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Hydrophobic Properties of Antimutagenic Benzalacetones and Related Compounds

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The π values of benzalacetones (BZ) and *trans*-1,1,1-trifluoro-4-phenyl-3-buten-2-ones (TF) with a substituent on the benzene ring were analyzed by the directional Hammett-type treatment. The correlation equation showed that π_{BZ} and π_{TF} values are altered from the π value of monosubstituted benzenes, π_{PhX}, mainly by the change in the hydrogen bonding behavior of the variable substituent caused by the electron-withdrawing fixed substituent. The $\log k'$ values for BZ and TF derived from reversed-phase liquid chromatography (RPLC) were correlated with $\log P$ values determined by using different compositions of methanol–phosphate buffer (pH 7.4) as eluents. A good linear correlation was obtained at 50% methanol concentration.

Key words hydrophobicity; capacity factor; partition coefficient; antimutagenic activity; benzalacetone

Recently, we have found that benzalacetone shows antimutagenic activity.[1] Based on a comparision of the antimutagenic effects of monosubstituted benzalacetones (BZ) and some structurally related compounds on UV-induced mutagenesis in *Escherichia coli*, an α,β-unsubstituted carbonyl system was suggested to be necessary for the appearance of the activity. Since the α,β-unsubstituted carbonyl system is conjugated with the benzene ring in BZ, substituents on the benzene ring are expected to affect the potency by modifying the degree of conjugation with the carbonyl moiety, which is probably the reaction center. Therefore we decided to perform structure–activity relationship studies of benzalacetones by analyzing the substituent effects on the activity.

In quantitative structure–activity relationship (QSAR) studies, quantified potencies are described in terms of appropriate combinations of physicochemical parameters such as hydrophobic, electronic, steric and hydrogen bonding parameters of tested compounds.[2,3] When analyzing the antimutagenic activity, the hydrophobicity, usually expressed by $\log P$ (P: octanol–water partition coefficient), is expected to be important, because the test molecule must penetrate the cell through the membrane to produce the activity.[2,3] The permeation of drugs is usually related to their $\log P$ values. The development of procedures for predicting $\log P$ values before synthesis is very important for rational drug design. Hence, we conducted a systematic study of the hydrophobicity of benzalacetone derivatives preparatory to QSAR analyses.

$\log P$ has an additive-constitutive property. This means that one can calculate $\log P$ values of compounds with multi substituents on the parent compound by using the substituent hydrophobicity parameter, π_X, which is derived from $\log P$ value of the parent compound ($\log P_H$) and that of a compound with the X-substituent ($\log P_X$), as shown by $\pi_X = \log P_X - \log P_H$. However, when electronic and steric interactions between the substituents are involved, corrections for such interactions are required. For this purpose, Fujita has proposed a bi-directional treatment for analyses of π values of disubstituted benzenes as described later.[4]

Reversed-phase liquid chromatography (RPLC) is also used to estimate $\log P$ values. In RPLC, $\log k'$ (k': capacity factor) value is used as a hydrophobicity index. Extensive studies have been made to find optimal chromatographic conditions, such as stationary phase and mobile phase compositions, under which good linear correlations are obtained between $\log k'$ and $\log P$.[5-9] According to our continuing systematic studies on the relationship between $\log k'$ and $\log P$ with a Capcell pak C_{18} column and various compositions of methanol–phosphate buffer (pH 7.4) solutions as the mobile phase, eluents containing around 50% MeOH usually give the best result; an almost linear relationship exists, excluding amphiprotic compounds (hydrogen donors).[9-11]

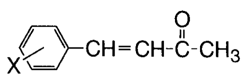
With these findings in mind, we first analyzed the π values of BZ by the bi-directional treatment, and then studied the relationship between $\log P$ and $\log k'$ under various mobile phase conditions to examine whether the optimal conditions we found remain valid in the present case. Since our preliminary analyses of antimutagenic activity of the above-mentioned compounds showed that introduction of an electron-withdrawing moiety tends to increase the activity,[12] we also prepared derivatives of the *trans*-1,1,1-trifluoro-4-phenyl-3-buten-2-one series (TF) for analogous studies. The hydrophobic properties of BZ and TF are compared and discussed.

Experimental

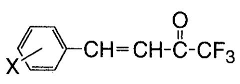
Materials The compounds used in this study are monosubstituted benzalacetones (BZ) and 1,1,1-trifluoro-4-phenyl-3-buten-2-ones (TF), as listed in Tables 1 and 2. Unsubstituted BZ and TF are commercially available. Compounds of the BZ series were prepared by an aldol-type condensation as previously described.[1] Those of the TF series were prepared similarly with the appropriate benzaldehyde and trifluoroacetone, but by a modified method where sodium methoxide was used instead of sodium hydroxide as a base, because the reaction in aqueous sodium hydroxide gave the corresponding benzyl alcohol, a reduction product of the benzaldehyde used, as a main product. The structures of the compounds were confirmed by IR, NMR, and mass spectral analyses.

Partition Coefficients The 1-octanol–water partition coefficients were measured at 25 °C by the conventional shake–flask method as previously described.[13] The $\log P$ value was reproducible to within ±0.03.

RPLC Procedures The apparatus and the method of preparing



BZ



TF

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eluents were the same as those described in our previous paper.[14] A Capcell pak C_{18} column (4.6 mm × 15 cm, Shiseido) was used as the stationary phase. The eluents, MeOH–phosphate buffer (pH 7.4) solutions containing 30, 50 and 70% MeOH (hereafter designated as M30, M50 and M70, respectively), were prepared by volume. The capacity factor, k', was calculated from the retention time of each compound, t_R, and that of methanol, t_0, by using the equation, $k'=(t_R-t_0)/t_0$. All the measurements were performed at 25 °C. The $\log k'$ value was reproducible to within ±0.005.

The $\log k'$ value at 0% MeOH, $\log k_W$, was calculated by linear extrapolation from the plot of the $\log k'$ value against methanol concentration in the range from 30 to 70%. Plots for all compounds were linear in this region.

MO Calculations Semiempirical molecular orbital calculations were done using the AM1 method in the MOPAC 93 program package incorporated in the ANCHOR II (Fujitsu) modeling system.

Methods and Results

Analysis of π Values The $\log P$ values of BZ and TF are listed in Tables 1 and 2, respectively. The comparison of π values of BZ (π_{BZ}) and TF (π_{TF}) with those of monosubstituted benzenes, π_{PhX}, given in Table 3 shows that the π_{BZ} and π_{TF} values for electron-donating substituents such as *o*-OMe and *p*-OMe are greater than the π_{PhX} value, whereas π values for electron-withdrawing substituents such as CN and NO_2 are close to each other in all three systems, indicating that strong electronic interactions between the fixed and X-substituents alter the π value in Bz and TF. Fujita has reported a procedure to analyze the partition coefficient of *meta*- and *para*-disubstituted benzenes, X-C_6H_4-Y (X and Y are variable and fixed substituents, respectively), in terms of bi-directional Hammett-type relationships as shown by Eq. 1.[4)]

$$\pi_{X/PhY}=a\pi_{PhX}+\rho_Y\sigma^o_X+\sigma^o_Y\rho_X(m)+\sigma^o_Y\rho_X(p)+\text{const.} \qquad (1)$$

In Eq. 1, $\pi_{X/PhY}$ is the π value of a variable X-substituent in disubstituted benzenes. The parameters σ^o and ρ are the electronic substituent constant and the susceptibility constant, respectively. The parameters with the subscript X are independent variables. Those with the subscript Y, together with the "a" value, are obtained as the regression coefficients. The $\rho_Y\sigma^o_X$ term is attributable to the "forward" electronic effect of X on the hydrogen-bonding ability of Y with octanol, relative to that with water. The $\sigma^o_Y\rho_X$ term is the "backward" effect of Y on X according to the substitution positions, *meta* or *para*. To analyze the $\pi_{X/PhY}$ value of *ortho* substituents, additional correction terms for the steric effect (the *Es* parameter) and the inductive effect (the *F* parameter) are often needed.

We analyzed the π_{BZ} value by Eq. 1 using the parameters in Table 3. For the *m*- and *p*-substituted derivatives including unsubstituted BZ, an excellent correlation, shown by Eq. 2, was obtained.

$$\begin{gathered}\pi_{BZ}=0.989\pi_{PhX}+0.432\rho_X(p)-0.006 \qquad (2)\\ (0.058) \qquad (0.141) \qquad (0.036)\\ n=22,\quad r=0.993,\quad s=0.066,\quad F=657.5\end{gathered}$$

In Eq. 2 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 F ratio between the variances of the observed and calculated values. The figures in parentheses are the 95%

Table 1. Hydrophobicity Parameter of BZ

	Substituent	$\log P$	π_{BZ}	$\pi_{BZ(Calcd)}$[a)]	Dev.[b)]
1	H	2.18	(0.00)	0.00	0.00
2	*o*-Me	2.60	(0.42)	0.55	−0.13
3	*m*-Me	2.68	(0.50)	0.55	−0.05
4	*p*-Me	2.65	(0.47)	0.55	−0.08
5	*p*-Et	3.26	(1.08)	1.01	0.08
6	*o*-F	2.34	(0.16)	0.14	0.03
7	*m*-F	2.25	(0.07)	0.14	−0.07
8	*p*-F	2.22	(0.04)	0.14	−0.10
9	*o*-Cl	2.85	(0.67)	0.70	−0.03
10	*m*-Cl	2.81	(0.63)	0.70	−0.07
11	*p*-Cl	2.80	(0.62)	0.70	−0.08
12	*m*-Br	3.02	(0.84)	0.85	−0.01
13	*p*-Br	3.03	(0.85)	0.85	0.00
14	*o*-CF_3	3.14	(0.96)	0.87	0.09
15	*m*-CF_3	3.03	(0.85)	0.87	−0.02
16	*p*-CF_3	3.13	(0.95)	0.87	0.08
17	*o*-OMe	2.42	(0.24)	0.10	0.14
18	*m*-OMe	2.27	(0.09)	−0.02	0.11
19	*p*-OMe	2.25	(0.07)	0.10	−0.03
20	*p*-OEt	2.73	(0.55)	0.50	0.05
21	*p*-NMe_2	2.66	(0.48)	0.39	0.10
22	*p*-OAc	1.63	(−0.55)	−0.55	0.00
23	*m*-CN	1.59	(−0.59)	−0.57	−0.02
24	*p*-CN	1.64	(−0.54)	−0.57	0.03
25	*m*-NO_2	1.88	(−0.30)	−0.28	−0.02
26	*p*-NO_2	1.90	(−0.28)	−0.34	0.06
27	*o*-OH[c)]	2.19	(0.01)	−0.24[d)]	0.25[d)]
28	*p*-OH[c)]	1.86	(−0.32)	−0.24	−0.08

a) Calculated by using Eq. 3. *b*) Difference between π_{BZ} and $\pi_{BZ(Calcd)}$. *c*) Amphiprotic substituents. *d*) Not included in the correlation but calculated by using Eq. 3.

Table 2. Hydrophobicity Parameter of TF

	Substituent	$\log P$	π_{TF}	$\pi_{TF(Calcd)}$[a)]	Dev.[b)]
29	H	3.01	(0.00)	−0.05	0.05
30	*o*-Cl	3.50	(0.49)	0.58	−0.09
31	*m*-Cl	3.58	(0.57)	0.58	−0.01
32	*p*-Cl	3.63	(0.62)	0.58	0.04
33	*o*-OMe	3.39	(0.38)	0.35	0.03
34	*m*-OMe	3.05	(0.04)	−0.07	0.11
35	*p*-OMe	3.33	(0.32)	0.35	−0.03
36	*m*-CN	2.45	(−0.56)	−0.55	−0.01
37	*p*-CN	2.42	(−0.59)	−0.55	−0.04
38	*m*-NO_2	2.66	(−0.35)	−0.30	−0.05

a) Calculated by using Eq. 4. *b*) Difference between π_{TF} and $\pi_{TF(Calcd)}$.

Table 3. Substituent Parameters Used for Analyses

Substituent	π_{PhX}	σ^o_m	σ^0_p	ρ
H	0.00		0.00	0.00
Me	0.56	−0.07	−0.12	0.00
Et	1.02		−0.13	0.00
F	0.14	0.35	0.17	0.00
Cl	0.71	0.37	0.27	0.00
Br	0.86	0.38	0.26	0.00
CF_3	0.88	0.47	0.53	0.00
OMe	−0.02	0.06	−0.16	0.27
OEt	0.38		−0.14	0.27
NMe_2	0.18		−0.32	0.46
OAc	−0.64		0.31	0.18
CN	−0.57	0.62	0.69	0.00
NO_2	−0.28	0.70	0.82	0.00
OH	−0.67		−0.13	0.94

confidence intervals of the regression coefficients and the intercept. All the terms except the constant term were justified above the 99.9% level. Addition of the other correction terms involved in Eq. 1 did not give any significant improvement.

Incorporation of the *ortho* substituents in the data set yielded Eq. 3, being almost equivalent to Eq. 2.

$$\pi_{BZ}=0.988\pi_{PhX}+0.457\rho_X(p)-0.003 \qquad (3)$$
$$(0.061) \qquad (0.152) \qquad (0.038)$$
$$n=27, \quad r=0.990, \quad s=0.074, \quad F=584.3$$

In this equation, the *o*-OH derivative was excluded from the calculations because it gave a larger deviation than the others. Although various combinations of the above-mentioned parameters including *F* and *Es* were tested, none of them could predict the value of the *o*-OH satisfactorily. Therefore, this substituent could be regarded as an outlier.

Analogous analyses with all the TF derivatives in Table 2 gave the same type of correlation as Eq. 3 but with different coefficients as shown by Eq. 4.

$$\pi_{TF}=0.883\pi_{PhX}+1.542\rho_X(p)-0.049 \qquad (4)$$
$$(0.104) \qquad (0.451) \qquad (0.055)$$
$$n=10, \quad r=0.992, \quad s=0.065, \quad F=221.5$$

Although the number of data is not enough, all the *ortho* substituents were well incorporated in Eq. 4 as judged from the deviations from the calculated values given in Table 2.

Relationship between log *P* and log *k′* The log *k′* values obtained with M30, M50 and M70 as eluents are summarized in Table 4 together with the log k_W values (M0). Many articles have reported that the log k_W parameter gives the best correlation with log *P*,[5,6] whereas our conclusion to date is that M50 is the eluent of choice for reliable prediction of log *P*. The relationships between log *P* and log *k′* for BZ except for amphiprotic substituents, **27** and **28**, are formulated by Eqs. 5—7. Amphiprotics are known to deviate from the linearity for nonamphiprotics under the RPLC conditions used.[10,11,14] In accordance with our proposal, M50 again gave the best relationship.[9-11,14] As is clear in Fig. 1, the correlation for log k_W was much poorer.

$$\log k'_{M30}=0.660\log P+0.107 \qquad (5)$$
$$(0.053) \qquad (0.134)$$
$$n=26, \quad r=0.983, \quad s=0.063, \quad F=672.2$$

$$\log k'_{M50}=0.555\log P-0.491 \qquad (6)$$
$$(0.027) \qquad (0.069)$$
$$n=26, \quad r=0.993, \quad s=0.033, \quad F=1760.7$$

$$\log k'_{M70}=0.456\log P-1.078 \qquad (7)$$
$$(0.042) \qquad (0.108)$$
$$n=26, \quad r=0.976, \quad s=0.051, \quad F=349.8$$

We have found, in our earlier work on substituted benzenes and heteroaromatic compounds, that the log *k′* values for strong hydrogen accepting substituents such as COOR and $CONMe_2$ present positive deviations from the log *P*–log *k′* linearity formed by nonhydrogen bonding groups as the methanol concentration is decreased.[9,10] In the present case, a similar deviation was observed with the *p*-OAc substituent, which is also a strong hydrogen-bond acceptor (Table 4). Moreover, when a parent compound has a polar functional group, the electronic effect of the substituent introduced into the parent compound often becomes important in water-rich eluents.[10,14] Then, the addition of the σ parameter to the equation improves the correlation.[10,14] However, the σ parameter did not work for the above correlation equations. Attempts to find other parameters that would improve the correlation failed.

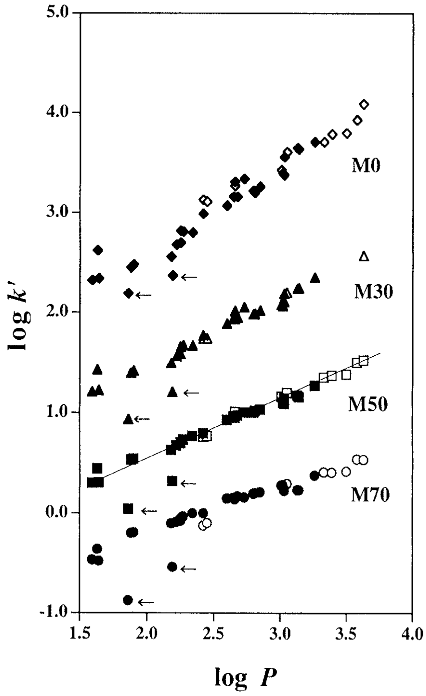

Fig. 1. Relationship between log *k′* and log *P* for BZ and TF

The points for each mobile phase are differentiated by different shapes of symbols. Closed symbols: BZ. Open symbols: TF. The points with an arrow represent amphiprotic substituents.

As shown in Fig. 1, the data for derivatives of BZ and TF lie along a single straight line. The data for BZ and TF could be combined to give a single correlation equation. The best correlation was obtained with M50, as shown by Eq. 8.

$$\log k'_{M50}=0.568\log P-0.568 \qquad (8)$$
$$(0.023) \qquad (0.062)$$
$$n=36, \quad r=0.993, \quad s=0.037, \quad F=2531.5$$

The deviations of the observed log *k′* values from those calculated by using Eqs. 6 and 8 (Table 4) were almost equivalent, indicating that incorporation of the TF data in the data set for log k'_{M50} did not modify the quality of the correlation.

Discussion

When we compare Eqs. 3 and 4, several points should be noted. The coefficient of $\rho_X(p)$, which represents the σ_p^o value of the fixed substituent, for TF was much more positive than that for BZ. This means that the $-CH=CHCOCF_3$ group is much more electron-withdrawing than $-CH=CHCOMe$, as would be expected, because an F atom has extremely high electronegativity. The resonance electronic interaction between the fixed and

Table 4. logk' Values of BZ and TF

	Substituent	logk' M30[a]	logk' M50[a]	logk' M70[a]	logk' M0[b]	Dev. M30[c]	Dev. M50[d]	Dev. M70[e]	Dev. M50[f]
BZ									
1	H	1.494	0.630	−0.101	2.56	−0.109	−0.030	0.016	−0.039
2	*o*-Me	1.889	0.932	0.147	3.07	0.009	0.032	0.064	0.025
3	*m*-Me	1.953	0.976	0.172	3.16	0.022	0.032	0.053	0.023
4	*p*-Me	1.945	0.963	0.155	3.16	0.034	0.039	0.054	0.027
5	*p*-Et	2.355	1.273	0.378	3.71	0.041	0.008	−0.008	−0.009
6	*o*-F	1.670	0.770	0.003	2.80	−0.042	0.012	0.038	0.010
7	*m*-F	1.586	0.706	−0.054	2.70	−0.067	−0.004	0.022	−0.003
8	*p*-F	1.566	0.677	−0.087	2.68	−0.068	−0.017	0.002	−0.015
9	*o*-Cl	2.023	1.033	0.211	3.26	−0.019	−0.003	0.014	−0.016
10	*m*-Cl	1.987	1.020	0.204	3.20	−0.036	−0.003	0.016	−0.007
11	*p*-Cl	1.984	1.003	0.197	3.22	−0.026	−0.007	0.023	−0.018
12	*m*-Br	2.070	1.105	0.285	3.40	−0.084	−0.024	0.012	−0.041
13	*p*-Br	2.108	1.093	0.247	3.38	−0.052	−0.042	−0.032	−0.059
14	*o*-CF_3	2.246	1.157	0.232	3.64	0.016	−0.037	−0.097	−0.057
15	*m*-CF_3	2.190	1.142	0.226	3.56	0.031	0.008	−0.052	−0.010
16	*p*-CF_3	2.241	1.173	0.234	3.65	0.017	−0.016	−0.090	−0.035
17	*o*-OMe	1.773	0.797	0.002	2.99	0.032	0.012	0.019	−0.008
18	*m*-OMe	1.673	0.732	−0.031	2.81	0.007	0.012	0.035	0.012
19	*p*-OMe	1.661	0.699	−0.073	2.82	0.009	−0.011	0.002	−0.010
20	*p*-OEt	2.055	1.003	0.160	3.34	0.092	0.032	0.018	0.022
21	*p*-NMe_2	2.018	0.954	0.141	3.31	0.101	0.022	0.031	0.012
22	*p*-OAc	1.430	0.446	−0.358	2.62	0.183	0.075	−0.001	0.089
23	*m*-CN	1.206	0.302	−0.463	2.32	−0.017	−0.052	−0.088	−0.032
24	*p*-CN	1.221	0.304	−0.472	2.34	−0.035	−0.075	−0.120	−0.058
25	*m*-NO_2	1.395	0.533	−0.195	2.45	−0.017	0.026	0.048	0.034
26	*p*-NO_2	1.419	0.545	−0.193	2.48	−0.021	0.011	0.022	0.035
27	*o*-OH[g]	1.205	0.319	−0.536	2.37	−0.414[h]	−0.364[h]	−0.435[h]	−0.356[h]
28	*p*-OH[g]	0.935	0.041	−0.873	2.19	−0.471[h]	−0.465[h]	−0.624[h]	−0.446[h]
TF									
29	H	2.083	1.161	0.282	3.43				0.021
30	*o*-Cl	—[i]	1.384	0.419	3.80				−0.034
31	*m*-Cl	—[i]	1.507	0.539	3.93				0.043
32	*p*-Cl	2.575	1.526	0.537	4.09				0.034
33	*o*-OMe	—[i]	1.374	0.408	3.79				0.018
34	*m*-OMe	2.200	1.200	0.294	3.61				0.037
35	*p*-OMe	—[i]	1.356	0.413	3.71				0.034
36	*m*-CN	1.744	0.771	−0.095	3.11				−0.051
37	*p*-CN	1.743	0.764	−0.121	3.13				−0.041
38	*m*-NO_2	1.938	1.008	0.151	3.27				0.066

a) Eluent: the figure represents the volume % of MeOH. *b*) logk_W values. See Experimental. *c*) Difference between logk'_{M30} and that calculated by using Eq. 5. *d*) Difference between logk'_{M50} and that calculated by using Eq. 6. *e*) Difference between logk'_{M70} and that calculated by using Eq. 7. *f*) Difference between logk'_{M50} and that calculated by using Eq. 8. *g*) Amphiprotic substituents. *h*) Not included in the correlation but calculated by using the equation given in the footnote. *i*) Retention time was too long to be measured.

X-substituents is expected to be enhanced in a derivative with an electron-donating substituent (interaction between donor–acceptor of π electron pairs), and to a greater extent in TF than in BZ. On the other hand, the interaction in a derivative with an electron-withdrawing substituent would be reduced. The π electron density calculated by the AM1 method confirmed this. The π electron density of the O atom in the *p*-$\underline{O}$Me group (electron-donating) was -0.338 in BZ and -0.207 in TF while that of the N atom in the *p*-C$\underline{N}$ group (electron-withdrawing) was -0.218 in BZ and -0.194 in TF. These results show that the electrons are more delocalized in *p*-OMe-TF than in *p*-OMe-BZ. The more delocalized the molecule is, the more the log$P$ increases. The fact that the π value for *p*-OMe-TF is more positive than that for *p*-OMe-BZ can be understood on this basis. On the other hand, the degree of delocalization is small in *p*-CN-TF, which results in a π value similar to that of benzonitrile.

It is noteworthy that the $\rho_Y\sigma^\circ_X$ term was insignificant, indicating that $\rho = 0$ for both fixed substituents. There is a tendency for the ρ values of highly electron-withdrawing substituents to be small, for example, the values of CN is zero.[4] The π values for BZ and TF seem to be mainly governed by the change in the hydrogen-bonding effect of the X-substituent which is brought about by the strongly electron-withdrawing fixed substituent.

The coefficient of π_{PhX} is usually near 1.[4] Although the "a" value in BZ conformed to this rule, that in TF was somewhat smaller. Analyses with a larger number of compounds will be needed to solve this problem.

The reason why *o*-OH-BZ must be excluded from the analysis may be attributed to its specific structure. This compound is reported to exist as a dimer owing to hydrogen-bonding.[15] A more detailed study of its structure would be desirable.

It is of interest that logk' values in both series, BZ and

TF, are linearly correlated with $\log P$, whereas the correlations of the π value with π_{PhX} are different. This may be related to the fact that the ρ values of the fixed substituents were zero. The finding that the best correlation was obtained at 50% MeOH is important. The points for BZ and TF are seen to be separated in the plots for $\log k_{\mathrm{W}}$, suggesting that differentiation between BZ and TF becomes more significant as the methanol concentration is decreased. By modeling the chromatographic system with the octane–water partitioning system, we have shown in the preceding paper[9] that the RPLC system with eluents containing about 50% MeOH has properties more similar to the octanol–water partitioning system than with eluents of other compositions. The present result affords an additional example supporting our proposal.[9]

Although the number of data used for analyses is small, the present results indicate that the $\log P$ values for BZ and TF can be successfully predicted by the bi-directional as well as the RPLC procedures. These results should be helpful for QSAR studies.

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