Hydrophobicity Parameters Determined by Reversed-Phase Liquid Chromatography. XI. Prediction of log *P* Values for Phenyl *N*-Methyl and Phenyl *N*,*N*-Dimethylcarbamates

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Capacity factors, k', for *m*- and *p*-substituted phenyl *N*-methyl (2) and phenyl *N*,*N*-dimethyl (3) carbamates were measured on an octadecyl silica column using methanol-buffer (pH 7.4) mixtures as the mobile phase. The relationship between $\log P$ (P: 1-octanol–water partition coefficient) and $\log k'$ was studied as a function of the mobile phase composition. An eluent containing 50% MeOH gave good but separate $\log k'$–$\log P$ linearities for (2) and (3). As the methanol concentration in the mobile phase was decreased, the correlation became more complicated due to the intervention of hydrogen-bond effects. In a water-rich eluent, the $\log k'$ values for the combined data set of (2) and (3) were found to be expressed by a correlation equation of the type, $\log k' = a \log P + \rho\sigma^{\circ} + h_A HB_A + h_{AM} HB_{AM} + \text{const.}$, where σ° represents the Hammett type electronic substituent constant. HB_A and HB_{AM} are indicator variables for hydrogen-accepting substituents and compounds (2) (amphiprotics), respectively. As expected, the $\log k_W$ approach failed to give reliable $\log P$ values due to the strongly hydrogen-accepting property of the fixed substituents.

Key words hydrophobicity; HPLC; partition coefficient; hydrogen bond; electronic effect; phenyl carbamate

The logarithm of the 1-octanol–water partition coefficient, $\log P$, is conventionally used as a hydrophobicity parameter.[2] This parameter has often been estimated from the logarithm of the capacity factor, $\log k'$, obtained from reversed-phase high-performance liquid chromatography (RPLC).[3-7] The $\log P$ value of a compound is predicted from $\log k'$ values for a set of congeneric compounds on the assumption that the $\log P$ value is linearly correlated with $\log k'$. However, our previous studies have shown that this approach is applicable only in limited cases where the solutes either have no strongly hydrogen-bonding functional groups or share a common hydrogen-bonding pattern.[8,9] Therefore, corrections for the hydrogen-bond effects are required in most cases when polar functional groups are present. In addition, the correlation between $\log P$ and $\log k'$ varies not only with the organic modifier used in the mobile phases, but also with the composition of eluents which contain a common organic solvent.

We have previously studied the correlation between $\log P$ and $\log k'$ for various series of monosubstituted heteroaromatic compounds, such as pyridines,[8] diazines,[8,10,11] furans,[12] and thiophenes,[1] using an octadecyl silica (ODS) column, Capcell Pak C_{18}, with methanol-buffer (pH 7.4) mixtures as the mobile phase, and found the following general trends. i) Compounds with non-hydrogen-bonding and hydrogen-accepting substituents yield a good linear relationship at around 50% methanol. ii) With decreased methanol content, the relationship becomes more complicated. Strongly hydrogen-accepting substituents begin to yield larger $\log k'$ values in comparison to those with non-hydrogen-bonding and weakly hydrogen-accepting substituents. This trend is obvious when the methanol content is less than 30%. iii) The amphiprotic (or hydrogen-donating) substituent has a lower $\log k'$ value than non-amphiprotics with the equivalent $\log P$ value (amphiprotic effect). Under the above circumstances, the $\log k_W$ value, the $\log k'$ value extrapolated to 0% methanol, which has been conventionally used as a standardized parameter to estimate $\log P$ values ($\log k_W$ approach), often yields erroneous results. For example, when we estimate $\log P$ values of substituted azines (pyridines) and diazines (pyrazines, pyrimidines and pyridazines), which contain one or two strongly hydrogen-accepting ring nitrogen(s), from the k_W values, the predicted $\log P$ values are usually over-estimated.[8,10] A similar trend is observed in some benzenoid systems containing strong hydrogen-acceptor(s). We have found that hydrophobicity indices of *m*- and *p*-substituted benzyl *N*,*N*-dimethylcarbamates (**1**) derived from the k_W approach are greatly over-estimated (0.6—1.0 log unit) for all substituents examined due to the strong hydrogen-accepting property of the fixed $CH_2OCONMe_2$ substituent.[13]

In this work, our interest has been focused on the relationship between $\log P$ and $\log k'$ for *m*- and *p*-substituted phenyl *N*-methyl and *N*,*N*-dimethylcarbamates (**2** and **3**). These compounds are known to inhibit acetylcholinesterase (AChE).[14] Fujita and coworkers have demonstrated in a structure-activity relationship study that the enzyme activity in the presence of carbamates (**2**) is closely related to the hydrophobicity of **2**. They also analyzed precisely their $\log P(\pi)$ values on the basis of the concept that the fixed and variable substituents interact mutually to alter the hydrogen-bonding ability of both substituents.[15,16] Our aims in studying these compounds are multiple. Firstly, it is of interest to examine how the direct electronic interactions between the fixed substituent and variable X-substituents affect the relationship between $\log P$ and $\log k'$ in comparison with the results in the case of **1**, where such electronic interactions are diminished by the screening effect of the methylene group $\underline{CH_2}OCONMe_2$. Secondly, we wanted to study systematically the amphiprotic effect of the substituent $OCON\underline{H}Me$ by comparing the $\log k'$

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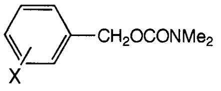

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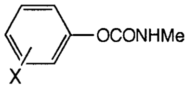

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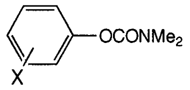

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values for series **2** and **3**. Finally, we were interested in comparing the $\log k_W$ values and $\log P$ to examine to what extent the $\log k_W$ approach may over-estimate the hydrophobicity of **2** and **3**. From the results obtained, a practical procedure to predict $\log P$ values by RPLC was developed.

Experimental

Materials Most of the compounds were kindly supplied by Professors T. Fujita and T. Nishioka of Kyoto University. The others were prepared as previously described.[16] HPLC-grade methanol and water, and phosphate buffer solution (pH 7.4) were purchased from Nacalai Tesque Inc.

Chromatography A Shimadzu LC9A liquid chromatograph, equipped with a SIL-6A auto injector, an SPD-6AV UV (Shimadzu) detector and an ERC-7510 refractive index (Erma Optical Works) detector, was used. Commercial Capcell Pak C_{18} columns (4.6 mm × 5 and 25 cm, Shiseido) were used without further treatment. The MeOH–phosphate buffer (pH 7.4) eluents were prepared by volume. Appropriate quantities of samples were dissolved in MeOH and aliquots of 1—2 μl were injected at 25 °C. The flow rate was 0.5—1.5 ml/min. Retention times were measured with eluents containing 30, 50 and 70% methanol using a C-R4A Chromatopac (Shimadzu). The capacity factor, k', was determined from the retention time of each sample, t_R, and that of methanol, t_0, as $k'=(t_R-t_0)/t_0$. The $\log k'$ value at 0% MeOH, $\log k_W$, was calculated by linear extrapolation from the plot of $\log k'$ value against methanol concentration in the range from 30 to 70%.[17]

Partition Coefficients The 1-octanol–water $\log P$ values were taken from ref. 15, unless otherwise noted. Those for the others were measured in this study at 25 °C by the conventional shake-flask method.[13] The concentration of solutes in both phases was determined by RPLC using the same apparatus as described above. The experimental error of duplicate $\log k'$ determinations was ±0.005.

Results and Discussion

Relationship between $\log P$ and $\log k'$ $\log k'$ values of compounds **2** and **3** obtained at 30, 50 and 70% MeOH (M30, M50 and M70, respectively) are summarized in Tables 1 and 2. The retention times for **2** and **3** were measured on columns 25 and 5 cm in length, respectively. The $\log k'$ values of several compounds (**3**) were also measured on the 25-cm column ($\log k'_{25}$) with an M50 eluent to compare with those obtained on the 5-cm column ($\log k'_5$), and it was indicated that the data obtained with the two columns are compatible: $\log k'_5 = 0.997 \log k'_{25} + 0.021$. The $\log P$ and $\log k_W$ values are given in Table 3. Plots of $\log k'$ against $\log P$ (Fig. 1) show that the M50 eluent yields the best linear relationships in both series, in conformity with our earlier results. It should be noted that the series **2** compounds, which have the common amphiprotic substituent, OCONHMe, form a lower line. Such an amphiprotic effect is usually observed.

In previous studies,[8,10] we have shown that the relationship between $\log P$ and $\log k'$ for monosubstituted pyridines and diazines is expressed by a correlation equation,

$$\log k' = a \log P + \rho\sigma^\circ + h_A HB_A + h_{AM} HB_{AM} + \text{const.} \qquad (1)$$

where σ° is the electronic substituent constant of the X substituent. HB_A and HB_{AM} are indicator variables which take the value of 1 for H-accepting and amphiprotic substituents, respectively, and 0 for others. The coefficients and constant (const.) are determined by regression analyses. All the terms other than the $\log P$ term are regarded as correction terms for hydrogen-bond effects which hamper the $\log k$–$\log P$ linearity, and the coefficients express the degree of contribution of each term. Which terms are needed is dependent on the RPLC conditions used for determination of $\log k'$ values. To apply this equation to the present data set containing both *m*- and *p*-substituted derivatives, Hammett type σ° values for *m*- and *p*-substituents were used. It is noteworthy that this type of correlation equation can also describe the correlation between $\log P$ values for **2** in 1-octanol–water and chloroform–water partitioning systems.[18] Analyses of the data in Tables 1 and 2 using the necessary parameters given in Table 4 gave excellent correlations as follows.

Table 1. $\log k'$ Values for Phenyl *N*-Methylcarbamates (**2**)

Substituent	Eluents		
	M30[a]	M50	M70
H	0.646	0.072	−0.482
p-Me	1.078	0.392	−0.269
p-Et	1.463	0.722	−0.023
p-Pr	1.918	1.075	0.223
p-iso-Pr	1.845	1.010	0.174
p-*tert*-Bu		1.245	0.334
p-F	0.727	0.158	−0.436
p-Cl	1.178	0.521	−0.155
p-Br	1.309	0.619	−0.082
p-I	1.512	0.765	0.014
p-OMe	0.765	0.083	−0.51
p-OEt	1.149	0.404	−0.274
p-OBu		1.141	0.258
p-NO_2	0.766	0.163	−0.439
p-SMe	1.199	0.506	−0.213
p-COMe	0.637	−0.105	−0.708
p-COEt	1.065	0.248	−0.420
m-Me	1.069	0.387	−0.255
m-Et	1.472	0.695	−0.038
m-Pr	1.922	1.035	0.195
m-iso-Pr	1.836	0.966	0.142
m-*tert*-Bu		1.186	0.292
m-CF_3	1.529	0.761	−0.007
m-F	0.827	0.220	−0.383
m-Cl	1.238	0.539	−0.141
m-Br	1.361	0.629	−0.075
m-I	1.548	0.754	0.002
m-OMe	0.817	0.152	−0.453
m-OEt	1.196	0.443	−0.235
m-O-iso-Pr	1.468	0.652	−0.093
m-OBu		1.172	0.277
m-NMe_2	1.052	0.333	−0.307
m-NO_2	0.775	0.168	−0.451
m-CN	0.574	−0.051	−0.706
m-COMe	0.627	−0.075	−0.673
m-COEt	1.039	0.258	−0.409

a) The figure represents the percentage by volume of methanol.

Correlations for **2**:

$$\log k'_{M30} = 0.708 \log P - 0.162\sigma^\circ + 0.101 HB_A - 0.147 \qquad (2)$$

$n=32$, $r=0.992$, $s=0.051$

$$\log k'_{M50} = 0.580 \log P - 0.120\sigma^\circ - 0.589 \qquad (3)$$

$n=36$, $r=0.996$, $s=0.035$

$$\log k'_{\mathrm{M70}} = 0.435 \log P - 0.107\sigma^{\circ} - 1.015 \qquad (4)$$

$$n=36,\ r=0.995,\ s=0.030$$

Correlations for **3**:

$$\log k'_{\mathrm{M30}} = 0.782 \log P - 0.105\sigma^{\circ} + 0.151 HB_{\mathrm{A}} + 0.079 \qquad (5)$$

$$n=22,\ r=0.997,\ s=0.043$$

$$\log k'_{\mathrm{M50}} = 0.608 \log P - 0.391 \qquad (6)$$

$$n=22,\ r=0.997,\ s=0.035$$

$$\log k'_{\mathrm{M70}} = 0.465 \log P - 0.105\sigma^{\circ} - 0.897 \qquad (7)$$

$$n=22,\ r=0.987,\ s=0.058$$

In these equations and throughout this paper, n is the number of compounds used for calculations, r is the correlation coefficient, and s is the standard deviation. The significance of each term is justified by the t test. The HB_{AM} term is not involved because compounds **2** and **3** have no amphiprotic X substituents. Comparison of the correlations reveals that the corresponding coefficients of each term for **2** and **3** are very similar to each other. Therefore, analysis of the combined data set of **2** and **3** was performed by adding the HB_{AM} parameter which takes a value of 1 for compounds **2** and 0 for compounds **3**. The results obtained are given in Table 5 (Eqs. 8—11). In a previous study,[13] we demonstrated that compounds **1** having non-amphiprotic X substituents yielded simple linear relationships, $\log k' = a \log P + \text{const.}$, in which the "$a$" values are 0.76, 0.58 and 0.45 at M30, M50 and M70, respectively. These "a" values are similar to the corresponding values in correlations for **2** and **3**, suggesting that the contribution of the hydrophobicity can be satisfactorily separated from other factors by Eq. 1.

The relationship is most complicated with M30, as shown by the fact that all the terms are needed in Eq. 8. The $\rho\sigma^{\circ}$ term represents the electronic effect of X on the hydrogen-bonding solvation of the fixed substituent and the HB_{A} term expresses the hydrogen-bonding effect of hydrogen-accepting X substituents. The positive h_{A} values

Table 2. $\log k'$ Values for Phenyl N,N-Dimethylcarbamates (**3**)

Substituent	Eluents		
	M30[a]	M50	M70
H	1.272	0.544	−0.148
p-Me	1.713	0.886	0.090
p-Et	2.111	1.180	0.312
p-Pr	2.592	1.541	0.569
p-iso-Pr	2.512	1.479	0.515
p-*sec*-Bu	2.946	1.803	0.744
p-F	1.357	0.613	−0.139
p-Cl	1.792	0.963	0.137
p-Br	1.918	1.046	0.214
p-OMe	1.420	0.580	−0.172
p-NO_2	1.307	0.542	−0.210
p-CN	1.121	0.304	−0.497
p-COMe	1.223	0.354	−0.463
m-Me	1.705	0.869	0.102
m-Et	2.105	1.173	0.319
m-F	1.410	0.653	−0.072
m-Cl	1.826	0.986	0.193
m-OMe	1.461	0.628	−0.125
m-NMe	1.711	0.823	0.049
m-NO_2	1.359	0.582	−0.148
m-CN	1.122	0.330	−0.469
m-COMe	1.247	0.373	−0.393

[a] The figure represents the percentage by volume of methanol.

Table 3. Prediction of $\log P$ Values for Phenyl Carbamates (**2** and **3**)

Substituent	$\log P$[a]	$\log k_{\mathrm{W}}$[b]	Δ[c]	$\log P_{\mathrm{calcd.}}$[d]	Δ[e]
Series 2					
H	1.16	1.49	0.33	1.21	0.05
p-Me	1.66	2.08	0.42	1.73	0.07
p-Et	2.24	2.58	0.34	2.27	0.03
p-Pr	2.88[f]	3.19	0.31	2.85	−0.03
p-iso-Pr	2.80	3.10	0.30	2.75	−0.05
p-*tert*-Bu	3.06			3.13	0.07
p-F	1.28	1.60	0.32	1.35	0.07
p-Cl	2.01	2.18	0.17	1.95	−0.06
p-Br	2.17	2.36	0.19	2.11	−0.06
p-I	2.46	2.64	0.18	2.34	−0.12
p-OMe	1.20	1.71	0.51	1.23	0.03
p-OEt	1.64	2.20	0.56	1.75	0.11
p-OBu	2.82			2.96	0.14
p-NO_2	1.46	1.67	0.21	1.36	−0.10
p-SMe	1.93	2.26	0.33	1.92	−0.01
p-COMe	1.01	1.62	0.61	0.92	−0.09
p-COEt	1.55	2.15	0.60	1.50	−0.05
m-Me	1.70	2.06	0.36	1.73	0.03
m-Et	2.20	2.60	0.40	2.23	0.03
m-Pr	2.87[f]	3.21	0.34	2.79	−0.08
m-iso-Pr	2.72[f]	3.10	0.38	2.67	−0.05
m-*tert*-Bu	2.93			3.03	0.10
m-CF_3	2.37	2.68	0.31	2.34	−0.03
m-F	1.49	1.74	0.25	1.45	−0.04
m-Cl	2.03	2.27	0.24	1.97	−0.06
m-Br	2.25	2.43	0.18	2.12	−0.13
m-I	2.49[f]	2.70	0.21	2.33	−0.16
m-OMe	1.30	1.76	0.46	1.34	0.04
m-OEt	1.76	2.26	0.50	1.82	0.06
m-O-iso-Pr	2.11	2.63	0.52	2.16	0.05
m-OBu	2.96			3.01	0.05
m-NMe_2	1.53[f]	2.06	0.53	1.64	0.11
m-NO_2	1.39	1.70	0.31	1.37	−0.02
m-CN	0.98	1.54	0.56	1.01	0.03
m-COMe	0.90	1.59	0.69	0.97	0.07
m-COEt	1.49	2.11	0.62	1.51	0.02
Series 3					
H	1.56	2.33	0.77	1.54	−0.02
p-Me	2.16[f]	2.93	0.77	2.10	−0.06
p-Et	2.55[f]	3.45	0.90	2.58	0.03
p-Pr	3.15[f]	4.10	0.95	3.17	0.02
p-iso-Pr	3.09[f]	4.00	0.91	3.07	−0.02
p-*sec*-Bu	3.62[f]	4.58	0.96	3.60	−0.02
p-F	1.58[f]	2.48	0.90	1.65	0.07
p-Cl	2.28	3.03	0.75	2.23	−0.05
p-Br	2.46[f]	3.19	0.73	2.36	−0.10
p-OMe	1.53	2.61	1.08	1.60	0.07
p-NO_2	1.50	2.44	0.94	1.54	0.04
p-CN	1.21[f]	2.33	1.12	1.15	−0.06
p-COMe	1.27[f]	2.48	1.21	1.23	−0.04
m-Me	2.05	2.90	0.85	2.07	0.02
m-Et	2.47[f]	3.43	0.96	2.57	0.10
m-F	1.75[f]	2.52	0.77	1.72	−0.03
m-Cl	2.33[f]	3.04	0.71	2.26	−0.07
m-OMe	1.60	2.64	1.04	1.68	0.08
m-NMe_2	1.93[f]	2.94	1.01	2.00	0.07
m-NO_2	1.56[f]	2.48	0.92	1.60	0.04
m-CN	1.23[f]	2.32	1.09	1.19	−0.04
m-COMe	1.29[f]	2.46	1.17	1.26	−0.03

[a] Taken from ref. 15 unless otherwise noted. [b] Calculated by linear extrapolation. See Experimental. [c] Difference between $\log k_{\mathrm{W}}$ and $\log P$. [d] Calculated by using Eq. 10. [e] Difference between $\log P_{\mathrm{calcd.}}$ and $\log P$. [f] This work.

indicate that the hydrogen-accepting substituents deviate upward in the plot of $\log k'$ against $\log P$. This follows the general behavior ii) described above.

In contrast to the results for **2** and **3**, the $\rho\sigma^\circ$ term is insignificant in correlations for **1**, even in a water-rich eluent,[13] reflecting the fact that the electronic interactions between the fixed and X substituents are more significant in phenyl carbamates than benzyl carbamates. In fact, larger electronic substituent effects have been observed in ^{13}C-NMR chemical shifts for **2** and **3** compared to those for **1**.[19] Although the σ° term is statistically significant in the correlation at M50, the linear relationship, Eq. 10, is considered to be accurate enough for prediction of $\log P$ values, judging from the differences between observed and calculated values shown in Table 3.

The h_{AM} value was negative in all cases, indicating that the amphiprotic OCONHMe group is more hydrophobic in the 1-octanol–water partitioning system than in the RPLC partitioning system because this substituent prefers to form hydrogen bonds as a hydrogen-donor with the more basic octanol. In the present case, the HB_{AM} term expresses the difference between the hydrogen-bonding effects of OCONHMe and OCONMe$_2$, and hence mainly the hydrogen-donating ability of the amide hydrogen OCON$\underline{\text{H}}$Me. The h_{AM} value was found to be more negative with decrease in the methanol concentration, indicating that the hydrogen-donor effect is enhanced in water-rich eluents.

Table 4. Substituent Parameters Used for Analyses

	σ° (p)	σ° (m)	HB_{A}
H	0	0	0
Me	−0.12	−0.07	0
Et	−0.13	−0.07	0
Pr	−0.13	−0.07	0
iso-Pr	−0.16	−0.07	0
sec-Bu	−0.16		0
tert-Bu	−0.17	−0.07	0
CF$_3$		0.47	0
F	0.17	0.35	0
Cl	0.27	0.37	0
Br	0.26	0.38	0
I	0.27	0.35	0
OMe	−0.16	0.06	1
OEt	−0.14	0.04	1
O-iso-Pr		0.04	1
OBu	−0.14	0.04	1
NMe$_2$		−0.15	1
NO$_2$	0.82	0.70	1
SMe	0.06		1
CN	0.69	0.62	1
COMe	0.49	0.34	1
COEt	0.46	0.34	1

$\log k_{\text{W}}$ Approach As described in the introduction, the $\log k_{\text{W}}$ parameter may be a direct indicator of $\log P$ for certain compounds which do not have very polar functional groups, that is, $\log k_{\text{W}} = \log P$.[4,20] However, our results obtained in the present case suggest that hydrogen-bond effects will interfere with the prediction of $\log P$ values by the $\log k_{\text{W}}$ approach. Therefore, we examined the relationship between $\log P$ and $\log k_{\text{W}}$. Extrapolated $\log k_{\text{W}}$ values are included in Table 3. Comparisons between $\log P$ and $\log k_{\text{W}}$ clearly indicate that the $\log k_{\text{W}}$ treatment over-estimates the hydrophobicity of all compounds studied. The corresponding correlation for $\log k_{\text{W}}$ to Eq. 10 is shown by the following equation.

$$\log k_{\text{W}} = 0.896 \log P - 0.557 HB_{\text{NH}} + 1.130 \tag{12}$$

$$n = 54,\ r = 0.981,\ s = 0.132$$

Equation 12 is much inferior to Eq. 10, supporting our claim that a monocratic method at a methanol content of

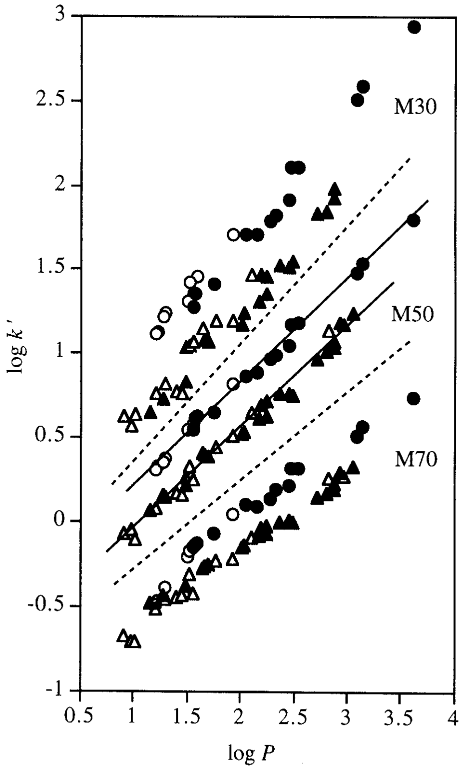

Fig. 1. Relationship between $\log k'$ and $\log P$ for Phenyl Carbamates (**2**) and (**3**)

Closed triangles, (**2**) nonhydrogen-bonders; open triangles, (**2**) hydrogen-acceptors. Closed circles, (**3**) nonhydrogen bonders; open circles, (**3**) hydrogen acceptors. A set of parallel lines represents the regression lines of Eq. 10. Plots for each eluent are separated by dotted lines.

Table 5. Correlations for Phenyl Carbamates (**2** and **3**) with Eq. 1[a)]

Eluent	a	ρ	h_{A}	h_{AM}	const.	n	r	s	Eq. No.
M30	0.738	−0.144	0.121	−0.401	0.188	54	0.996	0.050	8
M50	0.583	−0.094		−0.275	−0.324	58	0.997	0.032	9
	0.604			−0.207	−0.384	58	0.995	0.042	10
M70	0.445	−0.112		−0.180	−0.856	58	0.992	0.044	11

$\log k' = a \log P + \rho\sigma^\circ + h_{\text{A}} HB_{\text{A}} + h_{\text{AM}} HB_{\text{AM}} + \text{const.}$ *a*) For symbols see the text.

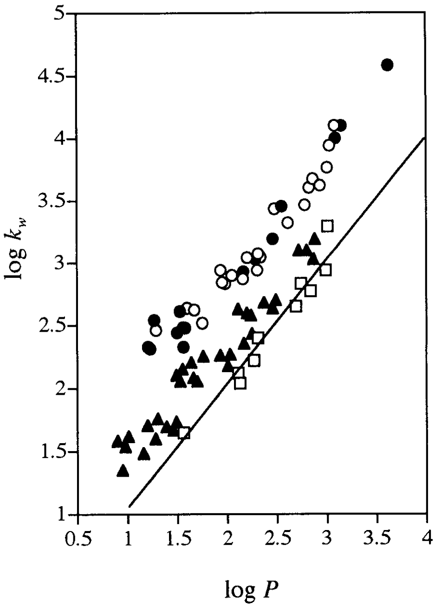

Fig. 2. Relationship between $\log k_W$ and $\log P$

Open circles, (**1**); triangles, (**2**); closed circles, (**3**); squares, PhX. The straight line represents $\log k_W = \log P$.

around 50% is more useful than the log k_W method.

$\log k_W$ values for **2** and **3** are plotted against $\log P$ in Fig. 2. For comparison, the results of series **1** compounds as well as monosubstituted benzenes (PhX) with the same X substituents as those included in **2** and **3** are added in Fig. 2. From Fig. 2, it can be seen that series **1** and **3** exhibit similar behavior and their log k_W values are larger than the corresponding $\log P$ values to a greater extent than in series **2**, while most monosubstituted benzenes fell on the straight line of $\log k_W = \log P$. Therefore, the extent to which the predicted $\log P$ values are over-estimated by the $\log k_W$ approach seems to be mainly governed by the hydrogen-bonding ability of the fixed substituents (OCONHMe and OCONMe$_2$). Although a quantitative measure of hydrogen-bond basicity of OCONMe$_2$ is not available, it seems reasonable to treat the OCONMe$_2$ substituent as a strong hydrogen-acceptor since the CONMe$_2$ substituent is known to have a large hydrogen-bond basicity.[21,22] All our results so far obtained support the hypothesis that the difference between $\log k_W$ and $\log P$ for hydrogen-acceptors can be a good measure of hydrogen-accepting ability. Previously, we have found that the $\log k_W$ approach under-estimates the hydrophobicity of hydrogen-donors.[9] However, Fig. 2 shows that the $\log k_W$ approach over-estimates the hydrophobicity even for series **2** compounds, suggesting that the over-estimating hydrogen-acceptor effect ($\underline{\text{O}}$C$\underline{\text{O}}$$\underline{\text{N}}$HMe) exceeds the under-estimating hydrogen-donor effect of amide-hydrogen (OCON$\underline{\text{H}}$Me).

Substituent Effect on Retention Behavior In a previous study,[13] we have shown that the substituent effect on the retention behavior is well characterized in terms of the a_X value as defined by Eq. 13.

$$\log k'_X = a_X \log k'_H + \text{const}. \tag{13}$$

In Eq. 13, $\log k'_X$ and $\log k'_H$ are $\log k'$ values for derivatives with an X substituent and without a substituent (*i.e.* X = H), respectively, at 30 to 70% MeOH concentrations. When $\log k'_X$ values obtained at 30, 50 and 70% MeOH for a given substituent were plotted against the corresponding $\log k'_H$ values, a straight line was obtained. The a_X value, the slope of the line, is thought to express the relative sensitivity of retention for a given substituent X to the change in the mobile phase properties compared to the unsubstituted compound. This a_X parameter is almost equivalent in nature to the S parameter, which is the slope of the plot of $\log k'_X$ against methanol content in the mobile phase (ϕ), as shown by $\log k'_X = \log k_W + S\phi$. However, we believe that the a_X parameter is a better indicator of substituent hydrogen-bonding property because the hydrogen-bonding property of the parent

Table 6. a_X Values Derived from Eq. 13 for Phenyl Carbamates (**2** and **3**)

Substituent	*p*-**2**	*m*-**2**	*p*-**3**	*m*-**3**
Me	1.194	1.174	1.143	1.129
Et	1.317	1.339	1.267	1.259
Pr	1.502	1.531	1.425	
iso-Pr	1.482	1.502	1.406	
sec-Bu			1.551	
CF$_3$		1.362		
F	1.031	1.073	1.054	1.044
Cl	1.181	1.222	1.165	1.150
Br	1.233	1.273	1.200	
I	1.328	1.371		
OMe	1.131	1.126	1.121	1.117
OEt	1.262	1.269		
O-iso-Pr		1.384		
NMe$_2$		1.205		1.171
NO$_2$	1.068	1.087	1.068	1.061
SMe	1.251			
CN		1.135	1.139	1.120
COMe	1.193[a]	1.153[a]	1.187	1.156
COEt	1.317[a]	1.284[a]		

a) r (correlation coefficient) = 0.999. For the others r = 1.00.

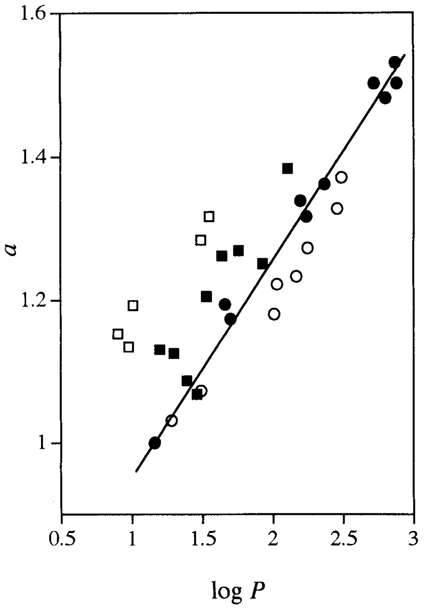

Fig. 3. Relationship between a and $\log P$ for Phenyl Carbamates (**2**)

Closed circles, alkyls and CF$_3$; open circles, halogens; open squares, CN, COR; closed squares, other hydrogen-acceptors. The straight line represents the trend in the non-hydrogen bonders and not the regression line.

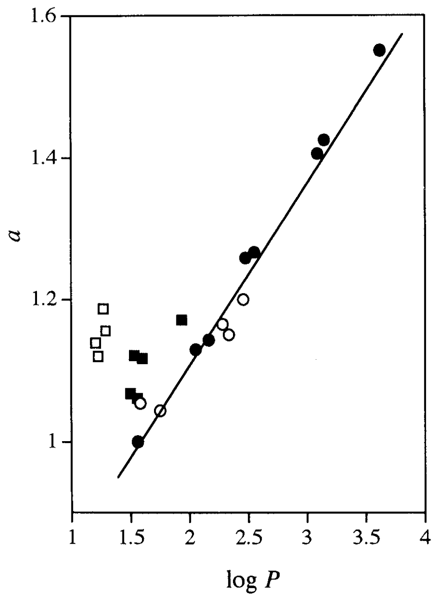

Fig. 4. Relationship between a and $\log P$ for Phenyl Carbamates (**3**)

For symbols see Fig. 3. The straight line represents the trend in the non-hydrogen bonders and not the regression line.

compound can be mostly eliminated in this parameter.

The a_X parameters derived from the **2** and **3** series are summarized in Table 6, and are plotted against $\log P$ in Figs. 3 and 4. We have found in an analogous plot for compounds **1** that non-hydrogen-bonding substituents such as alkyl groups and halogens show a linear relationship with $\log P$, but hydrogen-bonding substituents deviate upward to various degrees depending on the hydrogen-bonding ability of X.[13] As shown in Figs. 3 and 4, **2** and **3** exhibited similar trends. Whereas alkyl substituents gave a linear relationship, strong hydrogen-acceptors such as COR and CN presented more positive deviations than weak hydrogen-acceptors such as OR and NMe_2. In contrast to the case of **1** where halogens fit the straight line for alkyl groups, halogens deviated downward slightly from the line for alkyl groups, suggesting that the electronic effect is involved in the retention mechanism of phenylcarbamates. As mentioned above, an inspection of plots of a_X against $\log P$ seems to be a good means to examine whether factors other than the hydrophobic factor are involved in the retention mechanism.

Conclusions

From the results described above, we conclude that M50 is the best eluent to predict $\log P$ values for compounds **2** and **3**. It should be noted, however, that separate calibration curves are needed for each series because compounds **2** exert an amphiprotic effect. As expected, the $\log k_W$ approach greatly over-estimated the $\log P$ values for both series because of the overall strong hydrogen-accepting properties of the fixed substituents. The correlation in water-rich eluents was more complicated than that for **1** since the electronic interactions between the fixed and X substituents, affecting the hydrogen-bonding ability of each hydrogen-bonding substituent, are more important in polar solutions. The results obtained in this work again indicate that we should be very careful to consider the hydrogen-bonding properties of the solutes if we wish to obtain reliable $\log P$ values by the RPLC method.

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