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CORRELATIONS BETWEEN LIQUID CHROMATOGRAPHIC CAPACITY RATIO DATA ON LICHROSORB RP-18 AND PARTITION COEFFICIENTS IN THE OCTANOL–WATER SYSTEM

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SUMMARY

Retention data of methylbenzenes, *n*-alkylbenzenes, fused arenes, polyphenyls, chlorobenzenes, -anilines and -phenols and some polar monosubstituted benzenes have been measured on LiChrosorb RP-18, using methanol–water mixtures as eluents at 25°C.

The important effect of solute activity coefficients in water on capacity ratio (k) data, holding for water as eluent, and on partition coefficients in the octanol–water system ($P_{\text{oct.}}$) is shown. The log k–log $P_{\text{oct.}}$ correlation is improved by using (linearly extrapolated) log k values in water, instead of those in methanol–water mixtures. At similar log $P_{\text{oct.}}$ values the log k values of the polar benzenes are slightly higher than those of the lipophilic compounds. Consequently, two log k–log $P_{\text{oct.}}$ regression equations are proposed. Steric and intramolecular electronic effects on the values for log $P_{\text{oct.}}$ of halogenated anilines and phenols are described quantitatively. The results cast doubt on the reliability of Rekker's f-method for the prediction of log $P_{\text{oct.}}$ values of highly substituted aromatic compounds.

INTRODUCTION

Solute partition coefficients in the octanol–water system play an important role in quantitative structure–activity relationships developed by Leo *et al.*[1]. Log $P_{\text{oct.}}$ values are usually determined by the shake-flask method. However, as this method is elaborate and troublesome, in particular for highly lipophilic compounds, reversed-phase high-performance liquid chromatography (RP-HPLC) has been proposed as a convenient and precise alternative[2–9]. Several column materials have been applied.

Mirrlees *et al.*[5] coated trimethylsilylsilica with a thin layer of octanol and used water (saturated with octanol) as eluent. An excellent correlation between chromatographic capacity ratios (k) and $P_{\text{oct.}}$ values was obtained, as expected. More recently, Miyake and Terada[7] improved the column stability by suspending hot Corasil I in octanol. However, as the hydrolytic stability of the Si–O–C bonds formed is poor, a long lifetime of such columns is not expected. In this respect Si–C bonds encountered

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in alkylmethyldichlorosilane-treated silicas offer better prospects, although the applicable pH range of the eluent is limited (about 4–7.5). Log k–log $P_{oct.}$ correlations on these alkyl-bonded phases are less accurate than the results reported by Mirrlees *et al.*[5], but improved results can be achieved by optimizing the chromatographic conditions, as will be shown below.

In a previous paper on this subject[10], log k values of some chlorobenzenes, -toluenes and -anilines on LiChrosorb RP-18, using methanol–water (70:30) as eluent, were correlated with calculated log $P_{oct.}$ values applying Rekker's *f*-method[11]. In this work, log k values of apolar and polar (proton donor and acceptor) aromatic solutes are directly related to experimental log $P_{oct.}$ values $\lesssim 5$. Previously, we rejected log $P_{oct.}$ data >4 on the basis of systematic deviations between experimental and calculated log $P_{oct.}$ values for chlorobenzenes[10]. However, it will be shown below that these deviations are due to crowding effects which are ignored in the *f*-method. Special attention will be paid to the chromatographic measuring technique, to eluent effects on the accuracy of log k–log $P_{oct.}$ correlations and to substituent effects in planar aromatic molecules on log k and on experimental log $P_{oct.}$ values.

THEORETICAL

The logarithm of the capacity ratio of a solute (1) on LiChrosorb RP-18 in water (2) can be described by the equation

$$\log k_0 \equiv \log\left(\frac{\bar{n}_1}{n_1}\right) = \log\left(\frac{\bar{x}_1 \bar{n}_2}{x_1 n_2}\right) = \log\left(\frac{\bar{n}_2}{n_2}\right) + \log\left(\frac{\gamma^x_{1,\text{water}}}{\gamma^x_{1,\text{interface}}}\right) \tag{1}$$

This equation is based on a displacement adsorption model in which the solute is distributed between a homogeneous interfacial layer and the bulk eluent (2). In eqn. 1, $\bar{n}_1$ (or $\bar{n}_2$) denotes the number of moles of adsorbed solute (or water) whereas n_1 (or n_2) is the number of moles of the solute (or water) in the mobile eluent. Analogously, $\bar{x}_1$ and x_1 are the molar fractions of the solute in the interfacial layer and in the eluent, respectively. At a sufficiently small solute sample size they are inversely proportional to the corresponding activity coefficients, $\gamma^x_{1,\text{interface}}$ and $\gamma^x_{1,\text{water}}$, respectively. Eqn. 1 also holds when methanol–water mixtures are used as eluents[12–14]. The amount and composition of the adsorbed eluent can be estimated from isotherm data[15]. The former appears to correspond with about a monolayer[12].

The partition coefficient, P, of a solute between an organic solvent and water can be described by

$$\log P \equiv \log\left(\frac{c_{1,\text{org.}}}{c_{1,\text{water}}}\right) = \log\left(\frac{v^0_{\text{water}}}{v^0_{\text{org.}}}\right) + \log\left(\frac{\gamma^\infty_{1,\text{water}}}{\gamma^\infty_{1,\text{org.}}}\right) \tag{2}$$

where $c_{1,\text{org.}}$ and $c_{1,\text{water}}$ are the solute concentrations in the organic and in the aqueous phase, respectively, and $v^0_{1,\text{org.}}$ and v^0_{water} are the molar volumes of the organic and the aqueous phase, respectively. As the solubility of the organic solvent in water is sufficiently small (as is the case for the n-alkane and the octanol phase considered in this paper), $\gamma^{\infty}_{1,\text{water}}$ is applied in eqn. 2. The activity coefficient in the organic phase is denoted by $\gamma^{\infty}_{1,\text{org.}}$. Combination of eqns. 1 and 2 yields

$$\log k_0 = \log\left(\frac{\bar{n}_2 v^0_{\text{org.}}}{n_2 v^0_{\text{water}}}\right) + \log\left(\frac{\gamma^{\infty}_{1,\text{org.}}}{\gamma^{\infty}_{1,\text{interface}}}\right) + \log P \tag{3}$$

As the magnitude of $\gamma^{\infty}_{1,\text{org.}}$ (and $\gamma^{\infty}_{1,\text{interface}}$) is generally unknown, in practice eqn. 3 is usually presented as a regression equation according to Collander[16]:

$$\log k_0 = A + B \log P \tag{4}$$

where A and B are parameters the magnitude of which depends on the temperature, the methanol content of the eluent and the class of solutes, as will be shown below. Comparison of eqns. 3 and 4 shows that the Collander equation holds only when log $(\gamma^{\infty}_{1,\text{org.}}/\gamma^{\infty}_{1,\text{interface}})$ is either constant or correlated with log P.

Further, log k–log $P_{\text{oct.}}$ correlations must be examined at various eluent compositions when optimal results are to be achieved. In view of the different solute distribution mechanisms (*i.e.*, adsorption *versus* partition), it is worth comparing contributions of substituent groups to log k_0 and to log P values. Such contributions may be different because adsorption data seem to be more susceptible to solute molecular structure differences than partition data, which limits the predictive value of the RP-HPLC technique. On the other hand, it needs no comment that similarities between group contributions from RP-HPLC data and from the large file of available log $P_{\text{oct.}}$ values (f- and π-data of Hansch and Leo[17] or f-data of Rekker[11]) are of common interest to the chromatographer and to the pharmaceutical scientist and toxicologist.

In this work we are dealing largely with extrapolated (and hence possibly biased) log k_0 values. These data appear to be useful in correlation studies. Outside this scope, the interpretation of the results should be restricted to strong and/or consistent trends among relative log k_0 values which are also observed on experimental data holding in methanol–water mixtures.

EXPERIMENTAL

Chemicals and adsorbent characterization

All solutes were of the highest available purity. Doubly distilled water and absolute methanol (analysed reagent grade; J. T. Baker, Deventer, The Netherlands) were degassed before use. LiChrosorb RP-18 (E. Merck, Darmstadt, G.F.R.) contains 4.4 μmole/m^2 of octadecylmethylsilyl groups on LiChrosorb Si 100 (S_{BET} = 282 m^2/g)[12].

Apparatus and RP-HPLC procedure

The apparatus, the column and the measuring technique have been described previously[12]. Methanol–water mixtures were used as eluents at 25°C, except for chlorophenols, which were eluted with acetate buffers (0.05 M acetate, corrected pH in methanol–water mixtures[18] equal to 4.5, to avoid adsorbent deterioration). The solute sample size was 20 μg or less. The reproducibility of triplicate retention volume measurements was 10 μl or 2% for strongly retained solutes. Peak symmetry was good. Capacity ratio data were determined from $k = (V_r - V_m)/V_m$, where V_r is the solute retention volume after correction for hold-up outside the column and V_m is the volume of mobile eluent in the column. V_m was obtained from $V_m = V_0 - V_s$, where V_0 is the void volume of the column (determined by picnometry[12]) and V_s is the volume of adsorbed eluent (estimated from isotherm data[15]).

RESULTS AND DISCUSSION

General observations

Log k values on LiChrosorb RP-18 at various volume fractions φ of methanol ($0.3 \leqslant \varphi \leqslant 0.9$; $k_\varphi \lesssim 65$) appear to be linearly related to φ:

$$\log k_\varphi = \log k_0 + b\varphi \tag{5}$$

Extrapolated log k_0 and b values are given in Table I. At $\varphi \lesssim 0.2$, poor wetting[19] of the RP-18 layer may affect k. Further, k values of polar solutes appear to be smaller in an aqueous acetate buffer than in water. Eqn. 5 also holds for other modifiers, such as acetonitrile and acetone, but in a smaller range of concentrations[20].

Retention mechanism

In Fig. 1 log k_0 is plotted against log P in n-alkane–water systems[17] (as log P data in hexane–, heptane– and octane–water are similar, mean values are presented). The data points of apolar solutes are close to the dotted line, which represents the relationship log k_0 = log P. This suggests that log k_0 values are controlled by a partition mechanism, as proposed by Lochmüller and Wilder[31] in their liquid droplet model. However, a partition mechanism is not consistent with the large deviations of the data points of the polar solutes from the dotted line in Fig. 1.

These deviations suggest that interactions in the interfacial RP-18–water layer contribute to the retention. From the large k/P values, previously obtained at 50% (v/v) methanol, it was pointed out that contributions of solute partitioning between the eluent and the RP-18 phase to k are small[12]. The same holds for the present data. Therefore, we prefer a description of solute retention in terms of a displacement adsorption model (eqn. 1). Note that log k_0 values of acidic chlorophenols, basic chloroanilines and of apolar compounds can be described with one regression equation on log $P_{\text{oct.}}$. Obviously, the sparingly available silanol groups are not readily accessible for solute molecules and adsorption to these sites can be ignored[10].

Eluent effects on log k–log $P_{\text{oct.}}$ correlations

Experimental log $P_{\text{oct.}}$ values are largely taken from a recent compilation by Hansch and Leo[17]. Mean values are given in Table I. The log $P_{\text{oct.}}$ values >5 and those of 1,3,5-trimethylbenzene and hexamethylbenzene are not used in log k–log P correlations. The former are hard to determine accurately, probably owing to the occurrence of non-centrifugable micro-droplets of octanol in the aqueous phase[10]. The latter two deviate strongly in a linear plot of log P values of methylbenzenes

TABLE I

EXTRAPOLATED log k_0 VALUES ON LICHROSORB RP-18 HOLDING FOR WATER AS ELUENT AT 25°C. VALUES FOR THE SLOPE OF PLOTS OF log k *VERSUS* VOLUME FRACTION OF METHANOL(b). LITERATURE DATA ON log $\gamma^x_{1,\mathrm{water}}$, log $P_{\mathrm{oct.}}$ AND ΔpK_a AND log $\hat{P}_{\mathrm{oct.}}$ VALUES FROM log P_{oct}–log k_0 CORRELATIONS

No.	*Solute*	*Log* $k_0 \pm s$	$-b \pm s$	*log* $\gamma^x_{1,\mathrm{water}}$	*log* $P_{\mathrm{oct.}} \pm s$	*log* $\hat{P}_{\mathrm{oct.}}$	$-\Delta pK_a$
	Methylbenzenes:			(ref. 21)	(ref. 17)		
1	H	2.11 ± 0.05	2.71 ± 0.07	3.38^{22}	2.14 ± 0.01	2.20	
2	Methyl	2.74 ± 0.05	3.28 ± 0.08	3.98	2.74 ± 0.05	2.78	
3	1,2-diMe	3.19 ± 0.03	3.64 ± 0.04	4.53	3.12	3.19	
4	1,3-diMe	3.30 ± 0.04	3.74 ± 0.06	4.60	3.20	3.29	
5	1,4-diMe	3.29 ± 0.02	3.69 ± 0.02	4.57	3.15	3.28	
6	1,2,3-triMe	3.71 ± 0.03	4.08 ± 0.04	4.95		3.66	
7	1,2,4-triMe	3.84 ± 0.03	4.20 ± 0.04	5.05		3.78	
8	1,3,5-triMe	3.90 ± 0.03	4.23 ± 0.04	5.15	(3.42)	3.84	
9	1,2,3,4-tetraMe	4.20 ± 0.06	4.45 ± 0.06			4.11	
10	1,2,3,5-tetraMe	4.26 ± 0.07	4.48 ± 0.10			4.17	
11	PentaMe	4.7	4.9			4.56	
12	HexaMe	5.3	5.4		(4.31)	5.11	
	n-Alkylbenzenes:			(ref. 21)			
13	Ethyl	3.27 ± 0.04	3.77 ± 0.06	4.55	3.15	3.26	
14	Propyl	3.97 ± 0.01	4.43 ± 0.01	~5.18	3.63 ± 0.06	3.90	
15	Butyl	4.57 ± 0.01	4.95 ± 0.01	5.80	4.26	4.44	
	Fused arenes:			(refs. 23, 24)			
16	Naphthalene	3.48 ± 0.03	4.02 ± 0.05	4.82	3.38 ± 0.12	3.45	
17	Fluorene	4.26 ± 0.09	4.53 ± 0.13	5.81	4.18	4.17	
18	Phenanthrene	4.54 ± 0.12	4.80 ± 0.17	6.24	4.53 ± 0.07	4.42	
19	Anthracene	4.73 ± 0.12	4.95 ± 0.17	6.37	4.45	4.59	
20	Pyrene	5.10 ± 0.15	5.18 ± 0.22	6.60	4.88	4.93	
	Polyphenyls:						
21	Biphenyl	4.17 ± 0.01	4.68 ± 0.01	5.64	4.06 ± 0.08	4.08	
22	Bibenzyl	4.92 ± 0.07	5.33 ± 0.10		4.79	4.76	
	Halogenated benzenes:			(ref. 22)			
23	F	2.28 ± 0.03	2.99 ± 0.04	3.53	2.27	2.36	
24	Cl	2.80 ± 0.02	3.36 ± 0.04	4.09	2.84	2.83	
25	Br	2.90 ± 0.04	3.42 ± 0.06	4.38	2.99	2.92	
26	1,2-diCl	3.36 ± 0.01	3.88 ± 0.01	4.95	3.38	3.34	
27	1,3-diCl	3.49 ± 0.01	3.93 ± 0.01	4.83	3.38	3.46	
28	1,4-diCl	3.43 ± 0.02	3.90 ± 0.03	4.95	3.39 ± 0.01	3.41	
29	1,2,3-triCl	3.95 ± 0.03	4.33 ± 0.04	5.22	4.11^{10}	3.88	
30	1,2,4-triCl	4.03 ± 0.08	4.35 ± 0.11	5.46	3.93^{10}	3.96	
31	1,3,5-triCl	4.26 ± 0.08	4.45 ± 0.12	5.81	4.15^{10}	4.17	
32	1,2,3,4-tetraCl	4.53	4.75	6.22	4.46^{10}	4.41	
33	1,2,3,5-tetraCl	4.66	4.80	6.24	4.50^{10}	4.53	
34	1,2,4,5-tetraCl	4.65	4.80	6.17	4.52^{10}	4.52	
35	PentaCl	5.25	5.25	6.80	4.88^{10}	5.06	
36	HexaCl	5.90	5.70	7.47	(4.1–6.2^{25})	5.66	

(Continued on p. 6)

TABLE I *(continued)*

No.	*Solute*	*Log k_0 ± s*	*−b ± s*	*log $\gamma^{\infty}_{1,\text{water}}$*	*log $P_{\text{oct.}}$ ± s*	*log $\bar{P}_{\text{oct.}}$*	*−ΔpK_a*
	Chloroanilines:						(ref. 26)
37	2-Cl	1.89 ± 0.01	2.84 ± 0.02		1.91 ± 0.01	1.99	1.97
38	3-Cl	1.90 ± 0.01	2.91 ± 0.01		1.89 ± 0.01	2.00	1.12
39	4-Cl	1.92 ± 0.01	2.96 ± 0.02		1.83	2.02	0.59
40	2,3-diCl	2.67 ± 0.04	3.53 ± 0.07		2.78	2.71	2.88
41	2,4-diCl	2.75 ± 0.02	3.50 ± 0.03			2.78	2.62
42	2,5-diCl	2.71 ± 0.01	3.53 ± 0.01			2.75	3.09
43	2,6-diCl	2.67 ± 0.02	3.40 ± 0.03			2.71	4.20
44	3,4-diCl	2.63 ± 0.05	3.60 ± 0.09		2.69	2.67	1.64
45	3,5-diCl	2.88 ± 0.01	3.73 ± 0.01			2.90	2.23
46	2,3,4-triCl	3.35 ± 0.03	4.08 ± 0.04			3.33	
47	2,4,5-triCl	3.48 ± 0.01	4.18 ± 0.01			3.45	~3.53
48	2,4,6-triCl	3.55 ± 0.01	4.15 ± 0.03			3.52	
49	3,4,5-triCl	3.34 ± 0.02	4.15 ± 0.03			3.32	
50	2,3,4,5-tetraCl	4.12 ± 0.03	4.68 ± 0.04			4.04	
51	2,3,5,6-tetraCl	4.19 ± 0.03	4.63 ± 0.04			4.10	
52	PentaCl	4.72	5.00			4.59	
	Chlorophenols:						(ref. 27)
53	2-Cl	2.02 ± 0.02	3.13 ± 0.02		2.16 ± 0.03	2.12	1.46
54	3-Cl	2.29 ± 0.04	3.34 ± 0.07		2.50 ± 0.02	2.36	0.88
55	4-Cl	2.27 ± 0.03	3.35 ± 0.05		2.40 ± 0.03	2.35	0.59
56	2,3-diCl	2.81 ± 0.03	3.83 ± 0.03			2.84	2.30
57	2,4-diCl	2.90 ± 0.03	3.79 ± 0.05		3.06[28]	2.92	2.11
58	2,5-diCl	2.90 ± 0.02	3.88 ± 0.03		3.20[28]	2.92	2.49
59	2,6-diCl	2.59 ± 0.06	3.70 ± 0.10			2.64	3.21
60	3,4-diCl	3.04 ± 0.02	3.99 ± 0.03			3.05	1.41
61	3,5-diCl	3.27 ± 0.03	4.07 ± 0.04			3.26	1.81
62	2,3,4-triCl	3.58 ± 0.03	4.40 ± 0.05			3.54	3.03[29]
63	2,4,5-triCl	3.67 ± 0.02	4.41 ± 0.03		3.72	3.63	3.28[29]
64	3,4,5-triCl	3.81 ± 0.04	4.50 ± 0.06			3.75	2.16
	Polar benzenes:						
65	$-COHN_2$	0.98 ± 0.15	2.5 ± 0.3		0.65 ± 0.01	0.84	
66	$-NH_2$	1.05 ± 0.07	1.98 ± 0.13	2.15[30]	0.91 ± 0.05	0.90	0.00*
67	$-OH$	1.27 ± 0.02	2.35 ± 0.03		1.48 ± 0.01	1.11	0.00*
68	$-CH_2OH$	1.39 ± 0.02	2.55 ± 0.03		1.10	1.22	
69	$-NHCOCH_3$	1.38 ± 0.03	2.60 ± 0.06		1.23 ± 0.09	1.21	
70	$-CHO$	1.74 ± 0.06	2.8 ± 0.1		1.45 ± 0.02	1.54	
71	$-CN$	1.83 ± 0.05	2.9 ± 0.1		1.56	1.63	
72	$-NO_2$	1.91 ± 0.06	2.69 ± 0.04		1.84 ± 0.04	1.70	
73	$-COCH_3$	2.02 ± 0.05	3.1 ± 0.1		1.66 ± 0.06	1.80	
74	$-OCH_3$	2.23 ± 0.03	2.88 ± 0.04		2.08 ± 0.03	2.00	
75	$-CO_2CH_3$	2.44 ± 0.11	3.2 ± 0.2		2.18 ± 0.06	2.19	
76	$-N(CH_3)_2$	2.57 ± 0.05	3.09 ± 0.08		2.30 ± 0.01	2.31	
	Miscellaneous chlorinated compounds:						
77	Dieldrin	5.3 ± 0.2	5.8 ± 0.2			5.11	
78	Proclonol	5.5 ± 0.1	6.2 ± 0.2			5.29	
79	*p,p'*-DDT	6.7 ± 0.3	7.1 ± 0.4		(4.0–6.2)	6.38	

* pK_a = 4.62 (aniline)[26] and 10.00 (phenol)[27].

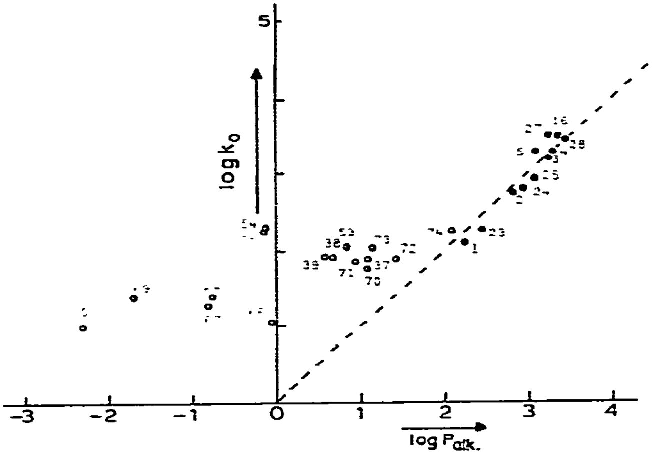

Fig. 1. log k_0 *versus* log P (*n*-alkane–water) for some apolar (numbers $\leqslant 28$) and polar (numbers $\geqslant 37$) solutes. Code according to Table I.

versus homomorphous chlorobenzenes. Such deviations are suspect because crowding effects are closely related in both solute series, as follows from a similar plot of log k_0 values on RP-18 (standard error of fit, $s_f = 0.04$).

Both log k_0 and log $P_{oct.}$ data appear to be linearly related to log $\gamma^{\infty}_{1,water}$ values given in Table I (Fig. 2). The following regression equations are obtained:

$$\log k_0 = (-0.84 \pm 0.09) + (0.89 \pm 0.02) \log \gamma^{\infty}_{1,water} \qquad (6)$$

with $s_f = 0.10$ (outliers: *n*-propylbenzene, *n*-butylbenzene and 1,2-dichlorobenzene), and

$$\log P_{oct.} = (-0.68 \pm 0.11) + (0.84 \pm 0.02) \log \gamma^{\infty}_{1,water} \qquad (7)$$

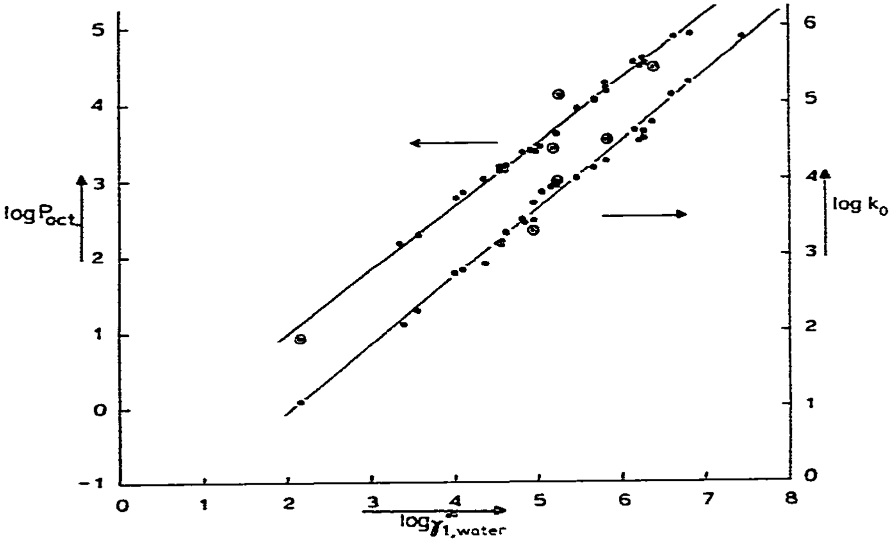

Fig. 2. log $P_{oct.}$ and log k_0 *versus* log $\gamma^{\infty}_{1,water}$. Outliers (⊙) deviate more than 0.2 from the lines.

TABLE II

VALUES OF α_1 AND α_2 IN THE REGRESSIONS OF log $P_{oct.}$ ON log k
For identification of solute classes, see Table III.

Solute class	φ	n	$\alpha_1 \pm s$	$\alpha_2 \pm s$	s_f
I, III–VII	0	36	0.28 ± 0.06*	0.91 ± 0.02*	0.11
	0.5		1.39 ± 0.07	1.39 ± 0.05	0.18
VIII	0	12	−0.07 ± 0.16*	0.93 ± 0.09*	0.16
	0.5		1.05 ± 0.10	1.30 ± 0.05	0.13
VIII–phenol	0	11	−0.22 ± 0.11	0.99 ± 0.06	0.10
	0.5		1.00 ± 0.07	1.36 ± 0.04	0.09

* Data used to calculate log $\hat{P}_{oct.}$ values given in Table I.

with $s_f = 0.12$ (outliers: 1,3,5-trimethylbenzene, anthracene, 1,2,3-trichlorobenzene and aniline). These equations clearly show the important influence of log $\gamma^{\infty}_{1,\text{water}}$ on log k_0 and log $P_{oct.}$, and suggest that log k_0, rather than log k_φ values in methanol–water mixtures, are preferred for correlations with log $P_{oct.}$, and *vice versa*. To verify this conclusion, log k data at $\varphi = 0.5$ and $\varphi = 0$ have been examined. It appears that the polar benzenes should be treated separately, whereas the *n*-alkylbenzenes are excluded throughout from the regressions for reasons given below. Results for log $P_{oct.}$–log k correlations are given in Table II. Generally, log k_0 gives better results, as is expected. The larger s_f value at $\varphi = 0$ for the class of polar benzenes is largely due to phenol, which shows a deviating behaviour, particularly at $\varphi = 0$. Estimated log $\hat{P}_{oct.}$ values from log $P_{oct.}$–log k_0 correlations (Table II, $\varphi = 0$) are given in Table I. Only a few spurrious outliers ($|\log P_{oct.} - \log \hat{P}_{oct.}| \geq 0.20$) are observed (1,2,3-trichlorobenzene and 2,5-dichlorophenol), probably owing to erroneous log $P_{oct.}$ values. Further, phenol shows a significantly larger affinity towards the octanol phase than to the RP-18–water interface. If log $\hat{P}_{oct.}$ is estimated from log k data measured at $\varphi = 0.5$, the number of outliers appears to be much larger. In addition, log $\hat{P}_{oct.}$ values of methylbenzenes are systematically overestimated in that case, whereas those of chlorobenzenes are underestimated. The reason for this poor result can be eluci-

TABLE III

VALUES OF a_1 AND a_2 IN EQN. 8 FOR VARIOUS SOLUTE CLASSES IN LICHROSORB RP-18/METHANOL–WATER SYSTEMS AT 25°C

Code	*Solute classes*	$a_1 \pm s$	$a_2 \pm s$	s_f
I	Methylbenzenes	−1.02 ± 0.03	−0.82 ± 0.01	0.03
II	*n*-Alkylbenzenes	−0.81 ± 0.09	−0.91 ± 0.02	0.02
III	Fused arenes	−1.47 ± 0.13	−0.73 ± 0.03	0.04
IV	Polyphenyls	−1.06	−0.87	
V	Halogenated benzenes	−1.25 ± 0.05	−0.77 ± 0.01	0.04
VI	Chloroanilines	−1.47 ± 0.08	−0.76 ± 0.02	0.08
VII	Chlorophenols	−1.64 ± 0.08	−0.76 ± 0.03	0.05
VIII	Polar benzenes	−1.70	−0.59 ± 0.10	0.17

dated as follows. Apart from the class of unrelated polar benzenes, the other solutes can be classified very well by sets of a_1 and a_2 parameters in the relationships between their b (eqn. 5) and log k_0 values:

$$b = a_1 + a_2 \log k_0 \tag{8}$$

The a_1 and a_2 values are given in Table III. Combination of eqns. 4 (with $P = P_{\text{oct.}}$), 5 and 8 yields

$$\log k_\varphi = \log k_0 + (a_1 + a_2 A)\,\varphi + a_2 B\varphi \log P_{\text{oct.}} \tag{9}$$

Hence, the scatter of the data points in log k_φ *versus* log $P_{\text{oct.}}$ plots is largely due to the last two terms of the right-hand side of eqn. 9, and is connected with the different (a_1, a_2) data sets for the various solute classes in Table III. Therefore, we conclude that the use of log k_φ values is not recommended when reliable log $\hat{P}_{\text{oct.}}$ estimates are required for solutes that belong to different classes.

Substituent effects

When log $P_{\text{oct.}}$ cannot be determined by means of the shake-flask method, calculated values can be obtained with the f-method, according to Rekker[11] or Hansch and Leo[17], or with the π-method[1,17]. Both are based on the additivity of atom or group contributions (f_i or π_i) to log $P_{\text{oct.}}$, but the approach is different. The f_i data of Rekker, given in Table IV, result from a statistical data reduction procedure in which contributions of groups in various molecular structures (aromatic or aliphatic) are averaged. Those for benzene fragments at various degrees of substitution are applied to obtain f_i (exp.) from log $P_{\text{oct.}}$ and $\hat{f}_i$ from log $\hat{P}_{\text{oct.}}$. For the substituted benzenes examined in this work it suffices to consider only f_i (exp.), $\hat{f}_i$ and f_i according to Rekker, as $\pi_i = f_i$ (exp.) $-$ (0.24 $\pm$ 0.04) (see Table IV).

Comparison of $\hat{f}_i$ and f_i (exp.) values shows that $\hat{f}_i$ for a phenolic OH group deviate significantly (more than 0.2) and that $\hat{f}_{\text{CH}_2}$ in n-alkylbenzenes is large. For that reason this solute class was excluded from the regressions in Table II. Steric shielding by adjacent methyl or chloro groups can be evaluated by calculating mean f_i values for isolated groups which are applied to estimate f_i (adj.) of adjacent ones. Crowding effects in methyl- and chlorobenzenes cause a reduction of f_i (exp.) of about 9%.

The f_i data of Rekker deviate from f_i (exp.) in several instances. The omission of steric shielding effects implies inaccurate log $P_{\text{oct.}}$ estimates for methyl- and chlorobenzenes by Rekker's f-method.

Another source of error may arise when contributions of intramolecular electronic effects are overlooked. They contribute significantly in monosubstituted anilines, phenols and benzyl alcohols, as was shown by Fujita *et al.*[32]. In the following only log $\hat{P}_{\text{oct.}}$ (and log $P_{\text{oct.}}$) values of non-ionized compounds will be considered in order to avoid complications. Usually, the electron-withdrawing action of substituent i on a "reactive" group j in a molecule i–$\varnothing$–j is of prime importance and interaction of j on i will be ignored for simplicity. These substituent effects can be evaluated from $\hat{f}_j$ values (j refers to NH_2 or OH) when log $\hat{P}_{\text{oct.}}$ values are combined with $f_{\text{nucl.}}$ of the benzene fragment and with $\hat{f}_i$ and $\hat{f}_i$ (adj.) values for isolated and adjacent or *ortho*-positioned substituents. If substituents affect $\hat{P}_{\text{oct.}}$ and the ionization constant in

TABLE IV

f VALUES ACCORDING TO REKKER[11] FOR VARIOUS BENZENE FRAGMENTS, AND f_i (exp.) CALCULATED FROM $\log P_{\text{oct.}}$ (TABLE I), $\hat{f}_i$ CALCULATED FROM $\log \hat{P}_{\text{oct.}}$ (TABLE I), f_i AND π_i FOR A CH_2 GROUP AND SOME SUBSTITUENTS IN AROMATIC MOLECULES

Benzene fragment	C_6H_5	C_6H_4	C_6H_3	C_6H_2	C_6H	C_6
$f_{\text{nucl.}}$	1.89	1.69	1.43	1.26	1.08	0.91

Group	*f_i (exp.) ± s*	*$\hat{f}_i$ ± s*	*f_i (ref. 11)*	*π_i (ref. 17)*
CH_2	0.51 ± 0.09	0.56 ± 0.02	0.53	
CH_3	0.80	0.81 ± 0.03	0.70	0.56
CH_3 (adj.)	0.72	0.72 ± 0.02	0.70	0.46
F	0.38	0.46 ± 0.03	0.40	0.14
Cl	0.89 ± 0.04	0.89 ± 0.03	0.92	0.68
Cl (adj.)	0.82 ± 0.04	0.80 ± 0.01	0.92	0.62
Br	1.10	1.03	1.13	0.86
I	1.36		1.45	1.12
$CONH_2$	−1.24 ± 0.01	−1.05 ± 0.15	−1.11	−1.49
NH_2	−0.98 ± 0.05	−0.99 ± 0.07	−0.85	−1.23
OH	−0.41 ± 0.01	−0.78 ± 0.02	−0.43	−0.67
CH_2OH	−0.79	−0.67 ± 0.02	−0.96	−1.03
$NHCOCH_3$	−0.66 ± 0.09	−0.68 ± 0.03	−0.51	−0.97
CHO	−0.44 ± 0.02	−0.35 ± 0.06	−0.38	−0.65
CN	−0.33	−0.26 ± 0.05	−0.21	−0.57
NO_2	−0.05 ± 0.04	−0.19 ± 0.06	−0.08	−0.28
$COCH_3$	−0.23 ± 0.06	−0.09 ± 0.05	−0.14	−0.55
OCH_3	0.19 ± 0.03	0.11 ± 0.03	0.22	−0.02
CO_2CH_3	0.29 ± 0.06	0.30 ± 0.11	0.27	−0.01
$N(CH_3)_2$	0.41 ± 0.01	0.42 ± 0.05	0.39	0.18

water (K_a) analogously, it is expected that

$$\hat{f}_j\,(i\text{–}\emptyset\text{–}j) \equiv \log \hat{P}_{\text{oct.}}\,(i\text{–}\emptyset\text{–}j) - f_{\text{nucl.}} - \hat{f}_i = \hat{\beta}_1 + \hat{\beta}_2\,(-\Delta \mathrm{p}K_a) \qquad (10)$$

where $-\Delta pK_a \equiv \log K_a\,(i\text{–}\emptyset\text{–}j) - \log K_a\,(\text{H–}\emptyset\text{–}j)$. Analogously, f_i (exp.) obtained from $\log P_{\text{oct.}}$ values of halogenated phenols and anilines[32] can be described with β parameters. The results are presented in Table V and give rise to the following comments:

(i) $\hat{\beta}_1 \neq \hat{f}_j\,(\text{H–}\emptyset\text{–}j)$ for *m*- and *p*-chloroanilines and -phenols. These discrepancies do not appear in β_1 values (compare data in Tables IV and V).

(ii) $\hat{\beta}_2$ (and β_2) is positive, *i.e.*, electron-withdrawing substituents decrease the polarity of the NH_2 and the OH group. This may be attributed to a diminished proton acceptor ability of these solutes, which will enlarge $\gamma^{\infty}_{i,\text{water}}$ (eqn. 7).

(iii) The fact that $\hat{\beta}_2 \neq 0$ indicates again that interactions in the interfacial water layer differ from those encountered in the bulk. This phenomenon has been discussed by Lewin[33].

Contributions of crowding and electronic effects largely cancel out in the log $\hat{P}_{\text{oct.}}$ values of chloroanilines, but to a smaller extent in those of the chlorophenols.

TABLE V

VALUES FOR β_1 AND β_2 IN EQN. 10 FOR SOME HALOGENATED ANILINES AND PHENOLS ($\hat{\beta}$ FROM log $\hat{P}_{oct.}$ AND β FROM log $P_{oct.}$)

Solute series	*n*	$\hat{\beta}_1 \pm s$	$\hat{\beta}_2 \pm s$	s_f
m-,*p*-Chloroanilines	4	−0.72 ± 0.09	0.18 ± 0.06	0.07
o-Chloroanilines*	5	−0.83 ± 0.12	0.16 ± 0.04	0.05
m-,*p*-Chlorophenols	5	−0.40 ± 0.06	0.23 ± 0.04	0.05
o-Chlorophenols*	6	−0.62 ± 0.06	0.17 ± 0.02	0.03
		$\beta_1 \pm s$	$\beta_2 \pm s$	s_f
m-,*p*-Halogenated anilines	5	−0.96 ± 0.08	0.30 ± 0.08	0.10
o-Halogenated anilines*	2	−1.27	0.34	
m-,*p*-Halogenated phenols	7	−0.31 ± 0.06	0.21 ± 0.04	0.04

* *o*-,*o*-Substituted solutes are excluded from the regressions.

Finally, it will be examined whether the log $\hat{P}_{oct.}$ ($\varphi = 0$) values of the examined non-planar solute molecules are plausible. As experimental log $P_{oct.}$ data are not available (or uncertain), we have to rely on calculated values.

For *p,p'*-DDT [$(p\text{-ClC}_6\text{H}_4)_2\text{CHCCl}_3$] the π-method yields

$$\begin{aligned}\log P_{oct.} &= 2\pi_{Cl}^{\varnothing} + 2\pi_{\varnothing} + (\pi_{CH_3}^{\varnothing} - 2\pi_H) + \pi_{CCl_3}\\ &= 1.42 + 4.26 + (0.56 - 0.46) + 1.31\\ &= 7.09\end{aligned}$$

in fair agreement with log $\hat{P}_{oct.} = 6.4 \pm 0.3$.

For proclonol [$(p\text{-ClC}_6\text{H}_4)_2\text{C(OH)}$ (cyclo-C_3H_5)]:

$$\begin{aligned}\log P_{oct.} &= 2\pi_{Cl}^{\varnothing} + 2\pi_{\varnothing} + (\pi_{CH_3}^{\varnothing} - 3\pi_H) + \pi_{OH} + (\pi_{cyclo\text{-}C_3H_6} - \pi_H)\\ &= 1.42 + 4.26 + (0.56 - 0.69) - 1.12 + (1.20 - 0.23)\\ &= 5.40\end{aligned}$$

This value is in good agreement with log $\hat{P}_{oct.} = 5.3 \pm 0.1$ and with the estimated value (5.17) from Rekker's *f*-method.

Unfortunately, log $P_{oct.}$ of dieldrin is not readily estimated because of its peri-fused ring structure. Hence, the value 5.32 obtained with Rekker's method (including correction terms for proximity effects[11]) is not certain, although in accord with log $\hat{P}_{oct.} = 5.1 \pm 0.1$. These results suggest that the RP-18 layer is to some extent penetrable (position of the centre of these non-planar molecules in the interfacial monolayer of adsorbed eluent). It is not ruled out that the RP-HPLC technique fails to predict log P values of still more bulky (or flexible) solute molecules correctly.

CONCLUSIONS

Extrapolated log k_0 values of planar non-ionized aromatic solutes on LiChrosorb RP-18, holding in water as eluent, are more accurately correlated with experimental log $P_{oct.}$ data than the commonly applied log k values determined in methanol–water mixtures. However, two separate correlations are required to obtain reliable log $\hat{P}_{oct.}$ estimates: one for lipophilic solutes (methyl- and chlorobenzenes, polycyclic aromatic compounds, chloroanilines and -phenols) and one for polar monosubstituted benzenes.

When *n*-alkylbenzenes and phenol are excluded from the log $P_{oct.}$–log k_0 regressions, the standard error of fit is 0.1. This figure is largely due to experimental errors of log $P_{oct.}$ (and log k_0) data.

Contributions of substituents to log $P_{oct.}$ can be predicted satisfactorily by means of the RP-HPLC technique (exceptions are the CH_2 group and the phenolic OH group). Steric shielding effects of vicinal methyl and chloro groups diminish the hydrophobicity of the solute. Intramolecular electronic effects in *ortho*-, *meta*-, or *para*-halogenated anilines and phenols decrease the polarity of the NH_2 and OH groups in these solute molecules. Neglect of these substituent effects (as in Rekker's *f*-method) can cause erroneous log $P_{oct.}$ estimates.

Whether the RP-HPLC technique also yields reliable log $\hat{P}_{oct.}$ values for non-planar bulky or flexible molecules deserves further investigation.

SYMBOLS

Subscripts (to γ^{∞}, c, n, v^0, x*):*

1	solute
2	water
interface	in the interfacial RP-18–water layer
org.	in the octanol (or *n*-alkane) phase
water	in water

Symbols:

α_1 and α_2	empirical parameters (Table II)
β_1 and β_2	empirical parameters
$\hat{\beta}_1$ and $\hat{\beta}_2$	empirical parameters
γ^{∞}	solute activity coefficient at infinite dilution (standard state: pure liquid solute)
φ	volume fraction of methanol in the eluent
π_i	contribution of group *i* (relative to that of a proton) to log $P_{oct.}$ according to the π-method
A and B	empirical parameters (eqn. 4)
K_a	ionization constant in water
P	solute partition coefficient in the *n*-octanol–water (oct.) or the *n*-alkane–water (alk.) system
$\hat{P}_{oct.}$	$P_{oct.}$ value from the log $P_{oct.}$–log $k_{(0)}$ correlations
V_m	volume of mobile eluent in the column
V_0	volume of the empty column minus the volume of the adsorbent in the column
V_s	volume of adsorbed eluent in the column
a_1 and a_2	empirical parameters (eqn. 8)
b	empirical parameter (eqn. 5)
c	concentration (mole/l)

$f_{\text{nucl.}}$	contribution of benzene fragments to log $P_{\text{oct.}}$ according to Rekker
f_i (exp.)	contribution of group *i* to experimental log $P_{\text{oct.}}$ values
$\hat{f}_i$	contribution of group *i* to log $\hat{P}_{\text{oct.}}$ values
k	chromatographic capacity ratio
k_φ	*k* value holding at φ
k_0	extrapolated *k* value holding at $\varphi = 0$
n_i	number of moles of *i* in the mobile phase
$\bar{n}_i$	number of moles of adsorbed *i*
s_f	standard error of fit
v^0	molar volume
x_i	mole fraction of *i* in the mobile phase
$\bar{x}_i$	mole fraction of *i* in the interfacial RP-18–water layer

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