ELSEVIER

Journal of Chromatography A, 752 (1996) 243–249

JOURNAL OF CHROMATOGRAPHY A

Linear free energy relationship analysis of microemulsion electrokinetic chromatographic determination of lipophilicity

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Received 13 February 1996; revised 21 May 1996; accepted 28 May 1996

Abstract

Log k' values for microemulsion electrokinetic chromatography (MEEKC) with a microemulsion of 1.44% (w/w) SDS, 6.49% (w/w) butan-1-ol and 0.82% (w/w) heptane are well correlated through the linear free energy relationship equation,

$$\log k' = -1.133 + 0.279 R_2 - 0.692 \pi_2^H - 0.060 \Sigma\alpha_2^H - 2.805 \Sigma\beta_2^O + 3.048 V_x \quad \text{(i)}$$

$n = 53$, $\rho = 0.9941$, S.D. $= 0.090$, $F = 791$

The solute descriptors are R_2, an excess molar refraction; π_2^H, the dipolarity/polarizability; $\Sigma\alpha_2^H$ and $\Sigma\beta_2^O$, the overall or effective hydrogen-bond acidity and basicity and V_x, the McGowan characteristic volume. The coefficients in Eq. i are almost exactly the same as those in the correlation of water–octanol partition coefficients, as log P_{oct}, confirming that the particular microemulsion system used is an exact model for water–octanol partition. The 53 solutes in Eq. i include phenols and heterocyclic bases (pyrimidines, pyrazines, pyrroles, indoles and furans) with no outliers at all, so that the microemulsion system can be used generally for the determination of solute lipophilicity.

Keywords: Lipophilicity; Octanol–water partition coefficient; Microemulsion electrokinetic chromatography; Linear free energy relationships

1. Introduction

There have been numerous attempts to devise rapid methods that can replace the "shake-flask" procedure for the determination of solute lipophilicity. Following the work of Hansch et al. [1], Hansch and Fujita [2] and Leo et al. [3], lipophilicity is now invariably defined in terms of the water–octanol partition coefficient, as log P_{oct}. Hence, any new method of lipophilicity determination is most reasonably evaluated in terms of correlations with values of log P_{oct}.

Various methods of calculating log P_{oct} have been devised [4] and a number of rapid chromatographic methods have been suggested. The use of reversed-phase high-performance liquid chromatography (RP-

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0021-9673/96/$15.00
PII S0021-9673(96)00518-3

HPLC) is one such method; values of the RP-HPLC capacity factor, k', are obtained for a training set of solutes with known water–octanol partition coefficients, using a given stationary phase and a given mobile phase, and a correlation equation of the type,

$$\log k' = q + o \log P_{oct} \quad (1)$$

is constructed. Then, further measurements of log k' in the same system can be used to estimate log P_{oct} for other solutes. It is now known, however, that the properties of the training set should be well matched to properties of the test set of compounds, especially as regards hydrogen-bond acidity and basicity, otherwise incorrect values of log P_{oct} will be calculated [5]. More recently, reversed-phase thin-layer chromatography (RP-TLC) has been suggested as a quick method for determining lipophilicity [6,7] and Dross et al. [7] have obtained a reasonable correlation of RP-TLC data with values of log P_{oct} for 65 varied solutes,

$$R_{Mw} = -0.151 + 1.008 \log P_{oct} \quad (2)$$

$$n = 65, \rho = 0.9699, \text{S.D.} = 0.294, F = 1000$$

R_{Mw} is the value of R_M extrapolated to 100% water, with $R_M = \log[(1-R_F)/R_F)$; n is the number of solutes, ρ is the correlation coefficient, S.D. is the standard deviation, and F is the F-statistic. Unfortunately, it seems [8] as though lipophilicity determinations through the RP-TLC system of Dross et al. [7] are not reliable for imidazoles, the only class of heterocyclic nitrogen bases studied. This would be a considerable restriction on the use of RP-TLC, since a great many drug molecules include nitrogen heterocycles as substructures.

Herbert and Dorsey [9] have investigated the use of micellar electrokinetic capillary chromatography (MECC), with sodium dodecyl sulfate (SDS) micelles, to estimate values of log P_{oct}. There were difficulties in dealing with solutes that were ionised in the aqueous phase that was buffered at pH 7.0, but for 59 neutral compounds the correlation between log k' and log P_{oct} had ρ = 0.979 (no S.D. value was given). Thus MECC is certainly a useful rapid method for the estimation of log P_{oct} for neutral solutes. Herbert and Dorsey [9] attempted to extend the method to other solutes, but only by constructing equations along the lines of Eq. (1) for a large number of separate families of compounds. A similar system of MECC was used by Smith and Vinjamoori [10], except that the running electrolyte was made up by addition of 10% propan-2-ol to an aqueous buffer (pH 7.4). A rather small training set of eleven solutes was used to construct a calibration equation, Eq. 1, with ρ = 0.9963, and this was then used to estimate further log P_{oct} values. Adlard et al. [11] also used MECC to estimate values of log P_{oct}. A training set of eighteen solutes yielded ρ = 0.988 and 0.990 with aqueous buffers at pH values of 8 and 9, respectively, and using deoxycholate micelles.

In another recent development, Ishihama et al. [12] investigated the use of microemulsion electrokinetic chromatography (MEEKC) for the determination of lipophilicity. They found that a dispersion solution of 1.44% (w/w) SDS, 6.49% (w/w) butan-1-ol and 0.82% (w/w) heptane in 0.1 *M* borate–0.05 *M* phosphate buffer, pH 7.0, gave good separations of test solutes and excellent correlations of retention data with log P_{oct}. This microemulsion system, which is an oil-in-water type [13], was suggested [12] to be a very good model of the water–octanol system. Ishihama et al. [12] defined a migration index scale, *MI*, as

$$MI = d + c \log k' \quad (3)$$

and, for the 53 varied solutes shown in Table 1, established that there was an excellent correlation of *MI* with log P_{oct},

$$\log P_{oct} = -0.854 + 0.518\, MI \quad (4)$$

$$n = 53, \rho = 0.996, \text{S.D.} = 0.094, F = 6083$$

Not only is Eq. (4) better than Eq. (2) and the various MECC equations [9–11], but Eq. (4) covers a wide range of compound types, including nitrogen heterocyclic bases and phenols. Since the MEEKC system of Ishihama et al. [12] seems to be the nearest experimental model to the water–octanol partition system, we felt it very desirable to set out the exact solute factors that influence the MEEKC system. These factors can then quantitatively be compared to those that influence log P_{oct}.

Table 1
Solute descriptors and MEEKC values of *MI* and log *k'*

Solute	log P_{oct}	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^O$	V_x	*MI*	log *k'*
Pyrimidine	−0.40	0.606	1.00	0.00	0.65	0.634	1.00	−1.463
Pyrazine	−0.26	0.629	0.95	0.00	0.61	0.634	1.28	−1.350
4-Methylpyrimidine	0.16	0.595	1.00	0.00	0.63	0.775	1.90	−1.099
2-Methylpyrazine	0.23	0.629	0.90	0.00	0.65	0.775	2.15	−0.998
4,6-Dimethylpyrimidine	0.62	0.580	1.00	0.00	0.65	0.916	2.65	−0.795
2-Ethylpyrazine	0.69	0.616	0.90	0.00	0.66	0.916	3.17	−0.585
Pyrrole	0.75	0.613	0.73	0.41	0.29	0.577	3.03	−0.641
Resorcinol	0.80	0.980	1.00	1.10	0.58	0.834	3.12	−0.605
N-Methylbenzamide	0.86	0.950	1.49	0.40	0.71	1.114	3.67	−0.382
2-CO_2Me-furan	1.01	0.560	1.00	0.00	0.50	0.893	3.74	−0.354
Benzyl alcohol	1.10	0.803	0.87	0.39	0.56	0.916	3.92	−0.281
N-Methylpyrrole	1.21	0.559	0.79	0.00	0.31	0.718	3.95	−0.269
Acetanilide	1.16	0.870	1.40	0.50	0.67	1.113	3.93	−0.277
Quinoxaline	1.32	1.300	1.22	0.00	0.59	1.003	4.21	0.164
4-Methoxyphenol	1.34	0.900	1.17	0.57	0.48	0.975	4.02	−0.241
Furan	1.34	0.369	0.53	0.00	0.13	0.536	4.17	−0.180
4-Nitroaniline	1.39	1.220	1.91	0.42	0.38	0.990	4.37	−0.099
Phenol	1.50	0.805	0.89	0.60	0.30	0.775	4.29	−0.131
2,5-Dimethylpyrrole	1.47	0.639	0.70	0.35	0.44	0.859	4.20	−0.168
Benzaldehyde	1.48	0.820	1.00	0.00	0.39	0.873	4.53	−0.034
2-CO_2Et-furan	1.52	0.560	1.00	0.00	0.50	1.033	4.67	0.022
Benzonitrile	1.56	0.742	1.11	0.00	0.33	0.871	4.51	−0.042
Acetophenone	1.58	0.818	1.01	0.00	0.48	1.014	4.87	0.103
Thiophene	1.81	0.687	0.57	0.00	0.15	0.641	5.23	0.249
2-Methylfuran	1.85	0.372	0.50	0.00	0.14	0.677	5.40	0.318
Nitrobenzene	1.85	0.871	1.11	0.00	0.28	0.891	5.15	0.217
p-Cresol	1.97	0.820	0.87	0.57	0.31	0.916	5.17	0.225
o-Cresol	1.98	0.840	0.86	0.52	0.30	0.916	5.09	0.192
m-Cresol	1.98	0.822	0.88	0.57	0.34	0.916	5.09	0.192
4-Nitroanisole	2.03	0.970	1.29	0.00	0.40	1.090	5.54	0.375
Methylphenylether	2.11	0.708	0.75	0.00	0.29	0.916	5.74	0.456
Methyl benzoate	2.12	0.733	0.85	0.00	0.46	1.073	5.82	0.488
Benzene	2.13	0.610	0.52	0.00	0.14	0.716	5.93	0.532
Indole	2.14	1.200	1.12	0.44	0.31	0.946	5.69	0.435
Ethyl phenyl ketone	2.19	0.804	0.95	0.00	0.51	1.155	5.83	0.492
4-Nitrotoluene	2.42	0.870	1.11	0.00	0.28	1.032	6.03	0.573
4-Chlorophenol	2.39	0.915	1.08	0.67	0.20	0.898	6.26	0.666
2-Ethylfuran	2.40	0.361	0.50	0.00	0.14	0.818	6.63	0.816
4-Ethylphenol	2.50	0.800	0.90	0.55	0.36	1.057	6.36	0.707
2-Methylindole	2.53	1.200	1.05	0.44	0.37	1.087	6.24	0.658
3-Methylindole	2.60	1.200	1.06	0.44	0.35	1.087	6.69	0.840
N-Methylindole	2.64	1.206	1.03	0.00	0.37	1.087	6.68	0.836
n-Propyl phenyl ketone	2.66	0.797	0.95	0.00	0.51	1.296	6.75	0.864
Benzofuran	2.67	0.888	0.83	0.00	0.15	0.905	6.85	0.905
Toluene	2.73	0.601	0.52	0.00	0.14	0.857	7.03	0.978
2-Naphthol	2.78	1.520	1.08	0.61	0.40	1.144	6.77	0.872
Chlorobenzene	2.89	0.718	0.65	0.00	0.07	0.839	7.26	1.071
4-*n*-Propylphenol	3.00	0.793	0.88	0.55	0.37	1.198	7.51	1.172
Ethylbenzene	3.15	0.613	0.51	0.00	0.15	0.998	8.05	1.391
Naphthalene	3.30	1.340	0.92	0.00	0.20	1.085	8.19	1.447
n-Propylbenzene	3.69	0.604	0.50	0.00	0.15	1.139	9.10	1.816
n-Butylbenzene	4.26	0.600	0.51	0.00	0.15	1.280	9.89	2.135
Anthracene	4.45	2.290	1.34	0.00	0.28	1.454	9.90	2.140

2. Methodology

The method is based [14] on the linear free energy relationship (LFER),

$$\log SP = c + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2 + vV_x \quad (5)$$

where SP is a property for a series of solutes in a fixed solvent system. The explanatory variables in Eq. (5) are solute descriptors as follows [14]: R_2 is an excess molar refraction, $\pi 2_i^H$ is the solute dipolarity/polarizability, $\Sigma\alpha_2^H$ and $\Sigma\beta_2$ are the solute overall or effective hydrogen-bond acidity and basicity, and V_x is the McGowan characteristic volume. We note that certain campounds such as anilines, pyridines and some heterocyclic amines have variable basicity [14,15]. For partition of these particular compounds between water and solvents that contain little water at saturation, such as chloroform or cyclohexane, the parameter $\Sigma\beta_2^H$ is used, whereas for partition between water and solvents that contain considerable water at saturation, such as octanol, a basicity parameter $\Sigma\beta_2^O$ is used [14,15]. In the case of all other solutes, the $\Sigma\beta_2^H$ parameter is used in all systems. For partitioning in RP-HPLC, RP-TLC and MEEKC systems, the $\Sigma\beta_2^0$ parameter seems the appropriate one to use for the compounds that have variable basicity.

An important application [16] of Eq. (5) is to log P_{oct} values themselves,

$$\log P_{oct} = 0.088 + 0.562R_2 - 1.054\pi_2^H + 0.034\Sigma\alpha_2^H - 3.460\Sigma\beta_2 + 3.841V_x \quad (6)$$

$n = 613$, $\rho = 0.9974$, S.D. = 0.116, $F = 23162$

The main solute factors that affect log P_{oct} are polarizability and volume, which increase log P_{oct}, and dipolarity and hydrogen-bond basicity, which decrease it. Significantly, hydrogen-bond acidity has no effect on values of log P_{oct}.

The general solvation equation, Eq. (5), has been applied to numerous physico-chemical processes, several of which have been put forward as models for water–octanol partitioning. In Table 2, a summary of the correlation equations in terms of the coefficients obtained is given [8,16–20]; the c-constant is not given as it is not important in terms of characterization of processes.

In order that a particular process should be a good model for log P_{oct}, however, the absolute values of the coefficients need not be the same as those in Eq. (6). It is sufficient that the ratios of the coefficients in the model process are the same (or nearly the same) as the ratios of the coefficients in Eq. (6). The various sets of ratios for the equations in Table 2 are in Table 3. The RP-HPLC and RP-TLC processes are somewhat similar to that of water–octanol partitioning, except that solute hydrogen-bond acidity affects the RP-processes, but not the partitioning.

3. Results and discussion

Ishihama et al. [12] listed 53 compounds for which *MI* values were obtained. Before analysing the *MI* values through Eq. (5), it is useful to check whether or not the 53 compounds form a representative subset of compounds with respect to water–octanol partitioning. We therefore first correlated log

Table 2
Coefficients in the general LFER solvation equation

Process	r	s	a	b	v
Water–octanol, log P, Eq. (6)	0.56	−1.05	0.03	−3.46	3.81
Water–octanol, log P, Eq. (7)	0.47	−0.90	0.03	−3.60	3.83
Water–isobutanol, log P	0.48	−0.64	−0.05	−2.28	2.76
Water–pentanol, log P	0.58	−0.79	0.02	−2.84	3.25
Water–alkane, log P	0.65	−1.66	−3.52	−4.82	4.28
Water–SDS, log P	0.54	−0.40	−0.13	−1.58	2.79
RP-HPLC[a], log k'	0.19	−0.51	−0.44	−1.62	1.78
RP-TLC[b], R_{Mw}	0.24	−0.66	−0.67	−3.01	3.60
MEEKC, log k'	0.28	−0.69	−0.06	−2.80	3.05

[a] For Nucleosil 5-C_{18} phase with water–methanol (50:50, v/v) as the eluent [19].
[b] Using water–methanol eluent [7]; coefficients from [8].

Table 3
Ratios of coefficients in the general LFER solvation equation

Process	r/v	s/v	a/v	b/v	v/v
Water–octanol, log *P*, Eq. (6)	0.15	−0.28	0.01	−0.91	1
Water–octanol, log *P*, Eq. (7)	0.12	−0.23	0.01	−0.94	1
Water–isobutanol, log *P*	0.17	−0.23	−0.02	−0.83	1
Water–pentanol, log *P*	0.18	−0.24	0.00	−0.87	1
Water–alkane, log *P*	0.15	−0.39	−0.82	−1.13	1
Water–SDS, log *P*	0.19	−0.14	−0.05	−0.57	1
RP-HPLC[a], log *k'*	0.13	−0.32	−0.22	−0.90	1
RP-TLC[b], R_{Mw}	0.07	−0.18	−0.18	−0.83	1
MEEKC, log *k'*	0.09	−0.23	−0.02	−0.92	1

[a] Average values for C_{18} phases with water–methanol eluents [20].
[b] [8].

P_{oct} through Eq. (5), using only the 53 compounds in Table 1,

$$\log P_{oct} = 0.053 + 0.474R_2 - 0.896\pi_2^H + 0.035 - \underset{0.049}{} \underset{0.044}{} \underset{0.052}{} \underset{0.034}{}$$
$$0.035\Sigma\alpha_2^H - 3.604\Sigma\beta_2 + 3.832V_x \quad (7)$$
$$\underset{0.034}{} \underset{0.066}{} \underset{0.059}{}$$

$n = 53,\ \rho = 0.9982,\ \text{S.D.} = 0.063,\ F = 2654$

In Eq. (7) we give the S.D. values for the coefficients, under each of the coefficients. There is satisfactory agreement between Eqs. (6,7), with differences between the coefficients being around two S.D. values or less. We can therefore take the 53-compound series as a representative sample of the 613 compounds in Eq. (6).

Application of the LFER equation, Eq. (5), to the 53 *MI* values leads to the regression equation,

$$MI = 1.816 + 0.688R_2 - 1.710\pi_2^H - 0.147\Sigma\alpha_2^H - 6.928\Sigma\beta_2 + 7.529V_x \quad (8)$$

$n = 53,\ \rho = 0.9941,\ \text{S.D.} = 0.223,\ F = 792$

The *MI* values are certainly well correlated with the descriptors in Eq. (5). It is noteworthy that there are no outliers at all. An easier comparison of equations can be made by reverting to the original log *k'* values [12] from which the *MI* values were calculated,

$$\log k' = -1.868 + 0.4048\,MI \quad (9)$$

Use of log *k'* rather than *MI* does not affect any goodness of fit in terms of ρ and *F* in regression equations, but makes it much easier to compare coefficients. Application of Eq. (5) leads to the equation,

$$\log k' = -1.133 + 0.279R_2 - 0.692\pi_2^H - 0.060\Sigma\alpha_2^H - 2.805\Sigma\beta_2 + 3.048V_x \quad (10)$$

$n = 53,\ \rho = 0.9941,\ \text{S.D.} = 0.090,\ F = 792$

The absolute values of the coefficients in Eq. (10) are rather smaller than those in Eq. (7) or Eq. (8) (see Table 2), but the relative values are almost identical (see Table 3). Hence, the solute factors that influence the MEEKC log *k'* values are exactly the same as those that influence log P_{oct}, except that they are somewhat attenuated in the MEEKC system. This can be seen through a regression of log P_{oct} against log *k'*,

$$\log P_{oct} = 1.542 + 1.276 \log k' \quad (11)$$

$n = 53,\ \rho = 0.9956,\ \text{S.D.} = 0.096,\ F = 5738$

The statistics are not quite the same as those given by Ishihama et al. [12] for regression vs. *MI*, because there are slight differences in the log P_{oct} values used. Using the data in Table 1, the latter regression equation is,

$$\log P_{oct} = -0.842 + 0.517\,MI \quad (12)$$

$n = 53,\ \rho = 0.9956,\ \text{S.D.} = 0.096,\ F = 5738$

As shown by Ishihama et al. [12], equations such as Eqs. (11,12) can be used to calculate log P_{oct} to about 0.1 log unit, much better than the RP-TLC

equation, Eq. (2). Furthermore, our analysis shows that the concordance between log P_{oct} and *MI* (or log k') is not due to some fortuitous cancellation of effects, but arises because the solute factors that influence the two processes are exactly the same. It should be noted, however, that although the solutes in Table 1 include a number of nitrogen bases, such as nitrogen heterocycles and 4-nitroaniline, none of these are strong proton bases and no strong proton acids are listed, either. Hence, estimations of log P_{oct} through Eq. (11) or Eq. (12) should be restricted to compounds that are not strong proton acids or strong proton bases, at least until further experiments indicate otherwise. In addition, the MEEKC method is not suitable for any charged species.

We can attempt to relate the coefficients in Eq. (10) to the composition of the separation solution, using the coefficients given in Table 2 for water–phase partitions. However, the scale to be used for the composition of the separation solution is not obvious. This could be set out as volume fraction, mass fraction or mol fraction of the various components. In the present case, there will be very little difference between volume fraction and mass fraction, because the densities of the components are rather similar, and so we use the weight fraction as given originally [12], viz. SDS(0.164), heptane(0.094) and butan-1-ol(0.742). The mol fraction of components in the separation solution will be very different, because of the large molecular mass of SDS and is calculated as SDS(0.050), heptane(0.081) and butanol(0.869). We have coefficients for the water–SDS partition [18], for water–alkane partition [16], in lieu of water–heptane, and for water–pentanol [17] partition as a model for water–butanol. We can then calculate the coefficients for partition between water and a phase consisting of the given mass fraction or mol fraction of SDS, alkane and pentanol. We can do exactly the same just using the mass fraction or mol fraction of heptane and butanol, that is, without taking the SDS component into account at all. The calculated coefficients are given in Table 4; both sets show good agreement with the observed values of the coefficients in Eq. (10). Finally, we calculate the coefficient ratios and again find that both sets are in good agreement with those from Eq. (10) and those from the water–octanol equation as well. We have repeated all of these calculations using isobutanol instead of pentanol, but the results are almost identical. Because the quantity of SDS is so small, it makes little difference to the calculated coefficients if it is included or not. However, recent work by Ishihama [13] has shown that *MI* values do not depend on the SDS concentration and also that other surfactants yield the same *MI* values as SDS does. This strongly suggests that the role of SDS is simply to act as a stabilizer and that our calculation using mol fractions of alkane and pentanol (or isobutanol) is the more relevant. Of course, all of these calculations depend on the composition of the microemulsion being given by the formal concentrations of the components in the separating solution. However, even if the calculations shown in Table 4 are approximate only, the method might still make it possible to design microemulsions that can model other processes, not just the water–octanol system.

Table 4
Calculation of coefficient ratios for water–phase systems

Phase	*r*	*s*	*a*	*b*	*v*
System coefficients					
SDS	0.54	−0.40	−0.13	−1.58	2.80
Alkane	0.65	−1.66	−3.52	−4.82	4.28
Pentanol	0.58	−0.79	0.02	−2.84	3.25
Calculated coefficients, mass fraction scale					
Total[a]	0.58	−0.81	−0.34	−2.82	3.27
Alkane–alcohol[b]	0.59	−0.89	−0.38	−3.06	3.37
Calculated coefficients, mol fraction scale					
Total[a]	0.58	−0.84	−0.28	−2.94	3.31
Alkane–alcohol[b]	0.58	−0.86	−0.28	−3.01	3.34
Ratio of coefficients					
	r/*v*	*s*/*v*	*a*/*v*	*b*/*v*	*v*/*v*
Mass fraction[a]	0.18	−0.25	−0.10	−0.86	1.00
Mass fraction[b]	0.17	−0.26	−0.11	−0.91	1.00
Mol fraction[a]	0.18	−0.25	−0.08	−0.89	1.00
Mol fraction[b]	0.17	−0.26	−0.08	−0.90	1.00
Octanol, Eq. (6)	0.15	−0.28	0.01	−0.91	1.00
MEEKC, Eq. (9)	0.09	−0.23	−0.02	−0.92	1.00

[a] SDS, alkane and alcohol.
[b] Alkane and alcohol only.

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