

Solute–Solvent Interactions in Chemistry and Biology. Part 7. An Analysis of Mobile Phase Effects on High Pressure Liquid Chromatography Capacity Factors and Relationships of the Latter with Octanol–Water Partition Coefficients

(the late) Mortimer J. Kamlet *Advanced Technology and Research Inc., 14900 Sweitzer Lane, Laurel, Maryland 20707, U.S.A.*

Michael H. Abraham*

Department of Chemistry, University of Surrey, Guildford, Surrey GU2 5XH

Peter W. Carr

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, U.S.A.

Ruth M. Doherty

Naval Surface Weapons Center, White Oak Laboratory, Silver Spring, Maryland 20910, U.S.A.

Robert W. Taft

Department of Chemistry, University of California, Irvine, California 92717, U.S.A.

log k' values on a C_{18} stationary phase with 90/10, 75/25, 60/40, 45/55 and 30/70 methanol–water mobile phases are correlated in terms of the generalized linear solvation energy relationship,

$$\log k' = XYZ_o + mV_1/100 + \pi^* + b\beta_m + a\alpha_m$$

where V_1 is the intrinsic (van der Waals) molar volume, and π^* , β_m , and α_m are the solvatochromic parameters that measure solute dipolarity–polarizability, hydrogen-bond acceptor basicity, and hydrogen-bond donor acidity. The correlation equations are combined with the corresponding equation for octanol–water partition coefficients to generate new equations that demonstrate the exact relationships between the various log k' s and log K_{ow} .

Excellent experimental data recently reported by Hafkenschid¹ has allowed us a unique opportunity to demonstrate how the methodology of linear solvation energy relationships (LSERs) can be used to unravel, identify, and evaluate the individual solute–solvent interactions that influence high pressure liquid chromatography (h.p.l.c.) capacity factors. These data also serve to demonstrate the relationships between octanol–water partition coefficients and h.p.l.c. capacity factors, and how these relationships change with changing mobile phase composition. Furthermore, the data for several compounds whose solvatochromic parameters are unknown allow us to show how h.p.l.c. capacity factors can be used to determine new β_m values.

In a series of papers and review articles^{2–4} we have shown that many properties, XYZ, that depend on solute–solvent interactions are well correlated by a generalized LSER of a simple and conceptually explicit form. A cavity term ($mV_1/100$) measures the endoergic process of separating the solvent molecules to provide a suitably sized enclosure for the solute. V_1 is the solute intrinsic (van der Waals) molar volume, computer calculated by the method of Leahy⁵ or Pearlman,⁶ or estimated by surprisingly effective atom or group additivity methods like those of Bondi⁷ or Abraham and McGowan,⁸ or those suggested in our recently published^{9–12} parameter estimation rules. Indeed, there is no significant decrease in the statistical goodness-of-fit, if, as in the present study, estimates by different methods are included in the same correlation. We use a scale of 1/100 for V_1 so that the parameter measuring the cavity term should cover roughly the same range as the other independent variables, and which also makes easier the evaluation of the relative contributions of the various solute–solvent interactions to the XYZ studied.

A dipolarity–polarizability term (π^*) measures the exoergic effects of solute–solvent dipole/dipole and dipole/induced

dipole interactions. The π^* solvatochromic parameter (so named because these parameters were originally determined from solvent shifts of u.v.–visible spectral band maxima) measures the ability of a compound to stabilize or be stabilized by a neighbouring charge or dipole by virtue of non-specific dielectric interactions. For 'select' compounds, non-poly-chlorinated aliphatic compounds with a single dominant bond dipole moment, π^* values are very nearly proportional to molecular dipole moments.

Exoergic hydrogen bonding terms measure the effects of specific association involving the solute as HBA base and the solvent as HBD acid ($b\beta_m$) and/or the solvent as HBA base and the solute as HBD acid ($a\alpha_m$). (HBA = Hydrogen-bond acceptor; HBD = hydrogen-bond donor.) The β_m and α_m solvatochromic parameters measure the ability of a solute to accept or donate a share of a proton in a solute–solvent hydrogen bond. The subscript m indicates that, for compounds that are capable of self association by hydrogen bonding (amphihydrogen bonding compounds), the parameter applies to the non-self-associated 'monomer' solute rather than the self-associated 'oligomer' solvent. For non-amphihydrogen bonding compounds, subject to some modifications in our parameter estimation rules^{9–12} for compounds which are hydrogen-bond acceptors at multiple sites, $\beta_m = \beta$. Accordingly our generalized LFER is given by equation (1).

Measured or reliably estimated solvatochromic parameters have been reported for about 400 compounds,^{9–14} and recently reported^{9–12} parameter estimation rules, which have been tested in more than 50 correlations (r values usually > 0.99), allow accurate estimations for even greater numbers of compounds. Back-calculations, of the type demonstrated in the present paper, will allow determination of many more measured h.p.l.c. capacity factors.

Table 1. Solvatochromic parameters used in the correlations

No.	Solute	$V_1/100$	π^*	β_m	α_m
1	<i>p</i> -Nitrophenol	0.676	1.15	0.32	0.93
2	<i>p</i> -Nitroaniline	0.702	1.25	0.48	0.47
3	Benzene	0.491	0.59	0.10	0
4	Toluene	0.592	0.55	0.11	0
5	Chlorobenzene	0.581	0.71	0.07	0
6	Nitrobenzene	0.631	1.01	0.30	0
7	Phenol	0.536	0.72	0.33	0.61
8	Aniline	0.562	0.73	0.50	0.16
9	Benzoic acid	0.650	0.74	0.40	0.75
10	<i>p</i> -Xylene	0.671	0.51	0.12	0
11	<i>p</i> -Chlorotoluene ^a	0.679	0.67	0.08	0
12	<i>p</i> -Nitrotoluene ^a	0.729	0.97	0.31	0
13	<i>p</i> -Cresol ^a	0.634	0.68	0.34	0.58
14	<i>p</i> -Toluidine ^a	0.660	0.69	0.51	0.14
15	<i>p</i> -Toluic acid ^a	0.748	0.70	0.41	0.73
16	<i>p</i> -Dichlorobenzene	0.671	0.70	0.03	0
17	<i>p</i> -Chloronitrobenzene ^a	0.721	1.01	0.26	0
18	<i>p</i> -Chlorophenol ^a	0.626	0.72	0.23	0.69
19	<i>p</i> -Chloroaniline ^a	0.652	0.73	0.40	0.20
20	<i>p</i> -Chlorobenzoic acid ^a	0.740	0.74	0.36	0.79
21	Mesitylene	0.769	0.47	0.13	0
22	1,2,4,5-Tetramethylbenzene	0.867	0.43	0.15	0
23	Naphthalene ^a	0.753	0.70	0.15	0
24	Phenanthrene ^a	1.015	0.80	0.20	0
25	Anthracene ^a	1.015	0.80	0.20	0
26	Pyrene ^a	1.156	0.90	0.25	0
27	Perylene ^a	1.415	1.00	0.30	0

^a One or more of parameters estimated from parameter estimation rules.⁹⁻¹²

The most important properties that have so far been correlated in terms of equation (1) are aqueous solubility^{9,10,15} and octanol-water partition coefficients.^{12,13,16} For reasons which have been discussed in some detail,^{9,17} and which relate to the process of separating the single solute molecule from the bulk liquid solute, separate aqueous solubility equations are required for aromatic and aliphatic solutes. The $\log S_w$ equations are given by equations (2) and (3), the $\log K_{ow}$ equation by equation (4).

$$XYZ = XYZ_0 + mV_1/100 + s\pi^* + b\beta_m + a\alpha_m \quad (1)$$

The data set leading to equation (2) contained liquid aliphatic non-HB, HBA, and HBD solutes, and the term in $a\alpha_m$ was not statistically significant at the 95% confidence level by Student's *t*-test.⁹ Equation (3) involved liquid and solid aromatic solutes, with the term in $(mp - 25)$ measuring the transformation of the solid solute to the 'supercooled liquid at 25 °C' (following Yalkowsky and Valvani).¹⁸ The term in $s\pi^*$ in equation (3) was not statistically significant at the 95% confidence level.

$$\log S_w(\text{aliphatics}) = 0.05 - 5.85V_1/100 + 1.09\pi^* + 5.23\beta_m \quad (2)$$

$n = 115, r = 0.9944, \text{ s.d.} = 0.153$

$$\log S_w(\text{aromatics}) = 0.53 - 5.51V_1/100 + 3.48\beta_m + 1.59\alpha_m - 0.0110(mp - 25) \quad (3)$$

$n = 97, r = 0.9938, \text{ s.d.} = 0.188$

$$\log K_{ow} = 0.37 + 5.35V_1/100 - 1.04(\pi^* - 0.35\delta) - 3.84\beta_m + 0.10\alpha_m \quad (4)$$

$n = 245, r = 0.9959, \text{ s.d.} = 0.131$

The δ parameter in equation (4) is a 'polarizability correction' parameter, intended to accommodate different dipolarity-polarizability blends in the XYZ studied. Values of δ are 0.0 for

non-polychlorinated aliphatic solutes, 0.5 for polychlorinated aliphatics, and 1.0 for aromatic solutes.

Other properties that have been correlated in terms of equation (1) are: solubilities in and partition among blood and body tissues,^{17,19} solubilities in polymers,²⁰ toxicities to a variety of species, including *Photobacterium phosphoreum*²¹ and the golden orfe fish,²² tadpole narcosis,²³ upper respiratory tract irritation to mice by airborne sensory irritants,²⁴ and mobile phase, stationary phase, and temperature effects on h.p.l.c. capacity factors.²⁵⁻²⁸ The correlation coefficients for the solubility, partition, and h.p.l.c. correlations were usually better than 0.993, and those for the toxicology correlations were usually better than 0.975. Furthermore, in a large proportion of these correlations, the precision was beyond the 'level of exhaustive fit,' a term coined by the chemometricians²⁹ to describe the condition where the standard deviation of the predictional equation compares favourably with the usual reproducibility of the measurement within or between the data sources. Under these circumstances, the predictional equation may often provide a better estimate of the property studied than the measurement (as is almost certainly the case for aqueous solubility and octanol-water partition coefficients of large molecules).

Results and Discussion

The data we have treated are h.p.l.c. capacity factors reported by Hafkenschid.¹ The stationary phase was 5 μm Hypersil ODS (Shandon Southern Instruments); the mobile phases were 90/10, 75/25, 60/40, 45/55, and 30/70 methanol-water compositions. The solvatochromic parameters used in the correlations are assembled in Table 1. Most of these were arrived at using our parameter estimation rules.⁹⁻¹² The data, expressed in terms of $\log k'$, are conveniently available in the original reference. All the data are for aromatic solutes.

The correlation equations are assembled in Table 2. For reasons which will be discussed below, correlations are given for the total data set (27 solutes) for which the solvatochromic parameters are available, and for a data set (20 solutes) from which strong HBD solutes have been excluded. Considering first the results for the total data sets, it may be seen that, as with all of our other h.p.l.c. correlations,²⁵⁻²⁸ statistical measures of goodness-of-fit are excellent, and the leading terms are the opposing cavity terms and the terms measuring hydrogen bonding by the solvent to HBA solutes. Increasing $V_1/100$, which leads to decreasing aqueous solubility, leads to increasing $\log k'$; increasing β_m , which leads to increasing aqueous solubility, leads to decreasing $\log k'$. Lesser terms in π^* and α_m , which also lead to increasing solubility [equations (2) and (3)], also lead to decreasing $\log k'$.

Hafkenschid carried out correlations of his $\log k'$ values with \log octanol-water partition coefficients and found that with the high volume fractions of methanol, statistical measures of goodness-of-fit are poor for the total set, but improve considerably if 'ionizable' solutes are excluded. He attributed this to stationary-phase hydrogen-bonding interactions with the ionizable solutes.

Our 20-solute correlations in Table 2 are for the data set from which strong HBD solutes have been excluded. Accordingly the terms in $a\alpha_m$ have not been included in the correlation equations. Two things may be seen: (a) The statistical measures of goodness-of-fit remain excellent, and (b) there are only minimal changes in the intercepts and the coefficients of the independent variables. On this basis we conclude that the poor $\log k'$ vs. $\log K_{ow}$ correlations do not result from any single specific property of the 'ionizable' solutes, but from basic deficiencies in the $\log K_{ow}/\log k'$ correlations, as will be quantitatively explained below.

Table 2. Correlation equations

$$XYZ = XYZ_0 + mV_1/100 + s\pi^* + b\beta_m + a\alpha_m [+ p(mp - 25)]$$

XYZ	XYZ ₀ (±)	m (±)	s (±)	b (±)	a (±)	p (±)	n ^a	r	s.d.
log k' (90/10)	-0.84 (0.05)	+1.51 (0.05)	-0.48 (0.06)	-1.39 (0.09)	-0.23 (0.04)		27	0.9939	0.051
	-0.81 (0.06)	+1.52 (0.06)	-0.50 (0.08)	-1.54 (0.11)			20	0.9918	0.060
log k' (75/25)	-0.55 (0.05)	+2.01 (0.06)	-0.52 (0.06)	-1.79 (0.09)	-0.21 (0.04)		27	0.9960	0.052
	-0.51 (0.06)	+1.96 (0.07)	-0.58 (0.08)	-1.88 (0.11)			20	0.9947	0.061
log k' (60/40)	-0.31 (0.06)	+2.64 (0.06)	-0.65 (0.07)	-2.15 (0.10)	-0.19 (0.05)		27	0.9969	0.057
	-0.27 (0.07)	+2.65 (0.07)	-0.69 (0.09)	-2.25 (0.12)			20	0.9963	0.065
log k' (45/55)	-0.12 (0.06)	+3.44 (0.07)	-0.78 (0.08)	-2.56 (0.12)	-0.14 (0.05)		27	0.9973	0.066
	-0.10 (0.07)	+3.44 (0.08)	-0.80 (0.10)	-2.66 (0.13)			20	0.9971	0.072
log k' (30/70)	-0.14 (0.07)	+4.36 (0.08)	-0.81 (0.08)	-2.82 (0.13)	(-0.09) ^b (0.05)		27	0.9978	0.071
	-0.13 (0.07)	+4.33 (0.07)	-0.75 (0.09)	-2.96 (0.12)			20	0.9985	0.064
log K _{ow}	0.34 (0.09)	+5.31 (0.10)	-0.62 (0.12)	-4.06 (0.18)	(+0.14) ^b (0.07)		27	0.9972	0.099
log S _w	-0.30 (0.26)	-5.07 (0.37)		+3.85 (0.32)	+1.77 (0.18)	0.0131 (0.0010)	27	0.9961	0.193

^a n = 27 includes the total data set; n = 20 excludes the strong hydrogen-bond donor solutes. ^b Values are not statistically significant at the 95% confidence level by Student's *t*-test.

In addition to acceptable statistical measures of goodness-of-fit, we have recently added another acceptability requirement for our linear solvation energy relationships, that they be 'robust'. A 'robust' correlation equation is one wherein the intercept and the coefficients of the independent variables do not change markedly between data sets. Comparison of the 27- and 20-solvent correlations in Table 2 confirms that the equations are quite 'robust'.

Another comparison, that allows us to evaluate both the 'robustness' and reliability of our correlations, is the following. In an earlier paper,³⁰ Hafkenschied and Tomlinson reported another set of measurements, using the same stationary phase and a mobile phase of 75/25 methanol-water. Our correlation of their data for 31 solutes is given by equation (5).

$$\log k'(75/25) = -0.66 + 2.08V_1/100 - 0.43\pi^* - 1.71\beta_m - 0.24\alpha_m \quad (5)$$

$n = 31, r = 0.9931, \text{s.d.} = 0.058$

It is seen that agreement of equation (5) with the (75/25) correlation in Table 2 is quite good, and that differences of about 0.10 in the coefficients of the independent variables represent the reproducibility we can expect from good experimental data.

Mobile Phase Effects on H.p.l.c. Retention.—We can best understand how h.p.l.c. capacity factors vary with mobile phase composition if we consider the h.p.l.c. response to solute solvatochromic parameters in terms of complementary solvent parameters.³¹ Thus, the solvent property complementary to solute intrinsic molar volume (V_1) is solvent cohesiveness, which is measured by the square of the Hildebrand solubility parameter (δ_H^2). Water is more cohesive ($\delta_H = 23.4$) than methanol ($\delta_H = 14.3$), so that the process of forming the cavity in the solvent becomes increasingly endoergic with increasing

water content. Accordingly, the *m* coefficients in Table 2 grow increasingly positive between 90/10 and 30/70 methanol-water.

The solvent property complementary to solute dipolarity-polarizability (π^*) is solvent dipolarity-polarizability (π^*). Water is more dipolar ($\pi^* = 1.09$) than methanol ($\pi^* = 0.60$). Accordingly the *s* coefficients become increasingly negative on going from 90/10 to 30/70 methanol-water.

The solvent property complementary to solute HBA basicity (β_m) is solvent HBD acidity (α). Water is a stronger HBD acid ($\alpha = 1.17$) than methanol ($\alpha = 0.93$). Accordingly the *b* coefficients become increasingly negative on going from 90/10 to 30/70 methanol-water.

The solvent property complementary to solute HBD acidity (α_m) is solvent HBA basicity (β). Methanol is more basic ($\beta = 0.62$) than water ($\beta = ca. 0.4$). Accordingly the *a* coefficients become increasingly negative on going from 90/10 to 30/70 methanol-water.

Plots of the variation of the *m*, *s*, *b*, and *a* coefficients against mobile phase composition are in the Figure. The plots are non-linear and thus reflect the fact that mixed solvent solvatochromic parameters do not vary linearly with composition. Indeed, the results in Table 2 lead us to marvel at the fact that log *k'* values are considered to vary linearly with mobile phase composition (as has been assumed by many workers who have extrapolated log *k'* values at different mobile phase compositions to arrive at log *k'_w* or log *k'_o* values corresponding to pure water mobile phases).³²

Relationship of H.p.l.c. Capacity Factors and Octanol-Water Partition Coefficients.—There have been literally hundreds of papers in the chromatographic and toxicology literature in which attempts have been made to relate capacity factors to octanol-water partition coefficients. An excellent review by Braumann³² gives 129 references. Generally, statistical measures of goodness-of-fit have been fair to good when total

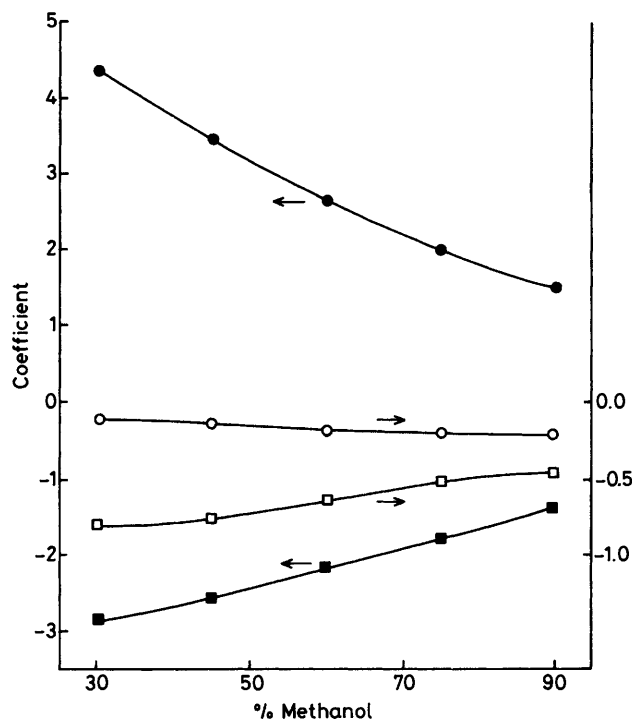


Figure. Plots of the coefficients m , s , b , and a against the mobile phase composition, % methanol. ● m , □ s , ■ b , ○ a . Note the scale change for s and a .

data sets have been correlated in equations of the form of equation (6), and have improved significantly, as in the present case, when subsets of the data were considered.

$$\log k_{ow} = x \log k' + y \quad (6)$$

This indicates another difference between equation (1) and single-parameter equations. The latter are most effective when restricted to compounds having similar functional groups, or when, as in the present instance, certain classes of compounds are excluded. This is equivalent to setting fixed values of the solvatochromic parameters, whereupon the capacity factors depend only on V_1 , or excluding compounds for which a certain parameter (usually α_m) is too large a value. The LSERs, on the other hand, perform best with the greatest diversity of chemical structures. This is because diversity leads to the greatest spread in the solvatochromic parameters, which leads to lesser uncertainties in the coefficients of those parameters.

There are certain interesting subtleties that deserve mention. Values of β_m for primary alcohols, ethers, aldehydes, ketones, and carboxylic acid esters are 0.44 ± 0.04 . Thus, we have seen assembled what seemed to be a diverse set of solutes, but which still gave excellent single-parameter correlations. In the polycyclic aromatic hydrocarbon (PAH) series, values of β_m and π^* show strong ($r > 0.95$) collinearity with V_1 . This accounts for the multifold excellent correlations that have been reported in this series with $\log K_{ow}$ or molecular connectivity. If, however, one affixes HBA and HBD substituents to the PAHs, these correlations will break down.

Although the correlations by equation (6) have been of some use in estimating octanol-water partition coefficients, they convey the unfortunate impression that $\log k'$ and $\log K_{ow}$ show similar responses to the fundamental physicochemical properties of the solutes that govern solubilities. That this is most certainly not the case is shown in the following analysis where we compare the LSERs for the $\log k'$ s at the various mobile

phase compositions with the LSER for octanol-water partition. For this comparison to be most rigorous, we have determined the LSER for octanol-water partition using the data reported by Hafkensheid for the same 27 compounds as led to the $\log k'$ correlations. The correlation, whose uncertainties and measures of goodness-of-fit are detailed in Table 3, is given by equation (7), which is seen to agree quite well with the 245-solute correlation [equation (4)]. The corresponding equation for $\log k'(90/10)$ is given by equation (8).

$$\log K_{ow} = 0.34 + 5.31V_1/100 - 0.62\pi^* - 4.06\beta_m + 0.14\alpha_m \quad (7)$$

$$\log k'(90/10) = -0.84 + 1.51V_1/100 - 0.48\pi^* - 1.39\beta_m - 0.23\alpha_m \quad (8)$$

In the first step of the analysis, we multiply equation (8) by 3.52, the ratio of the cavity terms in equation (7) and (8). This gives:

$$3.52 \log k'(90/10) = -2.95 + 5.31V_1/100 - 1.69\pi^* - 4.80\beta_m - 0.81\alpha_m \quad (9)$$

We next subtract equation (9) from equation (7) and move the term in $\log k'$ to the right hand side of the equation. This gives equation (10), which describes the *exact* relationship between $\log k'(90/10)$ and $\log K_{ow}$.

$$\log K_{ow} = 3.52 \log k'(90/10) + 3.29 + 1.07\pi^* + 0.74\beta_m + 0.95\alpha_m \quad (10)$$

Corresponding equations for the other methanol-water mobile phases, which we shall refer to as 'modified k'/K_{ow} equations', are assembled in Table 3, together with correlation coefficients for the total data set correlations by equation (6), and calculated $\log K_{ow}$ values for PhCl, whose measured $\log K_{ow}$ value is 2.84.

The following may be seen in Table 3. (a) The solvatochromic increments to the $\log k'$ term are all positive and decrease in magnitude between 90/10 and 60/40. At 45/55 and increasingly at 30/70 the β increment changes in sign, and hence oppose the increments in π^* and α_m . This introduces compensating errors at 45/55 and 30/70. (b) As a rough measure, the total effects of the increments are given by the sums of the s , b , and a terms, which are:

Mobile phase	$s + a + b$	r
90/10 methanol-water	2.76	0.9292
75/25	2.37	0.9596
60/40	1.47	0.9748
45/55	0.82	0.9874
30/70	0.03	0.9934

(c) Correspondingly, the correlation coefficients for the total data set correlations by equation (6) increase from 0.9292 at 90/10 to 0.9934 at 30/70. Indeed, r decreases approximately linearly with $(s + b + a)$ with a correlation coefficient of 0.95. (d) The values calculated for PhCl by the modified k'/K_{ow} correlations all agree quite well with the experimental value, with an average deviation of ± 0.06 log unit. (e) Values for PhCl calculated by equation (6) show poor agreement with the experimental value at 90/10, and increasingly better agreement at the lower methanol volume fractions. (f) The excellent correlation coefficient of 0.9934 for the 30/70 correlation by equation (6), the best that we have seen in a $\log k'/\log K_{ow}$ correlation, does not reflect a similarity in solute-solvent interactions, but rather is a result of compensating errors. (g) To whatever extent one still needs to use $\log k'$ values to estimate

Table 3. Relationship between h.p.l.c. capacity factors and octanol-water partition coefficients
$$\log K_{ow} = XYZ_o + k \log k' + s\pi^* + b\beta_m + a\alpha_m$$

Methanol-water	XYZ _o	k	s	b	a	In the correlation of log K _{ow} with log k'			
						Calcd. ^a PhCl	r	s.d.	Calcd. ^{a,b} PhCl
90/10	+3.29	+3.52	+1.07	+0.74	+0.95	2.80	0.9292	0.46	3.08
75/25	+1.79	+2.64	+1.02	+0.66	+0.69	2.85	0.9596	0.35	3.00
60/40	+0.96	+2.01	+0.69	+0.26	+0.52	2.72	0.9748	0.28	2.94
45/55	+0.52	+1.54	+0.58	-0.11	+0.35	2.73	0.9874	0.20	2.86
30/70	+0.51	+1.22	+0.36	-0.63	+0.24	2.76	0.9934	0.14	2.73

^a The experimental log octanol-water partition coefficient of PhCl is given ¹ as 2.84. ^b The calculation is by Hafkenscheid's 'all solutes' correlation.

log K_{ow} values (*vide infra*), we recommend a C₁₈ stationary phase with a 30/70 methanol-water mobile phase.

In addition, we recommend that the h.p.l.c. column and mobile phase be calibrated with compounds of the same general chemical nature as the unknown, whenever log K_{ow} is to be estimated from a log k' vs. log K_{ow} plot or from an extended correlation equation.

We can check on the reasoning that led to the equations in Table 3 by regressing log K_{ow} against a linear combination of log k', π*, β_m, and α_m. The resulting equation should agree within the combined uncertainties with the corresponding equation in Table 3. We have done this with the log k'(90/10) values and obtained equation (11), which does, indeed fulfil the above requirement.

$$\log K_{ow} = (3.31 \pm 0.17) + (3.43 \pm 0.15) \log k'(90/10) + (1.05 \pm 0.24)\pi^* + [0.84 \pm 0.44]\beta_m + (0.85 \pm 0.17)\alpha_m \quad (11)$$

$$n = 27, r = 0.9870, \text{ s.d.} = 0.213$$

The term in square brackets is statistically significant at only the 93% confidence level.

LSER versus H.p.l.c. Compared with LSER plus H.p.l.c.— We have mentioned the term 'level of exhaustive fit', which is the condition where the standard deviation of the correlation equation compares favourably with the usual reproducibility of the measurements between the data sources used in the correlation. Those familiar with the usual reproducibility of octanol-water partition coefficient measurements will recognize that equation (4), the LSER for octanol-water partition, has predictive capability that is well beyond the level of exhaustive fit. Further, equation (4) predicts octanol-water partition coefficients with greater precision and accuracy than any of the log K_{ow} vs. log k' correlations that we have yet encountered.

On this basis, we suggest that, for the hundreds of mono- and di-substituted benzene derivatives, polychlorinated benzenes and biphenyls, and polycyclic aromatic hydrocarbons of environmental interest, for which the solvatochromic parameters are known or can be estimated by our simple parameter estimation rules,⁹⁻¹² LSERs are preferable to h.p.l.c. methods for the prediction of octanol-water partition coefficients.

This is not to say that h.p.l.c. methods can not play a crucial role in the prediction of K_{ow}, and other solubility, partition, and toxicological properties. (a) There are thousands of compounds whose structures are too complex to be included in our parameter estimation rules. For such compounds a correlation, such as that with log k'(30/70), will give a good approximation of log K_{ow}. (b) Let us assume such a complex solute with

multiple hydrogen-bond donor and acceptor sites, aliphatic and aromatic moieties, and intra- as well as inter-molecular hydrogen bonding. There is no way that such a compound will ever be included in our parameter estimation rules. However, a few experiments with well chosen stationary and mobile phases (*i.e.*, large differences in responses to π*, β_m, and α_m) will give a set of log k' values which can be substituted into a number of equations to back-calculate 'effective' Σπ*, Σβ_m, and Σα_m values.

These could be used with already published equations to predict, not only octanol-water partition coefficients and aqueous solubilities, but also other solvent-water partition coefficients, toxicities to a variety of aquatic and mammalian species, equilibrium partition among blood and body tissues and effects thereon of structural modifications, and large numbers of h.p.l.c. capacity factors. The high precision of h.p.l.c. makes it our preferred method for the determination of new solvatochromic parameters.

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