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New chromatographic hydrophobicity index (φ_0) based on the slope and the intercept of the log k' *versus* organic phase concentration plot

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ABSTRACT

A new chromatographic hydrophobicity index (φ_0) is suggested as a measure of the lipophilic character of compounds in reversed-phase high-performance liquid chromatography (RP-HPLC). The parameter φ_0 is defined as the organic phase concentration (methanol or acetonitrile) in the mobile phase which is required for log $k' = 0$ (retention time is double the dead time), that is, the molar fraction of the compound is identical in the mobile and the stationary phases. The φ_0 values therefore range from 0 to 100%, and the higher the value the more hydrophobic is the compound. It is shown that the value of φ_0 is characteristic for a compound and depends only on the type of organic modifier, pH and temperature. It is independent of the RP column type and length, flow-rate and the mobile phase compositions where the actual retention measurements are carried out. The other advantages of φ_0 are that it can be precisely measured, as it has a concrete physical meaning, namely the organic phase concentration of the mobile phase at which the retention time is exactly double the dead time (not like log k' values extrapolated to water as mobile phase), and it is independent of the linear or quadratic function of the log k' *versus* φ relationships. The φ_0 values not only reflect the hydrophobic character of compounds but also provide a valuable means for method development in RP-HPLC as they reveal a mobile phase composition with known retention time values. The φ_0 values for over 500 compounds were calculated and are presented on the basis of their published retention data. The φ_0 values obtained with methanol and acetonitrile showed an excellent correlation with each other. Significant correlations were found between the φ_0 values and the logarithm of 1-octanol–water partition coefficients (log P).

INTRODUCTION

It has been recognized since the work of Overton [1] and Meyer [2] that the hydrophobic properties of drugs play an important role in their pharmacological activity. The hydrophobicity of drugs is most commonly characterized by their 1-octanol–water partition coefficients (log P) was proposed by Hansch and co-workers [3,4]. Consideration of this parameter in structure–activity and structure–toxicity studies might substantially reduce drug development costs [5]. Although the choice of 1-octanol as a solvent reflecting the properties of the lipid components of the cell membrane has occasionally been questioned, the large number of 1-octanol–water partition data collected by Hansch and Leo [6] has made the partition system a common reference standard.

Owing to several difficulties in making log P measurements by the traditional shake-flask method, several chromatographic approaches have been published, which were summarized in detail by Braumann [7] and Kaliszan [8]. In reversed-phase high-performance liquid chromatography (RP-HPLC) the chromatographic retention is governed by hydrophobic forces, and therefore various RP-HPLC retention data have been suggested for cal-

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culating the log P values of compounds. There are three main approaches. The first is the use of RP-HPLC log k' values obtained on a given column with a given mobile phase composition. The second approach is to use log k' values extrapolated to 0% organic modifier concentration (log k'_w). The log k'_w values can be directly obtained only for a relatively small number of compounds, and therefore some means of predicting this value must be utilized. Butte *et al.* [9] and Hammers *et al.* [10] used linear extrapolation from the log k' *vs.* organic modifier concentration (φ) plot to predict log k'_w values. However several results [11,12] showed that the linearity of the plot is not valid for a wide organic modifier concentration, and the log k'_w values are not the same when they were derived from data obtained by using acetonitrile or methanol as the organic modifier. Schoenmakers *et al.* [13] described quadratic relationships between log k' and φ values. Wells and Clark [14] suggested the application of the solvophobic theory proposed by Horváth *et al.* [15] for the prediction of log k'_w. The third approach [16] suggests a backwards extrapolation method for the log k' values referring to an optimum organic phase concentration in the mobile phase by which the 1-octanol–water partition system can be best modelled. The calculation is based on the slope and the intercept values from the linear portion of the log k' *vs.* φ plots.

The aim of this study was to find a chromatographic hydrophobicity index that can be easily and precisely measured, relatively independent of the applied chromatographic conditions (type and dimensions of the column, flow-rate, etc.). A large database was set up from published data and there is a good correlation with 1-octanol–water partition coefficients.

THEORETICAL BACKGROUND

The capacity factor, k', in chromatography is defined [17] as n_s/n_m, *i.e.*, the ratio of the total number of moles of X in the stationary phase (n_s) to the number of moles of X in the mobile phase (n_m). It also can be expressed by the concentrations of X molecules in the mobile and stationary phases according to the equation [18]

$$k' = (X)_s V_s/(X)_m V_m \quad (1)$$

where V_s and V_m are the volumes of the stationary and mobile phases, respectively, and (X) is the concentration of X. When $k' = 1$ (log $k' = 0$), and also the retention time is double the dead time [from $k' = (t_r - t_0)/t_0$], this means that

$$(X)_s V_s = (X)_m V_m \quad (2)$$

The distribution constant, K, which measures the equilibrium distribution of X between the stationary and the mobile phases, can be expressed by $(X)_s/(X)_m$, so by rearranging eqn. 2 we obtain

$$KV_s = V_m \quad (3)$$

V_s, the volume of the stationary phase, can be regarded as constant in a given column, hence V_m will be proportional to the distribution constant of compound X. If we consider that V_m can be varied by changing the non-polar volume fraction of the mobile phase, then we can accept that it will be proportional to the distribution constant of X (see Fig. 1).

In order to prove that φ_0 values are independent of the column constant (V_s/V_m), the following consideration can be made. k' is proportional to the distribution constant K according to the equation

$$k' = K(V_s/V_m) \quad (4)$$

Eqn. 4 can be written in logarithmic form:

$$\log k' = \log K + \log (V_s/V_m) \quad (5)$$

The log k' values are also dependent on the organic phase concentration and for the sake of simplicity we can consider a linear relationship (a properly small portion of any suggested curve can be regarded as linear, after all), which can be described by the equation

$$\log k' = \log K + \log (V_s/V_m) = S\varphi + \log k'_w \quad (6)$$

where S and log k'_w are the slope and the intercept values of the straight line. The intercept value theoretically means the log k' value extrapolated to pure water as mobile phase and can be expressed by the distribution constant and the phase ratio, as shown by the equation

$$\log k'_w = K_w + \log (V_s/V_m) \quad (7)$$

The slope S can also be written as the log k' change caused by changing the organic phase concentration in the mobile phase by 1%, which can be formulated by the equation

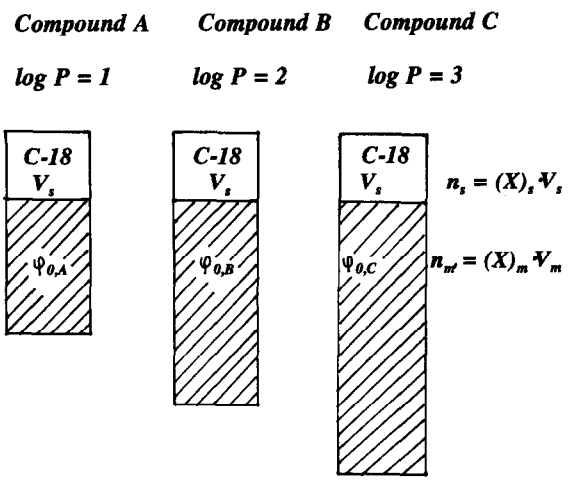

Fig. 1. Illustration of the chromatographic partitioning of compounds A, B and C with increasing hydrophobicity (log P values). For achieving a 1:1 molar distribution, the partitioning phase volumes have to be adjusted accordingly. V_s and V_m are the stationary and mobile phase volumes, n_s and n_m are the molar fractions of the compounds in the stationary and mobile phases, respectively, $(X)_s$ and $(X)_m$ are the concentrations of X molecules in the stationary and mobile phases, respectively, $K = (X)_s/(X)_m$ is the chromatographic partition coefficient and φ_0 is the chromatographic hydrophobicity index, *i.e.*, the adjusted organic phase volume to achieve a molar fraction distribution of 1:1 ($n_s = n_m$).

$$S = \log K_{x+1} - \log K_x \quad (8)$$

where x and $x+1$ refer to x% and $(x+1)$% volume fractions of organic modifier, respectively. The volume fraction of the organic phase in the mobile phase at which $\log k' = 0$ (φ_0) can be described on the basis of eqns. 6–9 by

$$\log k' = 0 = \log K_x + \log (V_s/V_m) = \varphi_0(\log K_{x+1} - \log K_x) + \log K_w + \log (V_s/V_m) \quad (9)$$

$$\varphi_0 = \frac{\log K_x - \log K_w}{\log K_{x+1} - \log K_x} \quad (10)$$

On the basis of eqn. 6, the hydrophobicity index φ_0 can also be expressed by the S and $\log k'_w$ values:

$$\varphi_0 = - \log k'_w/S \quad (11)$$

With the help of eqn. 11, the φ_0 values can be calculated from the experimental data. When the measured $\log k'$ values are close to zero, the application of the linear fit to the $\log k'$ *vs.* φ plot for the calculation of φ_0 does not result in large errors. In those cases when basic compounds are investigated, *e.g.*, as published by El Tayar *et al.* [19], two φ_0 values can be obtained. The correct φ_0 value is that obtained at lower organic phase concentrations, when only hydrophobic interactions govern the retention. The φ_0 value belonging to the higher organic phase concentration is caused by a dual retention mechanism (hydrophobic and silanophilic), so it cannot be regarded as the chromatographic hydrophobicity index.

A graphical illustration of the calculation of φ_0 values for various compounds is shown in Fig. 2. The hypothetical example shows situations when the $\log k'$ *vs.* φ plots are straight lines (compound 1), quadratic (compound 2), cross each other (compounds 2 and 3) and a dual retention mechanism (compound 4). When the mobile phase compositions are such that the measured $\log k'$ values are close to zero, the error of the linear extrapolation for the calculation of φ_0 values is negligible.

As the φ_0 values are dependent only on the distribution constants of the compounds in a given aque-

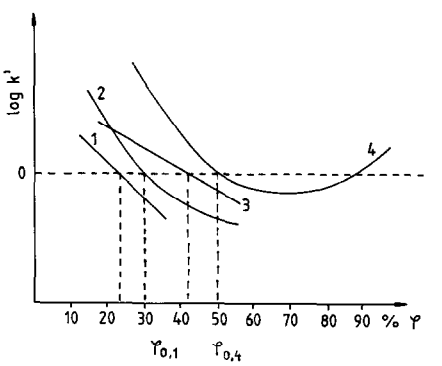

Fig. 2. Graphical illustration of the determination of the chromatographic hydrophobicity index (φ_0). Numbers refer to hypothetical compounds for which the $\log k'$ *vs.* φ plots are straight lines (1), cross each other (2 and 3) or show a dual retention mechanism (4).

ous–organic mixture, the value will depend only on the type of organic phase and the temperature. For ionizable compounds the pH also influences the distribution constant, so φ_0 will also depend on the pH. Consequently, the proper way of expressing φ_0 values is $\varphi_{0,op,T,pH}$, where op represents the type of organic phase and T represents temperature.

METHODS

Retention data ($\log k'$) values obtained in various mobile phase compositions were collected from the literature. The retention data for 22 nicotinate esters were published by Reymond *et al.* [20]. The measurements were carried out on LiChrosorb RP-18 (10 μm) column. The mobile phases were aqueous methanol or acetonitrile in various proportions buffered with 3-morpholinopropanesulphonate (0.02 *M*, pH 7.4). The retention data for 35 monohydroxyl aromatics were reported by Cooper and Hurtubise [21]. The measurements were carried out on a μBondapak C_{18} column with various mixtures of water and methanol. Braumann *et al.* [22] published data for 30 pesticides. The retention data were obtained by varying the methanol concentration in the mobile phase. Schoenmakers *et al.* [23] published retention data for 45 phenoxycarbonic acid derivatives, which were measured using water–acetonitrile mobile phases and a LiChrosorb RP-18 (10 μm) column. The acidic derivatives were measured with mobile phases that contained 0.5 *M* acetate buffer (pH 2.9) in order to decrease dissociation. The retention data for 113 aromatic hydrocarbons were measured by Opperhuizen *et al.* [24] on a Hypersil ODS (5 μm) column with methanol–water mixtures as mobile phases. The data for 143 acidic, basic and neutral drugs were published by Roos and Lau-Cam [25]. Three types of columns were used [μBondapack C_{18} (10 μm), Zorbax ODS (5 μm) and Ultrasphere ODS (5 μm)]. The mobile phases were variable proportions of methanol, 1.5 parts of acetic acid, 0.5 part of triethylamine and water to yield 100 parts by volume. The pH of the mobile phase was not given. Retention data for 26 drug molecules were published by Valkó [16,26] using both acetonitrile–buffer and methanol–buffer mobile phases. The pH of the mobile phase was adjusted according to the molecules investigated: pH 2 was used for the measurements of acidic compounds to reduce dissociation and pH 8 for the measurements of basic compounds. Retention data referring to acetonitrile–buffer + butanesulphonic acid mobile phases for eleven morphine derivatives were reported by Valkó *et al.* [27]. The same ion-pair chromatographic system was used for the measurements of eleven tricyclic drugs by Kálmán *et al.* [28]. The data for nineteen benzodiazepine derivatives were obtained by Valkó *et al.* [29] by varying the acetonitrile concentration in the mobile phase. Valkó and Slégel [30] published the φ_0 values referring to methanol for ten deoxyuridine derivatives. Data for eight aniline and eight phenol derivatives were measured by Gullner *et al.* [31] by changing the methanol concentration in the mobile phase. The φ_0 values of 42 adenosine monophosphates, 12 barbiturates and 10 penicillins and cephalosporins were also calculated on the basis of the published retention data of Braumann and Jastorff [32], Yamana *et al.* [33] and Toon *et al.* [34].

The linearity of the $\log k'$ *vs.* φ plots was checked over a suitable concentration range. The slope (S) and the intercept ($\log k'_w$) values were used for the calculation of φ_0 values when the correlation coefficient of the fit was higher than 0.998. The published slope and intercept values were used for the calculation of the chromatographic hydrophobicity index when the authors indicated acceptable high correlation coefficients for the linear fit. The $\log P$ values of over 500 compounds were calculated using the Pro-LogP Version 4.1 software package (CompuDrug Chemistry, Budapest, Hungary). The correlation analysis was carried out using the Drugidea program system developed for drug design (Chemicro, Budapest, Hungary).

RESULTS AND DISCUSSION

Table I gives the calculated chromatographic hydrophobicity indices ($\varphi_{0,ACN}$, $\varphi_{0,MeOH}$) and the calculated $\log P$ values for 22 nicotinate esters. The calculated $\log P$ and φ_0 values referring to methanol for 35 monohydroxyl aromatics are presented in Table II. The $\log P$ and φ_0 values for 30 pesticides and 45 phenoxycarbonic acid derivatives are summarized in Tables III and IV. The calculated $\log P$ and $\varphi_{0,MeOH}$ values for the 113 aromatic hydrocarbons are given in Table V. The φ_0 and $\log P$ data for 143 acidic, basic and neutral drugs are presented

TABLE I

CALCULATED LOG P, $\varphi_{0,ACN}$ AND $\varphi_{0,MeOH}$ VALUES FOR 22 NICOTINATES BASED ON THE RETENTION DATA PUBLISHED BY REYMOND *ET AL.* [20]

No.	Compound	Log P	$\varphi_{0,ACN}$	$\varphi_{0,MeOH}$
1	Methyl	0.830	31.75	44.93
2	Ethyl	1.339	42.91	54.93
3	*n*-Propyl	1.868	50.04	64.92
4	Isopropyl	1.868	49.21	62.86
5	*n*-Butyl	2.387	59.69	71.67
6	Isobutyl	2.387	58.91	67.50
7	*tert.*-Butyl	2.387	58.30	67.24
8	*n*-Hexyl	3.425	77.24	81.73
9	*n*-Octyl	4.463	84.93	87.64
10	Cyclohexyl	3.061	74.23	78.51
11	TTMCH[a]	4.618	81.66	84.40
12	2-Methoxyethyl	0.833	21.56	43.10
13	2-Butoxyethyl	2.390	54.27	67.91
14	THF[b]	1.507	39.62	52.53
15	2-Chloroethyl	1.784	43.24	57.27
16	3-Hydroxypropyl	0.216	−5.29	33.64
17	Carbamoylmethyl	−0.487	4.35	12.88
18	MCM[c]	0.032	11.47	23.15
19	Benzyl	2.488	54.37	70.90
20	*p*-Chlorophenyl	2.991	62.18	76.30
21	*p*-Nitrophenyl	2.014	58.31	67.92
22	2-Phenoxyethyl	2.568	53.23	68.93

[a] *trans*-,3,3,5-Trimethylcyclohexyl.
[b] Tetrahydrofurfuryl.
[c] Methylcarbamoylmethyl.

TABLE II

CALCULATED LOG P AND $\varphi_{0,MeOH}$ VALUES FOR 35 HYDROXYL AROMATICS BASED ON THE RETENTION DATA PUBLISHED BY COOPER AND HURTUBISE [21]

No.	Compound	Log P	$\varphi_{0,MeOH}$
23	1-Acenaphthenol	2.296	65.82
24	5*H*-Dibenzo[*a*,*d*]cyclohepten-5-ol	3.200	71.65
25	7,12-Dimethyl-9-hydroxybenz[*a*]anthracene	6.643	83.65
26	2-Hydroxybenzo[*c*]phenanthrene	5.557	80.16
27	3-Hydroxybenzo[*c*]phenanthrene	5.557	82.04
28	1-(1-Hydroxymethyl)pyrene	5.739	81.29
29	1-(Hydroxymethyl)benzo[*a*]pyrene	5.816	85.77
30	4-Hydroxymethylpyrene	5.739	76.52
31	9-Hydroxyphenanthrene	4.332	76.55
32	13-Hydroxypycene	7.456	90.23
33	1-Hydroxypyrene	5.220	81.32
34	4-Hydroxypyrene	5.220	81.12
35	1-Indanol	1.542	53.89
36	5-Indanol	2.690	64.68
37	1-Naphthol	2.770	64.77
38	2-Naphthol	2.770	62.67
39	3-Phenylphenol	3.444	70.83
40	1,2,3,4-Tetrahydro-4-hydroxy-4-methylphenanthrene	3.853	78.16
41	1,2,3,4-Tetrahydro-1-naphthol	2.061	62.77
42	5,6,7,8-Tetrahydro-1-naphthol	3.209	71.28
43	5,6,7,8-Tetrahydro-2-phenanthrol	3.334	82.35
44	*o*,*o*′-Biphenol	2.919	61.13
45	*p*,*p*′-Biphenol	2.919	55.40
46	1,2-Dihydroxybenzene	0.972	28.65
47	1,3-Dihydroxybenzene	0.972	20.69
48	1,4-Dihydroxybenzene	0.972	23.72
49	1,3-Dihydroxynaphthalene	2.245	54.79
50	1,6-Dihydroxynaphthalene	2.245	48.39
51	1,7-Dihydroxynaphthalene	2.245	54.03
52	2,3-Dihydroxynaphthalene	2.245	56.33
53	2,6-Dihydroxynaphthalene	2.245	45.09
54	2,7-Dihydroxynaphthalene	2.245	49.69
55	2,5-Dihydroxynaphthalene	2.245	64.69
56	2,6-Dihydroxytoluene	1.491	24.74
57	3,5-Dihydroxytoluene	1.491	35.25

in Table VI. The $\varphi_{0,ACN}$ and $\varphi_{0,MeOH}$ data and log P values for 16 drug molecules are presented in Table VII. Tables VIII and IX contain the calculated data for morphine and tricyclic derivatives obtained from their ion-pair chromatographic retention data. The calculated hydrophobicity index data for benzodiazepine, deoxyuridine and aniline derivatives are shown in Table X, XI and XII, respectively. Tables XIII, XIV and XV give the chromatographic hydrophobicity index values for adenosine monophosphate, barbiturate and β-lactam antibiotic derivatives, respectively.

The exact mechanism governing solute retention in RP-HPLC is of considerable research interest. At present, the most widely accepted mechanism and most extensive treatment of solute retention in RP-HPLC is the solvophobic model developed by Horváth *et al.* [15]. It was assumed that the stationary phase consists of a uniform layer of covalently bound alkyl ligates and the solvophobic theory was employed to treat quantitatively the role of the eluent in determining retention behaviour on such non-polar stationary phases. As Horváth *et al.* [35] revealed, under many practical conditions in reversed-phase chromatography, particularly when binary aqueous eluents with organic solvents are employed, the retention behaviour and selectivity are governed mainly by solvent effects. Therefore, we believe that the derived φ_0 values are independent of the reversed-phase stationary phase applied

TABLE III

CALCULATED LOG P AND $\varphi_{0,MeOH}$ VALUES FOR 30 HERBICIDES BASED ON THE RETENTION DATA PUBLISHED BY BRAUMANN *ET AL.* [22]

No.	Compound	Log P	$\varphi_{0,MeOH}$
58	Fenuron	1.18	50.47
59	Metoxuron	1.98	56.62
60	Monuron	1.91	62.96
61	Monolinuron	1.99	67.21
62	Chlortoluron	2.55	69.24
63	Metobromuron	2.37	69.49
64	Diuron	2.68	72.37
65	Linuron	2.76	75.28
66	Chloroxuron	3.65	77.70
67	Neburon	4.31	80.29
68	Simazine	1.51	66.48
69	Atrazine	2.05	71.81
70	Propazine	2.59	76.05
71	Prometryn	1.91	85.30
72	Desmetryn	2.46	86.16
73	Terbutryn	2.56	87.55
74	2,4-D	2.22	54.24
75	MCPA	2.30	57.25
76	2,4,5-T	2.99	62.00
77	Dichlorprop	2.75	62.23
78	Mecoprop	2.83	64.40
79	Fenoprop	3.52	68.21
80	MCPB	3.53	73.67
81	2,4-D-M	2.64	77.44
82	MCPA-M	2.72	78.51
83	Dichlorprop-M	3.17	81.30
84	Mecoprop-M	3.25	81.76
85	2,4,5-T-M	3.41	82.82
86	MCPB-M	3.95	85.90
87	Fenoprop-M	3.94	85.99

if no dual retention mechanism [36] takes place, and the physico-chemical basis for retention on the investigated stationary phases can be regarded as "homoenergetic", as was discussed by Melander *et al.* [37].

The correlation between $\varphi_{0,MeOH}$ and $\varphi_{0,ACN}$ values for the compounds in Tables I, IV and VII was also investigated. These two values refer to isoelutropic eluent mixtures as they both mean the mobile phase composition at which the same retention ($\log k' = 0$) can be obtained. A significant correlation between the two types of chromatographic hydrophobicity index was found for 72 compounds as described by the equation

$$\varphi_{0,MeOH} = 0.82\varphi_{0,ACN} + 20.46 \quad (12)$$

$$n = 72,\ r = 0.96,\ s = 5.0$$

TABLE IV

CALCULATED LOG P, $\varphi_{0,ACN}$ AND $\varphi_{0,MeOH}$ VALUES FOR 45 SUBSTITUTED AROMATIC COMPOUNDS BASED ON THE RETENTION DATA PUBLISHED BY SCHOENMAKERS *ET AL.* [23]

No.	Compound	Log P	$\varphi_{0,ACN}$	$\varphi_{0,MeOH}$
88	Acetophenone	1.66	62.28	70.33
89	Aniline	1.10	–	58.74
90	Anisole	2.11	70.99	80.83
91	Benzaldehyde	1.48	61.26	67.92
92	Benzene	2.13	72.37	84.38
93	Benzonitrile	1.56	63.11	67.30
94	Benzophenone	3.18	78.26	84.68
95	Benzyl alcohol	1.10	43.01	58.33
96	Biphenyl	4.02	88.62	91.96
97	*n*-Butylbenzene	4.26	90.72	95.15
98	Chlorobenzene	2.81	77.41	85.62
99	*p*-Chlorophenol	2.39	59.86	71.67
100	*p*-Chlorotoluene	3.33	83.06	89.63
101	*o*-Cresol	1.96	58.17	68.30
102	*o*-Dichlorobenzene	3.38	83.28	90.06
103	Diethyl phthalate	3.15	71.43	78.38
104	2,4-Dimethylphenol	2.30	64.60	74.76
105	Dimethyl phthalate	2.11	62.45	68.63
106	*m*-Dinitrobenzene	1.49	64.81	72.90
107	*o*-Dinitrobenzene	1.58	64.17	69.66
108	*p*-Dinitrobenzene	1.46	64.95	69.08
109	2,4-Dinitrotoluene	1.98	68.85	79.00
110	Diphenyl ether	4.20	82.67	90.09
111	Ethylbenzene	3.15	78.34	90.34
112	*m*-Fluoronitrobenzene	1.99	68.93	78.02
113	*p*-Fluoronitrobenzene	1.99	67.27	73.63
114	*p*-Fluorophenol	1.77	51.20	60.00
115	*p*-Hydroxybenzaldehyde	1.35	37.33	53.28
116	*p*-Methoxybenzaldehyde	1.68	60.43	70.61
117	*p*-Methylbenzaldehyde	2.04	68.11	73.63
118	Methyl benzoate	2.12	69.73	79.44
119	Naphthalene	3.37	81.73	89.94
120	*p*-Nitroacetophenone	1.53	63.40	70.40
121	*p*-Nitrobenzaldehyde	1.20	60.87	63.94
122	Nitrobenzene	1.85	67.67	75.19
123	*m*-Nitrophenol	2.00	54.48	66.18
124	*o*-Nitrophenol	1.79	64.40	74.80
125	*p*-Nitrophenol	1.91	53.02	63.44
126	Phenol	1.46	48.40	57.02
127	2-Phenylethanol	1.36	50.00	64.06
128	*p*-Phenylphenol	3.20	68.18	80.65
129	3-Phenylpropanol	1.88	58.02	71.57
130	*n*-Propylbenzene	3.68	86.02	92.05
131	Toluene	2.69	77.55	86.35
132	2,3,5-Trichlorotoluene	2.92	85.63	91.65

where n is the number of compounds, r is the correlation coefficient and s is the standard error of the estimate. Eqn. 12 suggests a method for the calcula-

TABLE V

CALCULATED LOG P AND $\varphi_{0,MeOH}$ VALUES FOR 113 AROMATIC HYDROCARBONS BASED ON THE RETENTION DATA PUBLISHED BY OPPERHUIZEN *ET AL.* [24]

No.	Compound	Log P	$\varphi_{0,MeOH}$	No.	Compound	Log P	$\varphi_{0,MeOH}$
133	Benzene	2.022	56.10	190	2,2′,5-Trichlorobiphenyl	6.189	86.37
134	Toluene	2.541	67.67	191	2,3,4-Trichlorobiphenyl	6.189	90.63
135	Ethylbenzene	3.060	75.83	192	2,3′,4′-Trichlorobiphenyl	6.189	90.14
136	Propylbenzene	3.579	81.44	193	2,3′,5-Trichlorobiphenyl	6.189	90.59
137	Butylbenzene	4.098	85.88	194	2,3,6-Trichlorobiphenyl	6.189	113.06
138	Pentylbenzene	4.617	89.05	195	2,4,5-Trichlorobiphenyl	6.189	92.82
139	Hexylbenzene	5.136	91.53	196	2,4′-5-Trichlorobiphenyl	6.189	90.27
140	Heptylbenzene	5.655	103.01	197	2,4,6-Trichlorobiphenyl	6.189	90.93
141	Octylbenzene	6.174	95.31	198	2,2′,3,3′-Tetrachlorobiphenyl	6.929	87.46
142	Nonylbenzene	6.693	96.80	199	2,2′,3,5′-Tetrachlorobiphenyl	6.929	89.02
143	Decylbenzene	7.212	98.08	200	2,2′,4,4′-Tetrachlorobiphenyl	6.929	91.62
144	Chlorobenzene	2.762	66.20	201	2,2′,4,5′-Tetrachlorobiphenyl	6.929	90.99
145	1,2-Dichlorobenzene	3.502	73.82	202	2,2′,4,6-Tetrachlorobiphenyl	6.929	90.06
146	1,3-Dichlorobenzene	3.502	77.50	203	2,2′,5,5′-Tetrachlorobiphenyl	6.929	90.28
147	1,4-Dichlorobenzene	3.502	75.02	204	2,2′,5,6′-Tetrachlorobiphenyl	6.929	87.03
148	1,2,3-Trichlorobenzene	4.242	81.50	205	2,2′,6,6′-Tetrachlorobiphenyl	6.929	82.31
149	1,2,4-Trichlorobenzene	4.242	82.98	206	2,3′,4,4′-Tetrachlorobiphenyl	6.929	93.48
150	1,3,5-Trichlorobenzene	4.242	86.96	207	2,3,4,5-Tetrachlorobiphenyl	6.929	95.71
151	1,2,3,4-Tetrachlorobenzene	4.982	87.68	208	2,3′,4′5-Tetrachlorobiphenyl	6.929	93.17
152	1,2,3,5-Tetrachlorobenzene	4.982	90.00	209	2,3′,4,6-Tetrachlorobiphenyl	6.929	92.82
153	1,2,4,5-Tetrachlorobenzene	4.982	89.09	210	2,3′,5,5′-Tetrachlorobiphenyl	6.929	94.90
154	Pentachlorobenzene	5.722	93.81	211	2,3,5,6-Tetrachlorobiphenyl	6.929	93.07
155	Hexachlorobenzene	6.462	98.10	212	2,4,4′,6-Tetrachlorobiphenyl	6.929	92.89
156	2-Chlorotoluene	3.281	76.08	213	3,3′,4,4′-Tetrachlorobiphenyl	6.929	93.67
157	3-Chlorotoluene	3.281	75.90	214	2,2′,3,4,5′-Pentachlorobiphenyl	7.669	93.84
158	4-Chlorotoluene	3.281	75.22	215	2,2′,3′,4,5-Pentachlorobiphenyl	7.669	97.85
159	2,4-Dichlorotoluene	4.021	83.93	216	2,2′,3,5,6-Pentachlorobiphenyl	7.669	92.09
160	2,5-Dichlorotoluene	4.021	82.54	217	2,2′,4,5,5′-Pentachlorobiphenyl	7.669	94.21
161	2,6-Dichlorotoluene	4.021	84.17	218	2,2′,4,5,6-Pentachlorobiphenyl	7.669	91.47
162	3,4-Dichlorotoluene	4.021	80.78	219	2,3,4,5,6-Pentachlorobiphenyl	7.669	97.07
163	3,5-Dichlorotoluene	4.021	84.18	220	2,2′,3,3′,4,4′-Hexachlorobiphenyl	8.409	94.60
164	2,4,5-Trichlorotoluene	4.761	88.43	221	2,2′,3,3′,5,5′-Hexachlorobiphenyl	8.409	96.35
165	1-Chloronaphthalene	4.035	73.64	222	2,2′,3,3′,6,6′-Hexachlorobiphenyl	8.409	89.55
166	2-Chloronaphthalene	4.035	82.15	223	2,2′,3,4,4′,5′-Hexachlorobiphenyl	8.409	95.18
167	1,2-Dichloronaphthalene	4.775	81.12	224	2,2′,3,4,5,5′-Hexachlorobiphenyl	8.409	96.53
168	1,3-Dichloronaphthalene	4.775	87.21	225	2,2′,3,5,5′,6-Hexachlorobiphenyl	8.409	94.00
169	1,4-Dichloronaphthalene	4.775	89.04	226	2,2′,4,4′,5,5′-Hexachlorobiphenyl	8.409	96.82
170	1,5-Dichloronaphthalene	4.775	89.06	227	2,2′,4,5,5′,6′-Hexachlorobiphenyl	8.409	95.98
171	1,8-Dichloronaphthalene	4.775	84.59	228	2,2′,4,4′,6,6′-Hexachlorobiphenyl	8.409	95.49
172	2,3-Dichloronaphthalene	4.775	86.11	229	2,3,3′,4,4′,5-Hexachlorobiphenyl	8.409	98.84
173	2,7-Dichloronaphthalene	4.775	85.93	230	2,3,3′,4,5,6-Hexachlorobiphenyl	8.409	96.72
174	1,3,7-Trichloronaphthalene	5.515	93.43	231	3,3′,4,4′,5,5′-Hexachlorobiphenyl	8.409	94.26
175	2,3,6-Trichloronaphthalene	5.515	89.53	232	2,2′,3,3′,4,4′,6-Heptachlorobiphenyl	9.149	96.63
176	1,2,3,4-Tetrachloronaphthalene	6.255	98.64	233	2,2′,3,4,4′,5,6-Heptachlorobiphenyl	9.149	98.00
177	1,2,3,5-Tetrachloronaphthalene	6.255	98.32	234	2,2′,3,4,4′,5′,6-Heptachlorobiphenyl	9.149	97.44
178	1,3,5,7-Tetrachloronaphthalene	6.255	99.87	235	2,2′,3,4,5,5′,6,6′-Octachlorobiphenyl	9.889	97.26
179	1,3,5,8-Tetrachloronaphthalene	6.255	97.88	236	2,2′,3,3′,4,4′,5,5′-Octachlorobiphenyl	9.889	100.19
180	Octachloronaphthalene	9.215	112.06	237	2,2′,3,3′,4,4′,5,6-Octachlorobiphenyl	9.889	98.97
181	Biphenyl	3.969	74.68	238	2,2′,3,3′,4,4′,6,6′-Octachlorobipenyl	9.889	99.00
182	2-Chlorobiphenyl	4.709	81.86	239	2,2′,3,3′,4,5,5′,6-Octachlorobiphenyl	9.889	99.15
183	3-Chlorobiphenyl	4.709	85.29	240	2,2′,3,3′,5,5′,6,6′-Octachlorobiphenyl	9.889	97.49
184	4-Chlorobiphenyl	4.709	84.68	241	2,2′,3,4,4′,5,6,6′-Octachlorobiphenyl	9.889	99.84
185	2,2′-Dichlorobiphenyl	5.449	80.95	242	2,2′,3,3′,4,4′,5,5′,6-Nonachlorobiphenyl	10.629	101.38
186	2,4-Dichlorobiphenyl	5.449	88.30	243	2,2′,3,3′,4,4′,5,6,6′-Nonachlorobiphenyl	10.629	100.97
187	2,4′-Dichlorobiphenyl	5.449	89.55	244	2,2′,3,3′,4,5,5′,6,6′-Nonachlorobiphenyl	10.629	100.50
188	2,5-Dichlorobiphenyl	5.449	82.18	245	Decachlorobiphenyl	11.369	103.52
189	2,6-Dichlorobiphenyl	5.449	85.39				

TABLE VI

CALCULATED LOG P AND $\varphi_{0,MeOH}$ VALUES FOR 143 DRUG MOLECULES BASED ON THE RETENTION DATA PUBLISHED BY ROOS AND LAU-CAM [25]

No.	Compound	Log P	$\varphi_{0,MeOH}$	No.	Compound	Log P	$\varphi_{0,MeOH}$
246	Acetanilide	1.131	45.28	300	Ethinylestradiol	5.270	71.68
247	Acetophenazine	2.779	67.38	301	Fluphenazine	4.339	75.07
248	Acetyl sulphisoxazole	−2.192	50.48	302	Homatropine	1.889	28.16
249	Aminopromazine	4.189	68.77	303	Hydrochlorothiazide	−0.070	21.47
250	Amitriptyline	5.993	68.26	304	Hydrocortisone	2.029	62.92
251	Amodiaquin	4.468	60.04	305	Hydroxyamphetamine	1.444	6.79
252	Amphetamine	1.969	27.65	306	Hyoscyamine	2.119	38.54
253	Antazoline	3.233	52.94	307	Imipramine	4.532	68.16
254	Antipyrine	0.551	44.52	308	Isoproterenol	0.647	−5.23
255	Atropine	2.119	37.02	309	Lidocaine	3.134	35.53
256	Atropine methyl	2.679	35.78	310	Meclizine	5.696	84.74
257	Benzatropine	4.064	69.35	311	Medroxyprogesterone acetate	5.027	78.13
258	Bromodiphenhydramine	4.243	65.91	312	Mephentermine	2.792	34.80
259	Bromopheniramine	3.960	60.90	313	Mesoridazine	3.635	60.46
260	Bupivacaine	4.846	54.12	314	Mestranol	5.864	82.59
262	Butacaine	4.287	47.53	315	Metamphetamine	2.273	31.88
263	Butaperazine	4.393	77.70	316	Methapyriline	3.394	49.83
264	Caffeine	0.681	37.59	317	Methotrimeprazine	4.561	66.65
265	Carbinoxamine	2.748	57.47	318	Methoxyamphetamine	1.969	37.21
266	Chlorcyclizine	3.792	66.29	319	Methoxypromazine	4.042	65.61
267	Chloroprocaine	3.010	28.73	320	Methyldopate	0.650	26.71
268	Chlorpromazine	4.713	71.90	321	Methylparaben	1.586	55.04
269	Cinchonidine	3.034	52.38	322	Methyltestosterone	5.331	76.64
270	Chinconine	3.034	51.23	323	Naphazoline	2.629	43.56
271	Clenizole	4.709	68.46	324	Norethindrone	4.603	71.36
272	Cyclizine	3.052	49.85	325	Nortriptyline	5.627	69.43
273	Cyclothiazide	1.691	47.74	326	Oxyphencyclimine	3.990	65.95
274	Cycrimine	4.390	49.55	327	Perphenazine	3.930	74.59
275	Desipramine	4.166	56.27	328	Phenacetin	1.719	54.44
276	Dextromethorphane	4.730	48.96	329	Phenindamine	4.532	61.07
277	Dibucaine	3.779	62.95	330	Pheniramine	3.011	46.70
278	Dienestrol	5.883	61.85	331	Phenothiazine	3.764	73.78
279	Diethylstilbestrol	6.247	61.84	332	Phenoxybenzamine	5.401	61.27
280	Dihydrocinchonidine	3.398	55.41	333	Phentermine	2.488	35.32
281	Dihydrocinchonine	3.398	54.34	334	Phentolamine	3.147	49.25
282	Dihydroergocornine	2.339	52.46	335	Phenylpropanolamine	0.874	118.19
283	Dihydroergocristine	2.959	56.82	336	Phenylephrine	0.134	−20.1
284	Dihydroergocryptine	2.858	56.37	337	Phenyltoloxamine	4.425	60.71
285	Dihydroquinidine	3.467	57.68	338	Phthalylsulphathiazole	1.359	43.44
286	Dihydroquinine	3.467	58.85	339	Physostigmine	2.067	34.55
287	Diphenhydramine	3.294	46.99	340	Prednisolone	1.954	62.41
288	Diphenylpyraline	3.390	51.07	341	Prednisone	1.418	58.11
289	Doxylamine	2.527	38.60	342	Procaine	2.270	21.13
290	Dyphylline	−1.049	24.91	343	Prochlorperazine	4.506	82.87
291	Ephedrine	1.178	19.59	344	Progesterone	4.508	79.49
292	Ergonovine	1.750	30.92	345	Promazine	3.973	65.96
293	Ergotamine	1.846	63.40	346	Promethazine	4.551	65.04
294	Estradiol	4.960	73.05	347	Pyrantel	2.790	45.35
295	Estradiol benzoate	6.953	87.66	348	Pyrilamine	2.780	55.27
296	Estradiol cypionate	8.610	91.60	349	Pyrvinium	7.992	78.19
297	Estradiol valerate	7.417	87.51	350	Quinidine	3.103	55.14
298	Estriol	3.865	59.91	351	Quinine	3.103	55.59
299	Estrone	4.424	72.22	352	Salicylamide	0.206	40.64

TABLE VI *(continued)*

No.	Compound	Log P	$\varphi_{0,MeOH}$	No.	Compound	Log P	$\varphi_{0,MeOH}$
353	Salicylic acid	1.225	42.75	370	Sulphapyridine	0.325	28.93
354	Scopolamine	0.752	26.96	371	Sulphathiazole	0.050	27.08
355	Scopolamine aminoxide	0.941	26.07	372	Sulphisomidine	0.255	26.45
356	Spironolactone	5.053	70.03	373	Sulphisoxazole	−0.210	40.52
357	Succinylsulphathiazole	0.156	34.38	374	Testosterone	4.812	74.34
358	Sulphabenzamide	1.896	43.24	375	Testosterone cypionate	8.462	92.31
359	Sulphachlorpyridazine	−0.293	39.06	376	Testosterone enanthate	8.307	91.70
360	Sulphadiazine	−0.783	25.59	377	Testosterone propionate	6.231	84.28
361	Sulphadimethoxine	−0.645	50.36	378	Tetracaine	3.414	57.65
362	Sulphamerazine	−0.264	32.52	379	Theobromine	0.162	22.57
363	Sulphamethazine	0.255	37.52	380	Theophylline	−0.020	26.78
364	Sulphamethizole	0.405	27.11	381	Thioridazine	5.765	74.22
365	Sulphamethoxazole	0.262	39.90	382	Trichlormethiazole	0.872	42.64
366	Sulphamethoxypyridazine	0.400	37.50	383	Trimeprazine	4.492	66.53
367	Sulphanilamide	−0.726	−0.20	384	Tripelennamine	2.711	54.24
368	Sulphanilic acid	−1.690	−18.19	385	Tripolidine	4.707	58.94
369	Sulphaphenazole	1.999	46.52	386	Tropic acid	0.829	39.12

TABLE VII

CALCULATED LOG P, $\varphi_{0,ACN}$ AND $\varphi_{0,MeOH}$ VALUES FOR 26 DRUG MOLECULES BASED ON THE RETENTION DATA PUBLISHED BY VALKÓ [16,26]

No.	Compound	Log P	$\varphi_{0,ACN}$	$\varphi_{0,MeOH}$
387	Resorcinol	0.80	17.27	24.39
388	Sulphadimidine	0.32	30.57	40.55
389	Sulphamethoxypyridiazine	0.40	31.30	40.77
390	Barbital	0.65	26.44	39.76
391	Phenobarbital	1.42	42.04	53.14
392	Chloramphenicol	1.14	39.25	51.89
393	Salicylamide	1.28	34.16	46.72
394	Phenacetin	1.58	44.34	58.83
395	Vanillin	1.37	35.49	47.61
396	Benzaldehyde	1.45	51.98	–
397	Acetanilide	1.16	37.78	53.44
398	Nicotinamide	−0.57	6.57	21.77
399	Benzoic acid	1.87	44.08	56.20
400	Salicylic acid	2.25	47.34	59.93
401	Acetylsalicylic acid	1.23	39.60	–
402	Caffeine	−0.07	18.46	43.44
403	Hydrochlorothiazide	−0.07	1.95	25.79
404	Cortexolone	2.46	54.87	–
405	Dexamethasone	1.99	40.98	–
406	Desoxycortone	2.88	76.35	–
407	Sulphaguanidine	−1.22	0.41	–
408	Isoniazide	−1.14	1.59	–
409	Methyl salicylate	2.46	70.63	81.68
410	Hydrocortisone	1.61	33.80	–
412	Progesterone	3.87	95.36	–
413	Testosterone	3.31	75.87	–

tion of the hydrophobicity indices with methanol from those obtained with acetonitrile. The standard error of the estimate shows that in spite of the fact that the data for the 72 compounds were obtained with different columns and buffers or pure water, the hydrophobicity index values obtained with acetonitrile can be used to calculate those with methanol with only a ±5% error.

The correlation of $\varphi_{0,ACN}$ values with the calculat-

TABLE VIII

CALCULATED LOG P AND $\varphi_{0,ACN}$ VALUES FOR 12 MORPHINE DERIVATIVES BASED ON THE RETENTION DATA PUBLISHED BY VALKÓ *ET AL.* [27]

No.	Compound	Log P	$\varphi_{0,ACN}$
414	Azidomorphine	1.694	31.35
415	Azidocodeine	2.288	77.97
416	N-Cyclopropylmethylazidomorphine	2.887	63.93
417	Azidoethylmorphine	2.807	97.95
418	N-Phenylmethylazidoethylmorphine	4.465	86.56
419	N-Phenylmethylazidomorphine	3.352	74.93
420	Acetylazidomorphine	1.638	119.25
421	Norazidoethylmorphine	2.441	83.74
422	N-Cyclopropylmethylazidoethylmorphine	4.000	84.74
423	Norazidomorphine	1.328	31.40
424	Normorphine	1.497	12.42
425	Morphine	1.863	15.57

TABLE IX

CALCULATED LOG P AND $\varphi_{0,ACN}$ VALUES FOR 11 TRICYCLIC DRUG MOLECULES BASED ON THE RETENTION DATA PUBLISHED BY KÁLMÁN *ET AL.* [28]

No.	Compound	Log P	$\varphi_{0,ACN}$
427	EGYT-2347	5.713	86.64
428	EGYT-2509	3.980	88.00
429	EGYT-2474	4.499	84.41
430	EGYT-2541	3.832	90.85
431	RL-205	3.011	74.08
432	RL-215	3.773	93.62
433	RL-218	3.197	74.33
434	Peritol	6.587	88.38
435	Hybernal	4.772	114.49
436	Pipolphen	4.551	89.25
437	Melleril	5.790	111.33

ed log P values for the data for 140 compounds can be described by the equation

$$\varphi_{0,ACN} = 9.31\log P + 37.94 \quad (13)$$

$$n = 140,\ r = 0.88,\ s = 12.8$$

Eqn. 13 shows a significant correlation between the two parameters, although owing to the relatively

TABLE X

CALCULATED LOG P AND $\varphi_{0,ACN}$ VALUES FOR 18 BENZODIAZEPINE DERIVATIVES BASED ON THE RETENTION DATA PUBLISHED BY VALKÓ *ET AL.* [29]

No.	Compound	Log P	$\varphi_{0,ACN}$
438	7-Aminonitrazepam	0.950	51.41
439	Bromazepam	1.649	73.32
440	Uxepam	0.981	62.10
441	Oxazepam	1.180	62.48
442	Lorazepam	3.466	64.67
443	Nitrazepam	1.726	71.24
444	Clonazepam	2.466	68.87
445	Chlordiazepoxide	2.443	79.08
446	Alprazolam	3.609	84.53
447	Desmethyldiazepam	2.726	75.75
448	Flunitrazepam	1.814	75.34
449	Chlorazepat	−0.638	77.23
450	Diazepam	2.597	84.01
451	Midazolam	4.345	74.18
452	Medazepam	4.007	91.88
453	Prazepam	3.790	87.55
454	Clobazam	1.994	76.68
455	Tofizopam	3.647	81.37

TABLE XI

CALCULATED LOG P AND $\varphi_{0,MeOH}$ VALUES FOR 19 DEOXYURIDINE DERIVATIVES BASED ON THE RETENTION DATA PUBLISHED BY VALKÓ AND SLÉGEL [30]

No.	Compound	Log P	$\varphi_{0,MeOH}$
456	Deoxyuridine	−0.544	16.00
457	Ethyldeoxyuridine	0.494	24.68
458	Isopropyldeoxyuridine	1.013	30.27
459	*sec.*-Butyldeoxyuridine	1.532	46.06
460	*tert.*-Butyldeoxyuridine	1.532	46.46
461	Pentyldeoxyuridine	2.051	57.82
462	Hexyldeoxyuridine	2.570	61.24
463	Vinyldeoxyuridine	0.285	25.14
464	Butenyldeoxyuridine	1.323	48.41
465	Pentenyldeoxyuridine	1.842	58.40
466	Hexenyldeoxyuridine	2.361	67.40
467	Heptenyldeoxyuridine	2.880	72.19
468	Octenyldeoxyuridine	3.399	77.17
469	Propynyldeoxyuridine	0.285	25.97
470	Butynyldeoxyuridine	0.804	32.73
471	Hexynyldeoxyuridine	1.842	56.89
472	Heptynyldeoxyuridine	2.361	48.86
473	Octynyldeoxyuridine	2.880	69.24
474	Methyldeoxyuridine	0.016	21.19

TABLE XII

CALCULATED LOG P AND $\varphi_{0,MeOH}$ VALUES FOR 16 ANILINE AND PHENOL DERIVATIVES BASED ON THE RETENTION DATA PUBLISHED BY GULLNER *ET AL.* [31]

No.	Compound	Log P	$\varphi_{0,MeOH}$
475	*o*-Nitroaniline	1.129	60.77
476	*m*-Nitroanilinine	1.447	52.87
477	*p*-Nitroaniline	0.840	45.79
478	2,4-Dinitroaniline	0.894	64.23
479	2,4,6-Trinitroaniline	0.948	63.48
480	2-Chloro-4-nitroaniline	1.582	67.11
481	4-Chloro-3-nitroaniline	2.189	62.77
482	2,6-Dichloro-4-nitroaniline	2.324	78.05
483	*p*-Nitrophenol	1.291	57.60
484	2,4-Dinitrophenol	1.345	61.69
485	2,6-Dinitrophenol	1.634	57.72
486	2,4,5-Trinitrophenol	1.399	50.76
487	3,5-Dinitro-4-cyanophenol	0.987	57.41
488	3-Nitro-4-cyano-5-chlorophenol	2.341	71.72
489	3-Nitro-4-cyano-5-bromophenol	2.725	63.30
490	3-Nitro-4-cyano-5-iodophenol	3.367	55.86

TABLE XIII

$\varphi_{0,MeOH}$ VALUES FOR 42 ADENOSINE MONOPHOSPHATE DERIVATIVES BASED ON THE RETENTION DATA PUBLISHED BY BRAUMANN AND JASTORFF [32]

No.	Compound[a]	$\varphi_{0,MeOH}$
491	2-*n*-Hexyl	65.70
492	8-PCTP	60.13
493	6-Benzyloxy	62.23
494	Dibutyryl	55.69
495	2-Phenyl	51.39
496	2-*n*-Butyl	51.29
497	2'-DNP	54.04
498	2-Thiopropyl	52.20
499	6-(S_p)-DMA-S	46.28
500	2-*n*-Propyl	42.47
501	6-(R_p)-DMA-S	41.65
502	6-Thiomethyl	41.49
503	6-DMA	40.21
504	2-Ethyl	34.78
505	2-Thiomethyl	34.88
506	Monobutyryl	38.07
507	8-Bromo	30.99
508	8-Thioethyl	29.62
509	(S_p)-cAMPS	26.89
510	6-MA	29.65
511	8-Hydroxyisopropyl	27.77
512	1'N^6-Etheno	26.41
513	8-Methoxy	25.54
514	2-Chloro	31.77
515	(R_p)-cAMPS	23.75
516	6-Methoxy	31.91
517	6-Chloro	31.10
518	8-MA	23.61
519	cAMP	21.96
520	(S_p)-cGMPS	19.28
521	cPuMP	20.91
522	3'NH-cAMP	21.10
523	5'NH-cAMP	18.15
524	2-Methyl	16.99
525	8-Thio	13.46
526	8-Amino	14.89
527	8-DMA	14.90
528	cIMP	13.52
529	cGMP	13.13
530	N^1-Methoxy	12.76
531	N^1-Oxide	10.42
532	8-Hydroxy	7.04

[a] For abbreviations see ref. 32, Table I.

low correlation coefficient (r) and the high standard error of the estimate (s) it cannot be used for measurements of log P values. The plot of $\varphi_{0,ACN}$ values against log P is shown in Fig. 3. Similarly a statistically significant correlation could be found between the $\varphi_{0,MeOH}$ and the lof P values for the data for 448 compounds:

TABLE XIV

CALCULATED LOG P AND $\varphi_{0,MeOH}$ VALUES FOR 10 β-LACTAM ANTIBIOTICS BASED ON THE RETENTION DATA PUBLISHED BY YAMANA *ET AL.* [33]

No.	Compound	Log P	$\varphi_{0,MeOH}$
533	Carbenicillin phenyl	3.14	50.57
534	Dicloxacillin	2.83	47.92
535	Floxacillin	2.58	47.56
536	Cloxacillin	2.48	48.23
537	Phenethicillin	2.19	45.80
538	Penicillin V	1.62	43.78
539	Penicillin G	1.30	34.48
540	Ampicillin	0.94	37.60
541	Amoxicillin	0.48	8.89
542	Sulbenicillin	0.20	3.51

$$\varphi_{0,MeOH} = 7.08 \log P + 42 \quad (14)$$

$$n = 448, r = 0.787, s = 13.48$$

On the basis of eqn. 14, exact measurements of log P cannot be carried out from measurements of the chromatographic hydrophobicity index, but the good correlation shows that even for a large set of compounds a relationship exists. The high standard error of the estimate (±13%) may be due to the error in the calculation of partition coefficients, to

TABLE XV

CALCULATED LOG P AND $\varphi_{0,ACN}$ VALUES FOR 12 BARBITURATE DERIVATIVES BASED ON THE RETENTION DATA PUBLISHED BY TOON *ET AL.* [34]

No.	Compound	Log P	$\varphi_{0,ACN}$
543	5-Ethylbarbituric acid	−1.52	−2.93
544	5-Ethyl-5-methylbarbituric acid	0.02	−0.14
545	Barbital	0.68	3.92
546	5-Ethyl-5-*n*-propylbarbituric acid	0.87	10.65
547	Butethal	1.70	18.33
548	5-Ethyl-5-*n*-hexylbarbituric acid	3.08	32.44
549	5-Ethyl-5-*n*-heptylbarbituric acid	3.64	35.35
550	5-Ethyl-5-*n*-octylbarbituric acid	3.85	41.98
551	5-Ethyl-5-*n*-nonylbarbituric acid	4.13	46.26
552	Pentobarbital	2.13	22.35
553	Amobarbital	2.11	23.98
554	Phenobarbital	1.42	14.58

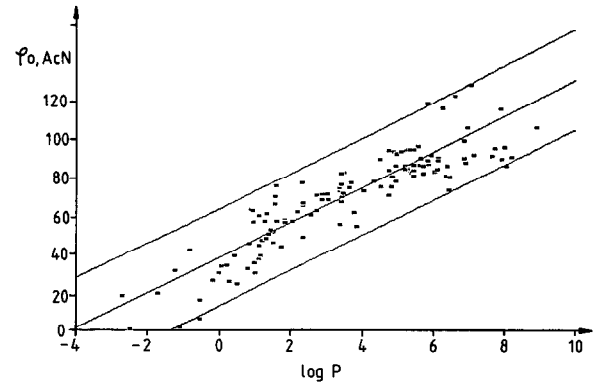

Fig. 3. Plot of log P values and $\varphi_{0,ACN}$ values for 140 compounds lised in Tables I–XV (eqn. 13).

the error in the measurements of φ_0 values and also to the error caused by differences in the chromatographic conditions applied. The main reason for the lack of high correlation coefficients (>0.99), however, is that we cannot expect from the reversed-phase chromatographic partition coefficients to be able to model properly another partition system such as 1-octanol–water for structurally unrelated compounds.

The advantage of the proposed chromatographic hydrophobicity index (φ_0) is that it can also be used for method development in RP-HPLC. When the structures of all the components in a mixture are known, the log P values can be calculated. From the log P values we can calculate the organic phase concentration at which the components will show $\log k' = 0$. The idea of using this kind of relationship was presented by Szepesi and Valkó [38]. On the basis of the relationships obtained and the suggested rule system, CompuDrug Chemistry (Budapest, Hungary) has developed an expert system (ELUEX) for HPLC method development. There is no need for preliminary experiments and it can therefore be regarded as unique at present.

In conclusion, a new chromatographic hydrophobicity index (φ_0) has been suggested. The value of φ_0 reflects the organic phase concentration in the mobile phase (%, v/v) at which the molar distribution of the compound between the mobile and the stationary phase is 1:1. This means that the retention time of the compound is exactly double the dead time, *i.e.* $\log k' = 0$. The hydrophobicity index relating to methanol showed a very good correlation with that relating to acetonitrile. Significant correlations were found between the log P values and the chromatographic hydrophobicity index values for a large number of compounds (140 and 448 compounds relating to acetonitrile and methanol, respectively).

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