Hydrophobicity Parameters Determined by Reversed-Phase Liquid Chromatography. VII.[1] Hydrogen-Bond Effects in Prediction of the log *P* Values for Benzyl *N,N*-Dimethylcarbamates

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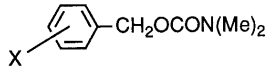
The log k' values (k': capacity factor) of *m*- and *p*-substituted benzyl *N,N*-dimethylcarbamates, I, were obtained by reversed-phase high-performance liquid chromatography (RPLC) on C18-bonded columns with methanol–buffer (pH 7.4) solutions as the mobile phase. The log k_W value, which is considered as a measure of the octanol–water log *P* value (*P*: partition coefficient), was calculated by linear extrapolation of the plot of log k' against methanol content in eluents. The log k_W values and the log k' values at 30, 50 and 70% MeOH concentrations were correlated with log *P* in terms of the hydrogen-bond ability of the substituent. As is usually observed the amphiprotic substituents, which act as both H-donor and H-acceptor, behaved differently from the others. A log k'–log *P* plot with very good linearity was obtained with an eluent containing 50% MeOH except for the above mentioned amphiprotic substituents. The log k_W values were much higher than the log *P* values. This was ascribed to the strong hydrogen accepting ability of the fixed substituent, $CH_2OCONMe_2$.

Keywords hydrophobicity; capacity factor; partition coefficient; hydrogen bond; RPLC; benzyl carbamate

Evaluation of the hydrophobicity of bioactive compounds is of great importance in quantitative structure–activity relationship (QSAR) studies.[2] The 1-octanol/water partition coefficient, log *P*, has been widely accepted as a hydrophobicity parameter. This parameter is conventionally measured by the shake–flask method. Recently, the latest development of reversed-phase high performance liquid chromatography (RPLC) techniques has enabled the capacity factor, log k', obtained by the use of alkyl-bonded stationary phases and methanol–water (or appropriately buffered solutions) mobile phases to be used to predict the log *P* value in many cases.[3-6] RPLC procedures are especially useful when the compounds of interest are very lipophilic or unstable. However, the establishment of a standard RPLC method has proven difficult, given the fact that log k' is highly dependent on the elution conditions. To remove the influence of the organic modifier in the eluents, a normalized parameter, log k_W, calculated by extrapolation from the linear portion of the plot of log k' against methanol content to 0% MeOH, is usually used.[3] It is reported that the log k_W approach reduces not only the hydrogen-bond effects but also the selective solute–solvent interactions, and gives hydrophobicity indices which are identical with log *P*.[3]

Our systematic studies on the relationship between log *P* and log k' (or log k_W) for various heteroaromatic compounds have shown that the above mentioned log k_W approach can predict well the log *P* value of compounds with non-hydrogen bonding and weakly hydrogen accepting functional groups; however, compounds with multi-functional groups present complicated features[7]: (1) although the log k_W treatment can reduce the hydrogen-bond effect of amphiprotics, it tends to overestimate the hydrophobicity of compounds with multi-hydrogen-accepting sites,[7] (2) the intra-molecular electronic interactions between substituents perturb the log *P*–log k' (or log k_W) linearity,[7a] leading to incorrect prediction of log *P* values. We have often observed that the capacity factors obtained in isocratic mobile phases correlate better with log *P* rather than the log k_W values.[1,7,8]

As a part of our efforts to establish a suitable RPLC system to predict log *P*, we measured log k' values of *m*- and *p*-substituted benzyl *N,N*-dimethylcarbamates (I) and compared them with log *P*. Compounds I were chosen because we found that they produce effects on the central nervous system (CNS) in mice and that their hydrophobicity (log *P*) was a determinant factor governing the potency of the anti-convulsant activity.[9] In addition, studies on carbamates are of interest in view of the fact that many bio-active compounds contain one or more carbamoyl moieties as active sites. Another reason to select I as a model is that the direct electronic interaction between the substituent X and the fixed carbamoyl moiety, which would result in complicated change of the solute–solvent interaction, can be eliminated in the benzyl system used. In this work, the correlation between log k' (or log k_W) and log *P* was studied in terms of the hydrogen bonding ability of the substituent.



I

Experimental

Compounds The general synthetic procedures were described in a previous paper.[9]

Partition Coefficients Some of the 1-octanol–water partition coefficients were taken from our previous paper.[9] The others were remeasured or newly measured in this work at 25 °C according to the previous method except that the concentrations were determined in both octanol and water phases by RPLC using methanol–water mobile phases of different compositions, thereby providing an appropriate retention time and a reasonable separation of peaks between a given sample and octanol. If necessary, the sample was diluted with methanol before injecting the analyte. This modified method was particularly effective to improve log *P* values of highly lipophilic compounds, without interference from the organic solvent.

Capacity Factor The apparatus and the procedure used were the same as previously described.[7b] Commercial Capcell Pak C_{18} (4.6 mm × 5, 15 cm, Shiseido) and Cosmosil 5C_{18}-AR (5 mm × 15 cm, Nacalai tesque) packed columns were used without further treatment. Commercial 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 eluent

was prepared by volume. The flow-rate was 1.0—1.5 ml/min. Retention times, t_R, were measured at 25 °C. The capacity factor, k', was determined by use of the equation $k'=(t_R-t_0)/t_0$, where t_0 is the retention time of methanol.

Results and Discussion

The $\log k'$ values of nineteen compounds (I) were measured on a Capcell Pak C_{18} with mobile phases containing 30, 50 and 70% methanol (M30, M50 and M70), and the results are plotted against the $\log P$ values in Fig. 1. The $\log k_W$ values were calculated by linear extrapolation from the range of 30 to 70% MeOH because many investigations including ours have shown that linear extrapolations give better correlations with $\log P$ than quadratic extrapolations.[6,7a,8] The results are listed in Table I with the $\log P$ values.

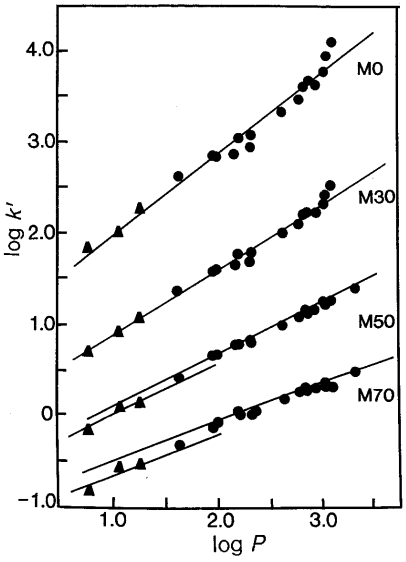


Fig. 1. Relationship between $\log P$ and $\log k'$ for I

Capcell Pak C_{18} column and MeOH–buffer (pH 7.4) mobile phases: M0, M30, M50 and M70 refer to the mobile phases containing 0, 30, 50 and 70% MeOH, respectively. The data at M30 were taken on a 5 cm column and those at M50 and M70 on a 15 cm column. The data at M0 are $\log k_W$ values (see Table I). Triangles: amphiprotic substituents (**12**, **13** and **19**).

Fairly good linear relationships are seen to hold at each mobile phase composition. The correlations obtained with Eq. 1 are presented in Table II.

$$\log k' = a \log P + c \quad (1)$$

Although the correlations are statistically satisfactory, closer examination demonstrates that the amphiprotic substituents (depicted by triangles in Fig. 1) tend to deviate downward from the regression lines at high methanol concentrations (50% and 70% MeOH). To describe the effect of amphiprotics (amphiprotic effect), a hydrogen-bond parameter for the substituent, HB_{AM}, was added to Eq. 1, as is usually tried in analyses where some hydrogen bond effects are expected.[4,7,10]

$$\log k' = a \log P + bHB_{AM} + c \quad (2)$$

In Eq. 2, HB_{AM} is 1 for the amphiprotic substituents, NH_2, NHAc and $CONH_2$, and 0 for the others. There are many cases in the literature where the use of discrete-type hydrogen bond parameters work well as a first approximation,[4,7,10] even if the authors did not always comment on it, and their physico-chemical significance was studied in detail.[10] The results are included in Table II. The HB_{AM} term was justified at M50 and M70 over the 97% level, though the correlations were improved only a little.

For comparison, the results of analyses using the data excluding the amphiprotic substituents are also included. It should be noted that the correlations for M50 and M70 are very stable, independent of the data set. The coefficients of $\log P$ and the intercepts are very similar to each other in Eqs. 6 and 11 and in Eqs. 8 and 12. On the other hand, the correlation between $\log k_W$ and $\log P$ depended most on the data set used and was somewhat poorer than those obtained from isocratic data. This may be due not only to extrapolation errors involved in the $\log k_W$ values but also to some factors (probably hydrogen-bond effect) acting in a different manner depending on the substituent X and the mobile phase composition.

Table I. Capacity Factors of I and Related Parameters

No.	Substituent	$\log P$ [a]	$\log k_W$ [b]	Δ [c]	$\log k'_{M50}$	HB_{AM}	$\log P_{M50}$ [d]	$\log P_{k_W}$ [e]	$\log k_W$ (PhX)	$\log P$ (PhX)
1	H	2.16	2.87	0.71	0.778	0	2.22	2.02	2.04	2.13
2	*p*-Me	2.78 [f]	3.46	0.68	1.098	0	2.76	2.66	2.65	2.69
3	*p*-F	2.30	2.94	0.64	0.834	0	2.31	2.09	2.22	2.27
4	*p*-Cl	2.93	3.62	0.69	1.172	0	2.89	2.83	2.77	2.84
5	*p*-Br	3.01	3.76	0.75	1.264	0	3.05	2.98	2.94	2.99
6	*p*-I	3.32	—	—	1.411	0	3.30	—	—	—
7	*p*-CF_3	3.08	4.10	1.02	1.281	0	3.07	3.34	3.29	3.01
8	*p*-OMe	2.20	3.04	0.84	0.781	0	2.22	2.21	2.12	2.11
9	*p*-SMe	2.86 [f]	3.67	0.81	1.141	0	2.84	2.88	2.83	2.74
10	*p*-CN	1.67	2.62	0.95	0.418	0	1.60	1.75	1.65	1.56
11	*p*-NO_2	1.95	2.84	0.89	0.657	0	2.01	1.99	1.91	1.85
12	*p*-NHAc	1.25	2.24	0.99	0.137	1	1.22	1.35	1.21	1.16
13	*p*-$CONH_2$	0.77 [f]	1.83	1.06	−0.165	1	0.71	0.90	0.90	0.64
14	*m*-Cl	2.82	3.60	0.78	1.163	0	2.87	2.81	2.77	2.84
15	*m*-OMe	2.31 [f]	3.07	0.76	0.803	0	2.26	2.23	2.12	2.11
16	*m*-$OCHMe_2$	3.03 [f]	3.94	0.91	1.248	0	3.02	3.18	—	—
17	*m*-NMe_2	2.61 [f]	3.32	0.71	0.991	0	2.58	2.50	2.40	2.31
18	*m*-NO_2	1.98 [f]	2.83	0.85	0.664	0	2.02	1.98	1.91	1.85
19	*m*-NH_2	1.06	1.99	0.93	0.093	1	1.15	1.08	0.99	0.90

a) Taken from ref. 9 unless otherwise noted. *b*) Calculated by linear extrapolation, see the text. Correlation coefficients are over 0.997 in all cases. *c*) Difference between $\log k_W$ and $\log P$. *d*) Calculated by using Eq. 6. *e*) Calculated by using Eq. 3. *f*) This work.

TABLE II. Correlations for I by Using Eqs. 1 and 2

Mobile phase[a]	Correlation equations	n	r	s	F	Eq. No.
	All compounds					
M0	$\log k_W = 0.904 \log P + 1.049$	18[b]	0.986	0.111	571.3	3
M30	$\log k' = 0.733 \log P + 0.135$	18[b]	0.995	0.057	1439.8	4
M50	$\log k' = 0.608 \log P - 0.581$	19	0.998	0.032	3542.4	5
	$\log k' = 0.581 \log P - 0.067 HB_{AM} - 0.508$	19	0.998	0.028	2238.7	6
M70	$\log k' = 0.496 \log P - 1.115$	19	0.992	0.049	994.5	7
	$\log k' = 0.452 \log P - 0.108 HB_{AM} - 0.996$	19	0.994	0.043	651.2	8
	Compounds other than amphiprotics					
M0	$\log k_W = 0.975 \log P + 0.861$	15[b]	0.971	0.114	214.9	9
M30	$\log k' = 0.756 \log P + 0.074$	15[b]	0.986	0.061	445.9	10
M50	$\log k' = 0.579 \log P - 0.502$	16	0.997	0.024	1991.1	11
M70	$\log k' = 0.447 \log P - 0.983$	16	0.987	0.036	539.0	12

a) The figure represents the % MeOH in the mobile phases. *b*) *p*-I was excluded because the retention time was too long to measure.

To investigate what kind of factors are involved in the $\log k'$ (or $\log k_W$) value besides the amphiprotic effect, we first examined whether the effect of hydrogen acceptors is significant by means of Eq. 13 with the data set without the amphiprotics,

$$\log k' = a \log P + bHB + c \tag{13}$$

where *HB* is an indicator variable which takes the value of 0 for the non-hydrogen bonders (alkyl, halogens and CF_3[10a]) and 1 for hydrogen acceptors (the others). While the *HB* term was insignificant at 50 and 70% MeOH, it became moderately significant, yielding b values of 0.05 and 0.10 at 30 and 0% MeOH, respectively, though justified only at the 87% level. In the $\log P$–$\log k'$ relationships so far examined, the coefficient of the *HB* term is usually positive in mobile phases rich in water and increases as the eluent approaches to 100% water. The present results seem to be in accord with this general trend.

Next, the substituent effect on the retention behavior was examined by using Eq. 14.

$$\log k'_X = a \log k'_H + c \tag{14}$$

In Eq. 14, $\log k'_X$ and $\log k'_H$ are $\log k'$ values for derivatives substituted by an X-substituent and the reference unsubstituted benzylcarbamate (I, X=H), respectively, ranging from 30 to 70% MeOH concentrations. The regression coefficient a expresses the relative sensitivity of retention for the substituent X to the change in the mobile phase property compared to H, and the intercept c represents the relative retention of X in the mobile phase at which k'_H is 1 (in this case, the mobile phase containing about 70% MeOH).

The results are summarized in Table III. The correlation coefficient is 1 in most cases, indicating that the mobile phase property (solvation ability) changes continuously in the region of 30 to 70% MeOH concentrations. If the retention is governed purely by the partitioning process, the a value is expected to correlate linearly with $\log P$. Minick and coworkers[6] found that the S parameter, the slope of the $\log k'_X$–%MeOH(ϕ) curve as shown by $\log k'_X = \log k_W + S\phi$, correlated well with $\log P$, but the S value itself was affected by the t_0 value. Although to correlate $\log P$ with the above a value is equivalent to correlating $\log P$ with S, the a value in Eq. 14 may be a better measure of substituent property because the error arising from the t_0 value is expected to be mostly eliminated by taking the ratio to the reference.

TABLE III. Correlations by Using Eq. 14

No.	Substituent	a	c	r[a]
1	H	1.000	0.000	1.000
2	*p*-Me	1.129	0.223	1.000
3	*p*-F	1.021	0.004	0.999
4	*p*-Cl	1.173	0.258	1.000
5	*p*-Br	1.197	0.328	1.000
6	*p*-I	—	—	—
7	*p*-CF_3	1.338	0.265	1.000
8	*p*-OMe	1.075	−0.038	1.000
9	*p*-SMe	1.207	0.213	1.000
10	*p*-CN	1.045	−0.377	1.000
11	*p*-NO_2	1.052	−0.173	1.000
12	*p*-NHAc	0.997	−0.612	1.000
13	*p*-$CONH_2$	0.948	−0.883	1.000
14	*m*-Cl	1.169	0.254	1.000
15	*m*-OMe	1.077	−0.017	1.000
16	*m*-$OCHMe_2$	1.280	0.276	1.000
17	*m*-NMe_2	1.108	0.142	1.000
18	*m*-NO_2	1.034	−0.128	1.000
19	*m*-NH_2	0.905	−0.600	1.000

a) Correlation coefficient.

The relationship between a and $\log P$ is shown in Fig. 2. The plots for nonhydrogen-bonders (group N) and hydrogen-bonders (group HB) yield different slopes, suggesting that a concomitant retention mechanism other than partition (mainly hydrogen-bond effects) is involved in the group HB compounds. The substituents such as SMe and $OCHMe_2$, are located near the plot for nonhydrogen bonders, suggesting that they are very weak H-acceptors and behave similarly to nonhydrogen-bonders. The a values for hydrogen-bonders exceed the expected values from the plot for nonhydrogen-bonders. The gap could be attributed to hydrogen-bond effects of the HB group substituents with the surrounding medium. The finding that the gap became larger with a decrease in $\log P$ can be understood in terms of the fact that hydrogen-bond effects become more important when compounds have a polar substituent, which tends to lower the $\log P$ value.

Many investigators have pointed out the possibility that silanophilic interactions retard the elution of H-acceptors.[3,11] We have shown in a previous study that silanol effects are almost negligible under our experimental conditions, by comparing the retention data with those measured with a masking agent and also by changing the buffer concentrations in the mobile phases.[7a] To confirm that the silanol effect is not responsible for the hydrogen-acceptor effect as observed above, we determined the $\log k'$ value on another C18-bonded column from a different supplier (Cosmosil C_{18}), and compared the retention data with those on Capcell Pak C_{18}. Excellent linearities were observed between the two columns at each mobile phase composition as shown by Eqs. 15—17, though the data at 30% MeOH could be obtained only for nine compounds because retention times for the others were too long to measure.

M30: $\log k'(\mathrm{CS}) = 1.000 \log k'(\mathrm{CP}) + 0.102$ (15)

$n=9$, $r=0.999$, $s=0.021$, $F(1, 7)=2973$

M50: $\log k'(\mathrm{CS}) = 1.059 \log k'(\mathrm{CP}) + 0.119$ (16)

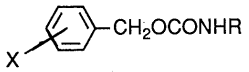
$n=19$, $r=0.999_7$, $s=0.013$, $F(1, 17)>9999.9$

M70: $\log k'(\mathrm{CS}) = 1.044 \log k'(\mathrm{CP}) + 0.142$ (17)

$n=19$, $r=0.999_7$, $s=0.010$, $F(1, 17)>9999.9$

In these equations, CS and CP refer to Cosmosil and Capcell Pak columns, respectively. The n value is the number of compounds used for calculations, r is the correlation coefficient, s is the standard deviation and F is the value of the F-ratio between regression and residual variances. Although the phase ratios for two columns are slightly different, the finding that the coefficients of the $\log k'$(CP) term are very close to 1 means that properties, of the stationary phases are very similar and hence, silanol effects, which should yield random deviations depending on the stationary phase, might not be responsible for the differentiation between non-hydrogen bonders and hydrogen bonders shown in Fig. 2.

As to the effect of amphiprotic substituents, the coefficient of the HB_{AM} term was negative, as is generally observed (amphiprotic effect).[4,7] We previously explained that this is because the acidic proton in amphiprotic substituents undergoes hydrogen-bonding more effectively with more basic octanol than with a less basic stationary phase.[7] Since amphiprotic substituents can behave as an H-donor as well as an H-acceptor, some H-acceptor effect should be involved in the apparent overall amphiprotic effects. Therefore, we tried to separate the H-donor effect by comparing the retention data with those of carbamates of type II where only non-hydrogen bonders were selected as X substituents.



II

20: X=H; R=H **21**: X=*p*-Me; R=H
22: X=*p*-Cl; R=H **23**: X=H; R=Me

The relationships between $\log k'$ and $\log P$ at different mobile phase compositions are shown in Fig. 3 together with those for the corresponding series-I compounds (**1**, **2** and **4**). It is seen that the $\log k'$ values of compounds I and II are related to $\log P$ by a set of parallel lines, with the upper line composed of I for all the mobile phase compositions studied. The distance between the two lines was uniformly 0.18, which is considered to reflect the acidity of the amide-hydrogen (OCONHR). In other words, the prediction by the $\log k_W$ approach gives smaller hydrophobicity indices for H-donors than for non-H-donors with the same $\log P$ value. This finding conforms to our previous result that the log k_W treatment underestimated the $\log P$ values of H-donors such as pyrrole and indole by about 0.2 whereas those of *N*-methyl analogs were correctly predicted.[1]

Apparently, the amphiprotic substituents of I showed no significant downward deviations from the regression line for the $\log P$–$\log k_W$ plot (MO). This may be the additive result of overestimating the effect of H-acceptor and underestimating the effect of H-donor.

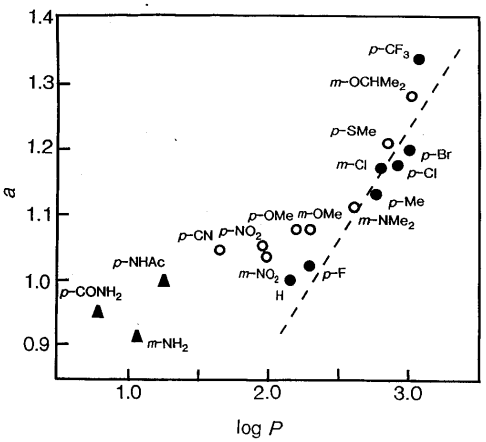


Fig. 2. Plot of a Value in Eq. 14 against $\log P$

Closed circles: non-hydrogen bonders, open circles: hydrogen acceptors, and triangles: amphiprotics. The dotted line represents the trend in the non-hydrogen bonders and not the regression line.

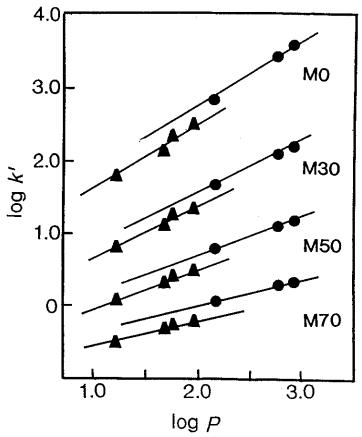


Fig. 3. Comparison of Relationships between Series-I and Series-II compounds

Circles: series-I compounds (**1**, **2** and **4**). Triangles: series-II compounds.

Let us now consider how we can most reliably predict the $\log P$ values from the results described above. In Eq. 3, the coefficient of $\log P$ is near unity but the intercept is much larger than zero, which is the value expected for an accurate prediction of $\log P$ by the $\log k_W$ method. Therefore, the $\log k_W$ value can't be used as a direct measure of $\log P$ in this case. For comparison, some of the $\log k_W$ values of monosubstituted benzenes, $\log k_W$(PhX), determined by a similar method are given in Table I. Interestingly, they are much closer to the $\log P$ values than in the case of I. The difference in feature between benzyl carbamates and monosubstituted benzenes suggests that the fixed substituent, $-CH_2OCONMe_2$, is a very strong H-acceptor, as shown by a substantial positive difference between $\log k_W$ and $\log P$ (0.7) for **1**. A similar difference was found for the substituent, $-OCONMe_2$.[12] Other cases of overestimation by the $\log k_W$ method that we have observed are heteroaromatic compounds with an ester group such as COOMe or COOEt; $\log k_W$ values were larger than $\log P$ by 0.3—0.4 for alkoxycarbonyl furans and by 0.7—0.8 for alkoxycarbonyl diazines. The fact that the overestimation was observed for compounds with ester and carbamoyl moieties can be understood by considering

that the magnitudes of the hydrogen-accepting parameter, pK_{HB}, for PhX (X=COOR, OCONζ) as defined by Taft and coworkers,[13] are large.

The results described above clearly demonstrate that care must be taken in using the $\log k_W$ method for the prediction of $\log P$, especially for compounds with strongly hydrogen-accepting groups. As far as compounds I without amphiprotic substituent are concerned, the use of the 50% MeOH solution as the mobile phase could predict the $\log P$ value most accurately, judging from the fact that it gave the best $\log k'$–$\log P$ linearity among the mobile-phase compositions tested. The same conclusion was drawn from the data on the heteroaromatic compounds mentioned above; the heteroaromatic compounds with a nonhydrogen-bonding substituent and the ester derivatives gave a good $\log k'$–$\log P$ linearity at 50% MeOH concentration whereas the $\log k_W$–$\log P$ relationship was not linear. In addition to our cases, some examples can be found in the literature showing that the use of 50% aqueous methanol is preferable for obtaining a better correlation with $\log P$.[14] All these results would mean that an eluent containing about 50% MeOH is much less discriminating between nonhydrogen-bonders and hydrogen-acceptors.

On the other hand, amphiprotics usually exhibit complicated behavior and should be treated separately. However, even for amphiprotics, better correlations should be obtained at 50% MeOH than 100% water when we take into account that the amphiprotic group has a hydrogen-accepting ability.

References and Notes

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