-OMe-6-CO_2Me-pyrazine	A	0.691	0.142	−0.341		1.45	0.69[c]	1.0
Pyrimidine	A	−0.366	−0.661	−0.855		−0.02	−0.44[c]	0.0
2-CO_2Me-pyrimidine	A	−0.439	−0.876	−1.163		0.08	−0.71[c]	1.0
5-CO_2Me-pyrimidine	A	0.101	−0.312	−0.611		0.62	0.03[c]	1.0
Pyridazine	A	−0.701	−1.004	−1.231	0.000	−0.09	−0.77[c]	0.0
4-CO_2Me-pyridazine	A	−0.111	−0.559	−0.888		0.45	−0.27[c]	1.0
Benzene	B	1.283	0.819	0.258	−0.032	2.07	2.13[c]	0.0
1-CO_2Me-benzene	B	1.457	0.774	0.127	−0.175	2.45	2.12[c]	1.0
Furan	B	0.645	0.306	−0.147	−0.379	1.23	1.34[d]	0.0
2-CO_2Me-furan	B	0.628	0.098	−0.411	−0.677	1.38	1.01	1.0
3-CO_2Me-furan	B	0.813	0.274	−0.276	−0.534	1.59	1.28	1.0
2-Br-5-CO_2Me-furan	B	1.289	0.637	−0.010	−0.322	2.26	1.84	1.0
N-Me-pyrrole	B	0.618	0.234	−0.185	−0.405	1.23	1.15	0.0
2-CO_2Me-pyrrole	B	1.220	0.576	0.300	−0.308	2.15	1.78	1.0
Thiophen	B	1.023	0.608	0.107	−0.164	1.72	1.82	0.0
Benzofuran	B	1.683	1.038	0.343	0.017	2.70	2.67[d]	0.0
2-CO_2Me-benzofuran	B	1.783	0.972	0.229	−0.112	2.94	2.53	1.0
Indole	B	1.115	0.531	−0.090	−0.395	2.03	2.14[d]	0.0
2-CO_2Me-indole	B	1.756	0.908	0.133	−0.215	2.96	2.45	1.0
3-CO_2Me-indole	B	1.492	0.647	−0.087	−0.405	2.66	2.57	1.0

a) Mobile phase composition; the figure represents the volume % of MeOH. Aqueous phase: phosphate buffer (pH 7.4). *b*) Calculated by linear extrapolation using the data for 30—70% MeOH. *c*) Taken from ref. 8 and the references cited therein. *d*) Taken from ref. 13.

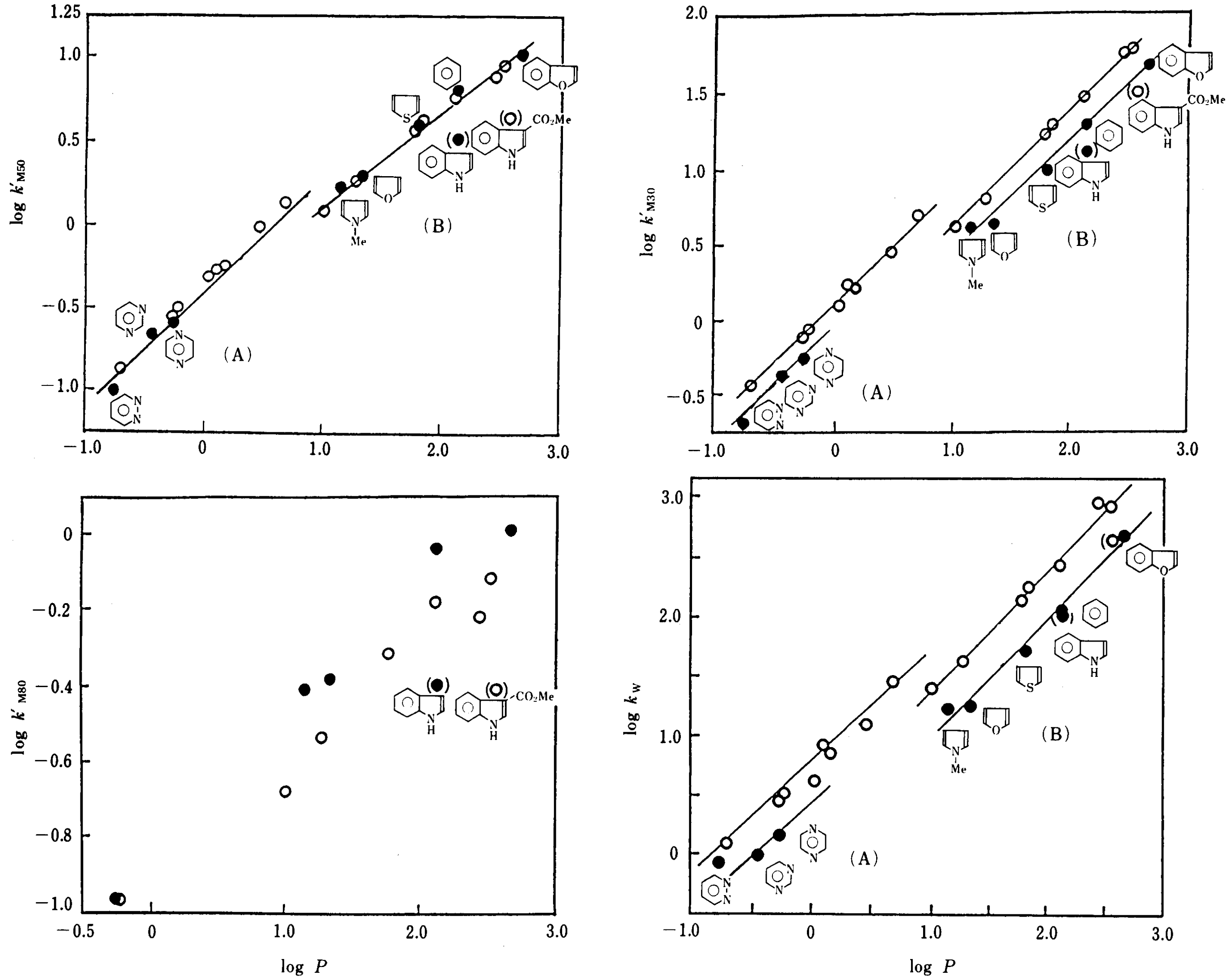

Fig. 3. Relationship between $\log k'$ ($\log k_w$) and $\log P$ for Heteroaromatic Compounds

Open circle, esters ($HB_{CO}=1$); closed circle, others ($HB_{CO}=0$). Only the structures of the parent compounds are represented.

bonded to the ring N-atom is acidic enough to act as an H-donor. On the other hand, 2-CO_2Me-indole is incorporated as a member of the compounds belonging to plot B. This would be rationalized by considering that the intramolecular hydrogen-bonding between the acidic hydrogen in the indole ring and the CO_2Me group eliminates the H-donating property of the molecule. Hence, it behaves similarly to the N-Me pyrrole analog. Hereafter, the two deviant compounds, as indicated above, will be excluded from the analyses. Thus, Eqs. 2 and 3 were derived for plots A and B, respectively.

$$\log k'_{M50}(\text{plot A}) = \underset{(0.050)}{0.759}\log P - \underset{(0.022)}{0.358} \qquad (2)$$

$n=11$, $r=0.996$, $s=0.032$, $F=1181.5$

$$\log k'_{M50}(\text{plot B}) = \underset{(0.037)}{0.559}\log P - \underset{(0.071)}{0.428} \qquad (3)$$

$n=12$, $r=0.996$, $s=0.031$, $F=1134.8$

The finding that the slope of plot A is somewhat larger than that of slope B could be partly artificial. In this work, the $\log k'$ values were calculated by using the retention time of methanol as t_0. However, this value should be somewhat larger than the real value. The use of a slightly overestimated t_0 value, instead of the real t_0 value, would produce somewhat underestimated $\log k'$ values when the solutes have very short retention times, whereas the influence is negligible in estimating the $\log k'$ values of solutes having a longer retention time. Therefore, plot A for M50, which includes solutes of very small retention, would tend to give a larger than actual slope. The fact that the slope of the $\log P$ term in Eq. 1 is also slightly larger than that in Eq. 3 could be explained on the same basis because half of the data points to yield Eq. 1 present very small (negative) $\log k'$ values.

For M30, the relationships for the ester groups and the others, including parent compounds, were expressed by Eqs. 4 and 5,

$$\log k'_{M30}(\text{plot A}) = \underset{(0.059)}{0.804}\log P + \underset{(0.058)}{0.165}HB_{CO} - \underset{(0.051)}{0.047} \qquad (4)$$

$n=11$, $r=0.998$, $s=0.031$, $F=876.2$

$$\log k'_{M30}(\text{plot B}) = \underset{(0.042)}{0.755}\log P + \underset{(0.046)}{0.200}HB_{CO} - \underset{(0.085)}{0.325} \qquad (5)$$

$n=12$, $r=0.997$, $s=0.035$, $F=873.5$

where the parameter HB_{CO} is an indicator variable which takes 1 for the esters and 0 for the others. The slopes of the $\log P$ and HB_{CO} terms in Eqs. 4 and 5, which were derived from relatively greater $\log k'$ values, are very close to each other, supporting our argument as mentioned above. The results at M30 clearly demonstrate that the $\log k'$ values for the esters are uniformly raised relative to the parent compounds regardless of the structure of the aromatic rings.

The $\log k'$ values for some compounds were also measured at an 80% MeOH concentration. The plot is included in Fig. 3 where the ester groups are located below the parent compounds, exhibiting a similar but more distinct trend than that observed in the furans.

The $\log k_W$ values obtained by linear extrapolations are given in Table II. Table II and Fig. 3 reveal that only the parent compounds in group B, such as benzene, furan, benzofuran, indole, N-Me pyrrole and thiophen, yield $\log k_W$ values almost equivalent to the corresponding $\log P$ values. Pyrrole is a very weak base because the electron pair on the ring N-atom is part of the aromatic system. Therefore, the hydrogen-bonding on the ring N-atom with hydrogen-donating solvent is not important, and hence, N-Me-pyrrole is considered to behave similarly to benzene. Furan, benzofuran, and thiophen seem to afford additional examples supporting our view that the $\log k_W$ approach is applicable to the solutes which include no or only one weak H-accepting site. Finding the $\log k_W$ value of indole (2.03) similar to the $\log P$ value (2.14) again suggests that the amphiprotic effect (or strictly speaking, hydrogen-donor effect) is reduced to a great extent in the $\log k_W$ value. However, the $\log k_W$ values of the parent compounds of diazines which have two H-accepting sites in the aromatic rings such as pyrazine, pyrimidine and pyridazine (group A), are higher than the $\log P$ values by about 0.4. It is shown in Fig. 3 that the $\log k_W$ approach usually overestimates the $\log P$ value for the esters by 0.3—0.4 relative to the other compounds of the same parent nucleus but with non-hydrogen-bonding substituents under the conditions of equivalent $\log P$. In other words, the overestimation of the esters would reach a range of 0.7 to 0.8 log unit in the diazine systems. The attempt to introduce one more CO_2Me to 3-CO_2Me-furan also showed an additional increase of 0.4; $\log k_W$ and $\log P$ values for 3,4-di-methoxycarbonyl furan were 1.64 and 0.79, respectively.

A similar trend involving the number of H-accepting sites governing the relationship of $\log P$ values between different partitioning systems has been observed in our current work; when the octanol–water $\log P$ value ($\log P_{oct}$) for monosubstituted diazines was compared with the $CHCl_3$–water $\log P$ ($\log P_{CL}$), the increment for substituents with one H-accepting site was larger in the $CHCl_3$ system than that in the octanol system by 0.3, and the increment for substituents with two H-accepting sites (ester groups) by 0.6.[12] Closer analysis of the relationship has revealed that the $\log P_{CL}$–$\log P_{oct}$ relationship is mostly governed by the difference between the hydrogen-bonding solvation at the hydrogen-accepting substituents with octanol and that with $CHCl_3$; the difference of 0.3 is interpreted to be the logarithm of the ratio of the bulk solvent molarity between $CHCl_3$ and octanol.[12] The value of 0.6 (twice 0.3) observed for the ester groups suggests that the hydrogen-bonding takes place at two sites in the substituents.

In principle, the ester effect observed in the $\log k'$–$\log P$ relationships should be analyzed similarly. However, the quantitative interpretation of the coefficient of the HB term is difficult at present because the partitioning mechanism between the stationary and the mobile phases is much more complicated than that between two immiscible solvents.

The present results have demonstrated that the relationship between $\log P$ and $\log k'$, including $\log k_W$, is affected mainly by the number of hydrogen-bonding sites. In addition to this, we have previously found that when the solute includes two (or more) functional sites, the electronic interactions between them also play an important role in governing the retention.[7] This effect has been shown to become more significant with a decrease in the MeOH concentration in the mobile phase.[7] Considering that heteroaromatic compounds always contain at least one hetero-atom (functional group) in the parent compound, most bioactive heterocyclic compounds are expected to present the complicated relationship between $\log P$ and $\log k_W$. Nevertheless, most of our results, obtained so far relating to different heteroaromatic systems, have shown that such perturbing factors as electronic effects and hydrogen-bonding effects, including the ester effect, are reduced at 50% and a fairly good $\log k'$–$\log P$ linearity is obtained for nonhydrogen-bonders and hydrogen acceptors. The problem of how to treat amphiprotics (H-donors) will be the subject of our future work.

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14) Generally, $\log k_W$ values obtained by extrapolation from the linear portion correlate better with $\log P$ than $\log k_W$ obtained by the quadratic model. See also refs. 1 and 6.