Chem. Pharm. Bull. **43**(12) 2238—2242 (1995)

Vol. 43, No. 12

Hydrophobicity Parameters Determined by Reversed-Phase Liquid Chromatography. X.[1] Relationship between Capacity Factor and Octanol–Water Partition Coefficients of Monosubstituted Thiophenes

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Received June 21, 1995; accepted August 21, 1995

Capacity factors, k', of monosubstituted thiophenes were obtained by reversed-phase high-performance liquid chromatography, using three kinds of octadecyl silica (ODS) columns and methanol-buffer (pH 7.4) eluents. The relationship between $\log k'$ and $\log P$ (P: octanol–water partition coefficient) was analyzed in terms of the H-bonding properties of the substituents as a function of the mobile phase composition. Non-hydrogen-bonders and H-acceptors gave a good linear $\log k'$–$\log P$ relationship in the eluent containing 50% methanol. As the methanol content was decreased, ester substituents, which are strong H-acceptors, deviated from the regression line. Amide groups, amphiprotic substituents, behaved differently from the non-amphiprotics, as is usually observed. The $\log k_W$ approach ($\log k_W$; the extrapolated $\log k'$ value in water) correctly predicted the $\log P$ value for non-hydrogen-bonders and weak H-acceptors such as H, alkyls, halogens and OMe, but over-estimated $\log P$ for the others. The H-bonding effect of the thiophene ring seems to be small, and hence, the retention behavior of thiophene derivatives is considered to be mainly dependent upon the H-bonding property of substituents.

Key words capacity factor; partition coefficient; hydrogen-bond effect; thiophene; hydrophobicity

The logarithm of the 1-octanol–water partition coefficient, $\log P$, is the most widely accepted parameter of hydrophobicity,[2] which is known to be a major factor controlling bio-activities.[3] In addition to the conventional shake-flask method, reversed-phase high-performance liquid chromatography (RPLC) has increasingly been used to determine $\log P$ values.[4-7] In RPLC, the logarithm of the capacity factor, $\log k'$, obtained in a chromatographic system composed of an octadecyl silica (ODS)-type stationary phase and methanol–water mixtures as the mobile phase is usually used as an alternative hydrophobicity index. The RPLC procedure is very useful when applied to a series of congeneric compounds which yield a linear relationship between $\log P$ and $\log k'$.

Previously, we have studied the relationship between $\log P$ and $\log k'$ for heteroaromatic compounds and found that the linear relationship is broken by hydrogen-bond effects of the ring hetero atom(s) and the substituents.[1,8,9] For example, the analysis of $\log k'$ values for monosubstituted pyridines and diazines (pyrazines, pyrimidines and pyridazines), ArX, has shown that non-hydrogen-bonding and H-accepting substituents give almost linear relationships in eluents of medium methanol content (50—70%), although amphiprotic substituents have smaller $\log k'$ values than expected from the regression line for non-amphiprotics.[1,8] However, the relationship became more complicated in water-rich eluents and correction terms for H-bond effects were required, as expressed by the following type of correlation equation, with substituents X such as alkyls, halogens, OR, SR, CN, NMe_2, Ac, CO_2R, NH_2, NHAc and $CONH_2$.

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

In Eq. 1, σ_I represents the electronic substituent constant of the variable substituent X.[10] The HB_A and HB_{AM} terms are indictor variables which take the value of 1 for CO_2R (strong H-acceptor) and amphiprotic substituents, respectively, and 0 for the others. The regression coefficients, a, ρ, h_A and h_{AM} are determined by the least-squares method. The $\rho\sigma_I$ term expresses the electronic effect of substituents X on the H-bonding ability of the ring N atom(s). The HB_A and HB_{AM} terms express the change in the H-bonding ability of the substituent X caused by the ring N atom(s). When the methanol content is very low, an additional indicator variable often becomes necessary for moderately H-accepting substituents such as Ac and CN.[11] Thus, the correlation becomes even more complicated.

To eliminate the effect of organic modifiers used in mobile phases, the $\log k_W$ value, the (extrapolated) $\log k'$ value at 100% water, has usually been used as a standardized hydrophobicity index.[4,6,12] It is reported that this parameter is a direct indicator of $\log P$ for certain compounds, that is, $\log k_W = \log P$.[4] However, for (di)azines as noted above, the $\log k_W$ approach fails to estimate $\log P$ values: the $\log k_W$ values were much larger than the $\log P$ values for all compounds due to the strong H-accepting property of the aza function(s) in the parent rings.

To elucidate the hydrogen-bonding effects exerted by the ring hetero atom, it is of interest to study the relationship between $\log P$ and $\log k'$ for other heterocyclic compounds. To our knowledge, little has been reported in the literature about the effects of ring O- and S-atoms on the hydrophobicity of O- and S-containing compounds. Therefore, we attempted to extend the above-mentioned procedure (Eq. 1) to analyze the $\log k'$ value of a series of monosubstituted thiophenes. The hetero atom effects in aza- and thio-series were compared.

Experimental

Materials Thiophenes with ester substituents (CO_2R) were prepared from thiophene carboxylic acid and an appropriate alcohol by Fisher's method. The amide derivatives were prepared by treating the corresponding esters with appropriate amines. The others were commercially available.

Partition Coefficients Partition coefficients were measured by the

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improved shake-flask method as previously described.[13)]

RPLC Procedures The apparatus was previously described.[13)] The following commercial columns were used without further treatment; Capcell pak C_{18} (4.6 mm × 15 cm, Shiseido), Chembond 5-ODS-H (4.6 mm × 15 cm, Chemco) and Cosmosil $5C_{18}$-AR (5.0 mm × 15 cm, Nacalai Tesque). As mobile phases, HPLC-grade MeOH–0.01 M phosphate buffer (pH 7.4) mixtures prepared by volume were used. Analytes were dissolved in methanol and 1—2 μl was injected at 25 °C. The flow rate was 0.5—1.5 ml. The capacity factor was determined from the retention time of the sample, t_r, by using the equation, $k' = (t_r - t_0/t_0)$, where t_0 is the retention time of methanol. The experimental error of duplicate $\log k'$ determinations was ± 0.005.

Results and Discussion

The monosubstituted thiophenes studied in this work are listed in Table 1. The ester (CO_2R) and amide ($CONH_2$ and CONHR) substituents were chosen as representatives of strong H-accepting and amphiprotic substituents, respectively. The $\log k'$ values were obtained with eluents containing 15, 30, 50 and 70% MeOH (M15, M30, M50 and M70, respectively) on a Capcell pak C_{18} column (Table 1), as used in our earlier studies. To examine the influence of the stationary phase, the same measurements were also made on Chembond (CB) and Cosmosil (CS) columns with the M30, M50 and M70 eluents. The results are summarized in Table 2. It is clear from Tables 1 and 2 that the retention behaviors of the three stationary phases strongly resemble each other, as shown by Eqs. 2—7.

$$\log k'_{M30}(CB) = 0.970 \log k'_{M30} + 0.241 \quad n=27,\ r=0.998,\ s=0.038 \tag{2}$$

$$\log k'_{M30}(CS) = 0.962 \log k'_{M30} + 0.151 \quad n=27,\ r=0.999,\ s=0.029 \tag{3}$$

$$\log k'_{M50}(CB) = 0.951 \log k'_{M50} + 0.240 \quad n=27,\ r=0.999,\ s=0.031 \tag{4}$$

$$\log k'_{M50}(CS) = 0.948 \log k'_{M50} + 0.130 \quad n=27,\ r=0.999,\ s=0.024 \tag{5}$$

$$\log k'_{M70}(CB) = 0.932 \log k'_{M70} + 0.209 \quad n=27,\ r=0.999,\ s=0.026 \tag{6}$$

$$\log k'_{M70}(CS) = 0.942 \log k'_{M70} + 0.086 \quad n=27,\ r=0.999,\ s=0.024 \tag{7}$$

In Eqs. 2—7 and throughout this work, the notation "$\log k'$" without the column name in parentheses represents $\log k'$ (CP), where $\log k'$ (CP) refers to the $\log k'$ value obtained on a Capcell pak C_{18} column, n is the number of compounds used for calculations, r is the correlation coefficient, and s is the standard deviation. As described in our previous work,[8)] the silanol-solute interaction is thought to be negligible with the Capcell pak. The excellent linear relationships between the retention data on the three columns indicates that these stationary phases are of similar quality, and hence the obtained results should represent a general trend.

The $\log k_W$ value was calculated by the linear extrapolation of a plot of $\log k'$ against volume % of methanol (30—70% MeOH) to 0% methanol. Our earlier studies have shown that the extrapolated $\log k_W$ values thus obtained give better correlations with $\log P$ than those derived from other extrapolations.[8,14)] The $\log k_W$ values obtained for the three columns are given in Table 3 together with the $\log P$ values. It can be seen from Table 3 and Fig. 1 that the $\log k_W$ approach works well to estimate the $\log P$ value of the compounds with non-hydrogen-bonding and weakly H-accepting substituents such as H, alkyls,

Table 1. $\log k'$ Values of Monosubstituted Thiophenes on Capcell Pak

Substituent	M15[a)]	M30	M50	M70
H	1.230	1.018	0.605	0.112
2-Me	1.795	1.503	0.979	0.386
2-Et	2.297	1.937	1.307	0.611
3-Me	1.765	1.469	0.953	0.363
2-Cl	1.946	1.645	1.067	0.418
2-Br	2.065	1.744	1.126	0.453
3-Cl	1.797	1.497	0.936	0.309
3-Br	1.941	1.617	1.019	0.374
2-OMe	1.555	1.232	0.711	0.149
2-CN	1.030	0.661	0.144	−0.363
2-NO_2	1.121	0.795	0.322	−0.186
2-Ac	1.107	0.636	0.063	−0.431
3-Ac	1.099	0.638	0.078	−0.413
2-CO_2Me	1.582	1.121	0.485	−0.101
2-CO_2Et	2.077	1.544	0.792	0.110
2-CO_2Pr		1.994	1.133	0.349
3-CO_2Me	1.557	1.100	0.482	−0.092
3-CO_2Et	2.049	1.511	0.789	0.123
3-CO_2Pr		1.959	1.125	0.360
2-CONHMe	0.593	0.130	−0.396	−0.824
2-CONHEt	0.892	0.387	−0.176	−0.650
2-CONHPr	1.278	0.718	0.090	−0.454
2-$CONH_2$	0.359	−0.067	−0.585	−1.026
3-CONHMe	0.569	0.129	−0.369	−0.792
3-CONHEt	0.855	0.373	−0.161	−0.620
3-CONHPr	1.232	0.693	0.095	−0.430
3-$CONH_2$	0.364	−0.037	−0.533	−0.955

[a)] Eluent: the figure represents the volume % of MeOH.

Table 2. Influence of Stationary Phases on $\log k'$ Values of Monosubstituted Thiophenes

Substituent	Chembond			Cosmosil		
	M30	M50	M70	M30	M50	M70
H	1.159	0.753	0.265	1.079	0.658	0.155
2-Me	1.663	1.139	0.546	1.556	1.025	0.420
2-Et	2.119	1.483	0.783	1.983	1.345	0.637
3-Me	1.631	1.116	0.526	1.527	1.002	0.400
2-Cl	1.790	1.226	0.578	1.714	1.133	0.473
2-Br	1.897	1.289	0.617	1.818	1.193	0.510
3-Cl	1.648	1.100	0.475	1.566	0.998	0.365
3-Br	1.774	1.198	0.543	1.686	1.089	0.430
2-OMe	1.409	0.893	0.330	1.332	0.795	0.222
2-CN	0.857	0.350	−0.154	0.822	0.288	−0.224
2-NO_2	0.992	0.521	0.018	0.958	0.484	−0.029
2-Ac	0.852	0.293	−0.199	0.800	0.218	−0.289
3-Ac	0.864	0.309	−0.178	0.791	0.227	−0.276
2-CO_2Me	1.343	0.707	0.119	1.253	0.608	0.007
2-CO_2Et	1.774	1.026	0.339	1.659	0.904	0.207
2-CO_2Pr	2.248	1.380	0.586	2.107	1.238	0.439
3-CO_2Me	1.323	0.706	0.131	1.226	0.601	0.015
3-CO_2Et	1.751	1.025	0.354	1.631	0.898	0.218
3-CO_2Pr	2.212	1.373	0.598	2.064	1.224	0.444
2-CONHMe	0.370	−0.136	−0.565	0.276	−0.245	−0.700
2-CONHEt	0.638	0.090	−0.383	0.527	−0.042	−0.535
2-CONHPr	0.986	0.364	−0.182	0.843	0.212	−0.351
2-$CONH_2$	0.168	−0.327	−0.764	0.048	−0.451	−0.909
3-CONHMe	0.373	−0.114	−0.529	0.277	−0.222	−0.660
3-CONHEt	0.626	0.101	−0.354	0.519	−0.027	−0.505
3-CONHPr	0.962	0.369	−0.158	0.830	0.217	−0.328
3-$CONH_2$	0.200	−0.274	−0.699	0.076	−0.403	−0.841

Table 3. Prediction of $\log P$ by Different Procedures

Substituent	$\log P$	Capcell pak		Chembond		Cosmosil		Capcell pak	
		$\log k_W$	$\Delta^{a)}$	$\log k_W$	$\Delta^{a)}$	$\log k_W$	$\Delta^{a)}$	$\log P_{\text{Calcd}}{}^{b)}$	$\Delta^{c)}$
H	1.89	1.71	−0.18	1.84	−0.05	1.79	−0.10	2.02	0.13
2-Me	2.47	2.35	−0.12	2.51	0.04	2.42	−0.05	2.61	0.14
2-Et	3.01	2.94	−0.07	3.13	0.12	3.01	0.00	3.13	0.12
3-Me	2.45	2.31	−0.14	2.47	0.02	2.38	−0.07	2.57	0.12
2-Cl	2.69	2.58	−0.11	2.71	0.02	2.66	−0.03	2.75	0.06
2-Br	2.84	2.72	−0.12	2.87	0.03	2.81	−0.03	2.84	0.00
3-Cl	2.55	2.40	−0.15	2.54	−0.01	2.48	−0.07	2.54	−0.01
3-Br	2.73	2.56	−0.17	2.71	−0.02	2.64	−0.09	2.67	−0.06
2-OMe	2.13	2.05	−0.08	2.23	0.10	2.17	0.04	2.19	0.06
2-CN	1.34	1.43	0.09	1.62	0.28	1.60	0.26	1.30	−0.04
2-NO_2	1.58	1.54	−0.04	1.73	0.15	1.71	0.13	1.58	0.00
2-Ac	1.27	1.42	0.15	1.63	0.36	1.60	0.33	1.17	−0.10
3-Ac	1.26	1.42	0.16	1.63	0.37	1.58	0.32	1.19	−0.07
2-CO_2Me	1.83	2.03	0.20	2.25	0.42	2.18	0.35	1.83	0.00
2-CO_2Et	2.39	2.61	0.22	2.84	0.45	2.74	0.35	2.32	−0.07
2-CO_2Pr	3.01	3.21	0.20	3.48	0.47	3.35	0.34	2.85	−0.16
3-CO_2Me	1.76	1.99	0.23	2.21	0.45	2.13	0.37	1.83	0.07
3-CO_2Et	2.32	2.54	0.22	2.79	0.47	2.68	0.36	2.31	−0.01
3-CO_2Pr	3.03	3.15	0.12	3.41	0.38	3.27	0.24	2.84	−0.19
2CONHMe	0.84	0.83	−0.01	1.06	0.22	1.00	0.16	0.82	−0.02
2-CONHEt	1.18	1.15	−0.03	1.39	0.21	1.31	0.13	1.16	−0.02
2-CONHPr	1.68	1.58	−0.10	1.85	0.17	1.73	0.05	1.58	−0.10
2-$CONH_2$	0.48	0.64	0.16	0.86	0.38	0.76	0.28	0.52	0.04
3-CONHMe	0.81	0.81	0.00	1.04	0.23	0.97	0.16	0.86	0.05
3-CONHEt	1.18	1.11	−0.08	1.35	0.17	1.28	0.10	1.19	0.01
3-CONHPr	1.65	1.52	−0.13	1.79	0.14	1.69	0.04	1.59	−0.06
3-$CONH_2$	0.50	0.64	0.14	0.87	0.37	0.76	0.26	0.60	0.10

a) The difference between $\log k_W$ and $\log P$. *b)* Calculated by Eq. 10. *c)* Difference between $\log P_{\text{Calcd}}$ and $\log P$.

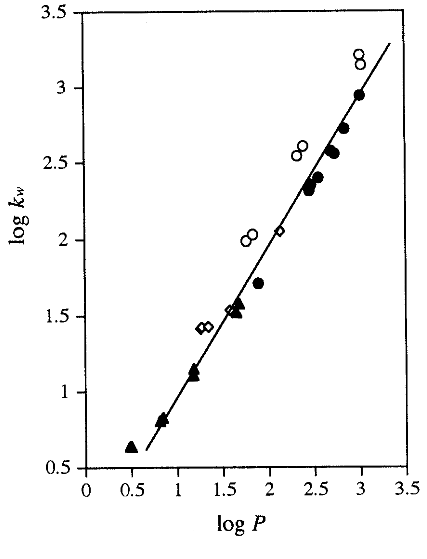

Fig. 1. Plot of $\log k_W$ against $\log P$ for Monosubstituted Thiophenes

Column; Capcell pak. Closed circles, H, alkyls and halogens; open circles, CO_2R; squares, OMe, CN and Ac; triangles, $CONH_2$ and CONHR.

halogens and OCH_3.[15)] This finding is in sharp contrast to the observation that the $\log k_W$ values of (di)azines with the same substituents are much larger than $\log P$,[8)] suggesting that the H-bonding property of the ring S atom is mild enough to make the thiophene ring behave as if it were a non-hydrogen-bonder. On the other hand, it seems that strong and moderate H-acceptors such as CO_2R and Ac deviate upward from the straight line of $\log k_W = \log P$ to different degrees depending on the H-accepting ability of the substituent. This tendency is in accord with our previous observation that the $\log k_W$ approach tends to over-estimate the $\log P$ value of H-acceptors. In the present case, the amphiprotic substituents, CONHR and $CONH_2$ were also situated near the line of $\log k_W = \log P$. We will discuss this problem later.

Since the $\log k_W$ approach failed to predict $\log P$ values of H-accepting substituents, analyses of the relationship between $\log k'$ and $\log P$ were performed at each mobile phase composition in order to see to what extent the H-bonding effect is involved in the correlation. As shown in Fig. 2, the M50 eluent gave the best correlation, although the amide groups (amphiprotic substituents) fell on a separate line parallel to the line for the others. Such strong H-acceptors as CO_2R deviate upward with a decrease in the methanol content and *vice versa.* Application of Eq. 1 to the analysis of the data in Table 1, using the following indicator variables for expressing H-bonding effects, produced excellent correlations, $HB_A = 1$ for CO_2R and 0 for the others and $HB_{AM} = 1$ for $CONH_2$ and CONHR and 0 for the others.

$$\log k'_{M15} = 0.716 \log P + 0.294 HB_A + 0.035 \qquad (8)$$

$$n = 25,\ r = 0.992,\ s = 0.074$$

$$\log k'_{M30} = 0.707 \log P + 0.121 HB_A - 0.172 HB_{AM} - 0.273 \qquad (9)$$

$$n = 27,\ r = 0.999,\ s = 0.033$$

$$\log k'_{M50} = 0.620 \log P - 0.254 HB_{AM} - 0.644 \qquad (10)$$

$$n = 27,\ r = 0.996,\ s = 0.055$$

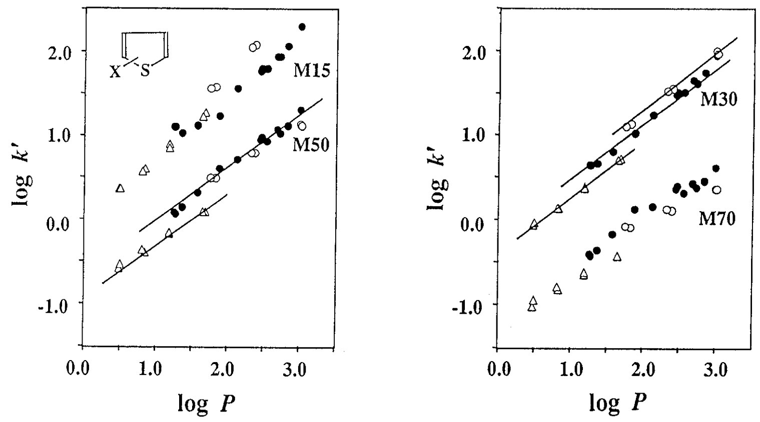

Fig. 2. Plot of $\log k'$ against $\log P$ for Monosubstituted Thiophenes

Column; Capcell pak. Open circles, CO_2R; triangles, $CONH_2$ and CONHR; closed circles, others.

$$\log k'_{\mathrm{M70}} = 0.508 \log P - 0.124 HB_{\mathrm{A}} - 0.283 HB_{\mathrm{AM}} - 0.964 \qquad (11)$$
$$n=27,\ r=0.992,\ s=0.067$$

The other stationary phases gave similar results (not shown).

The HB_{A} term was almost insignificant with the M50 eluent, indicating that eluents containing around 50% MeOH do not discriminate between non-hydrogen-bonders and H-acceptors. This is one of the general tendencies we have observed in other series of compounds.[8,11,13,14] With decrease in methanol concentration, however, H-acceptors began to deviate from the line for non-hydrogen bonders, and the HB_{A} parameter became significant. Although the correlation at 15% MeOH (Eq. 8) appears to be simple, close examination of the residuals indicated that medium H-accepting substituents begin to produce fairly large positive deviations from the calculated values, suggesting that an additional H-bond parameter for medium H-acceptors would be necessary to improve the quality of the correlation. Moreover, although the HB_{AM} term was insignificant at 15% MeOH, this might be coincidental (see below). From the results described above, it can be said that measurement with eluents containing around 50% MeOH would be the method of choice to predict reliably the $\log P$ values. Supporting data can be found in the literature, in that the $\log k'$ values at 50% MeOH give better correlations with $\log P$ rather than $\log k_{\mathrm{W}}$,[16] although this was not always specifically mentioned.

It should be noted that the σ_{I} term was insignificant in every eluent, suggesting that the H-bond solvation of the ring S atom with the surrounding medium is of small significance. Considering that the σ_{I} term becomes significant in water-rich eluents in the correlations of monosubstituted (di)azines, the hetero atom effect of the ring S atom might be negligible. This view is supported by comparing the substituent hydrophobicity constant, π, for each series. The π values of monosubstituted thiophenes are shown in Table 4 together with those of monosubstituted benzenes and pyrazines. It is interesting to note that thiophene-π values are in most cases intermediate between the benzene-π and pyrazine-π values, but are much closer to the former than the latter. Therefore, it can be said that the partition behavior of thiophenes is similar to that of benzenes rather than that of (di)azines.

Table 4. Comparison of π Values

Substituent	π(PhX)[a]	π(2-X-TH)[b]	π(3-X-TH)[c]	π(PR)[d]
Me	0.56	0.58	0.56	0.47
Et	1.02	1.12		0.95
Cl	0.71	0.80	0.66	0.96
Br	0.86	0.95	0.84	1.19
OMe	−0.02	0.24		0.99
CN	−0.57	−0.55		0.25
Ac	−0.55	−0.62	−0.63	0.46
NO_2	−0.28	−0.31		
CO_2Me	−0.01	−0.06	−0.13	0.03
CO_2Et	0.51	0.50	0.43	0.54
CO_2Pr		1.12	1.14	
CONHMe	−1.23[e]	−1.05	−1.08	−0.02
CONHEt	−0.85[e]	−0.71	−0.71	0.39
CONHPr	−0.41[e]	−0.21	−0.24	0.89
$CONH_2$	−1.49	−1.41	−1.39	−0.24

[a] Monosubstituted benzenes. Taken from, C. Hansch, and A. J. Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology," John Wiley & Sons, New York, 1979. [b] 2-Substituted thiophenes. [c] 3-Substituted thiophenes. [d] Monosubstituted pyrazines. Taken from ref. 8. [e] Our unpublished results.

As to the amide substituents, the $\log k'$ values were smaller than expected from the $\log P$–$\log k'$ relationship for non-amphiprotic substituents except for the M15 eluent. This is a phenomenon generally observed for amphiprotic (or H-donors) solutes and can be rationalized by considering that octanol is more basic than the mobile phases; the H-donating site in amide groups, CON$\underline{\mathrm{H}}$R, is solvated more effectively by octanol than the mobile phases (H-donor effect). Since the amphiprotic effect consists of H-accepting and H-donating effects, the amide group is considered to show a strong H-accepting property, as observed for ester substituents. On the other hand, we could estimate the H-donor effect from the distance between the two parallel lines at M50. As the methanol content is decreased, the H-donor and H-acceptor effects are expected to act in opposite directions. The fact that the HB_{AM} term is insignificant at M15 would mean that both effects are canceled out around 15% MeOH for the amide groups. Similarly, the finding that the $\log k_{\mathrm{W}}$ values of the amide groups are larger than $\log P$ in some cases

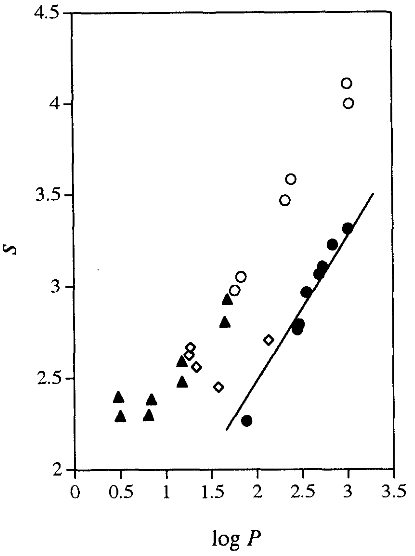

Fig. 3. Plot of s Values against log P

Column; Capcell pak. For symbols, see Fig. 1.

would mean that the H-acceptor effect exceeded the H-donor effect. Thus, the overall amphiprotic effects are considered to depend on the structure, and so it will be difficult to obtain straightforward correlations for a data set composed of various types of amphiprotics.

The slope, s, of the plot between $\log k'$ and the volume fraction of methanol, X, *i.e.* $\log k' = \log k_W - sX$, is a useful parameter representing the retention behavior of substituents. Several authors have shown that the s value is closely correlated to $\log P$. Chen *et al.* found that the s value is governed mainly by the interaction between the solute and the mobile phase.[17] The s values obtained in calculations of $\log k_W$ values in Table 3 are plotted against $\log P$ in Fig. 3. It can be seen that the relationship is almost linear for substituents of the same category. An important finding is that esters and amides gave greater s values than non-hydrogen-bonders, indicating that the H-bonding ability of these substituents changes more sensitively with change in the surrounding medium. This trend is essentially the same as that observed in benzene and furan derivatives.[18] Moderate H-accepting substituents are located in the region between strong H-bonders and non-hydrogen-bonders. All these results demonstrate that the s parameter for thiophenes reflects well the H-bonding properties of substituents.

In this study, we have found that the influence of the ring S atom in the thiophene ring is small and, therefore, the retention behavior of monosubstituted thiophenes is mainly governed by the H-bonding effects of substituents. Analyses of retention data at each methanol composition led us to conclude that the use of eluents containing around 50% MeOH is most reliable to predict the $\log P$ value of thiophenes containing non-hydrogen-bonding or H-accepting substituents. For amphiprotic solutes sharing a common H-bonding pattern, the same eluent as used for non-amphiprotics could be utilized so long as a separate calibration line is used. However, no universal method to estimate $\log P$ values for a data set containing various types of amphiprotic substituents has yet been established. For this purpose, quantitative parameterization of H-bonding ability would be required.

References and Notes

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