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# Solute effects on reversed-phase thin-layer chromatography A linear free energy relationship analysis

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**Abstract**

$RM_W$ values determined by Dross et al. using RP-18 precoated TLC plates and aqueous methanol mobile phases have been analysed using our general LFER to give the equation,

$$RM_W = 0.259 + 0.239R_2 - 0.662\pi_2^H - 0.666\Sigma\alpha_2^H - 3.006\Sigma\beta_2^O + 3.603V_X \quad \text{(i)}$$

$n = 76$, $\rho = 0.9891$, S.D. = 0.206, F = 635

The solute descriptors are, $R_2$ an excess molar refraction, $\pi_2^H$ 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 (i) are very similar to those for the correlation of water–octanol partition coefficients, confirming the suggestion that RP-TLC extrapolated RM values can be used as a measure of lipophilicity. However, for a number of solutes, particularly aromatic and heterocyclic nitrogen bases, $RM_W$ values do not correlate either with i, or with log $P_{oct}$, and hence care should be taken in the application of the RP-TLC method to these compounds.

More limited data by Podgorny and Kowalska on RP-18 plates with aqueous tetrahydrofuran (THF) mobile phases suggests that it is not always necessary to use extrapolated $RM_W$ values, but that RM values with 80% water–20% THF can be used to estimate log $P_{oct}$.

*Keywords:* Linear free energy relationships; Lipophilicity; Partition coefficients

## 1. Introduction

The lipophilicity of a compound is an important parameter in medicinal, pharmaceutical and environmental chemistry, and is usually defined as log $P$, where $P$ is a water–solvent partition coefficent. In principle, a number of solvents could be used in this definition, for example, olive oil [1], diethyl ether [2] and oleyl alcohol [3] have all been suggested. However, following the extensive work of Hansch et al. [4,5] and of Leo et al. [6], water–octanol has now been established as the preferred system. A number of methods of calculating water–octanol partition coefficients, as log $P_{oct}$, have been devised [7], but the experimental determination of log $P_{oct}$ still remains the cornerstone of lipophilicity. The tradi-

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tional "shake-flask" procedure is time-consuming, and much effort has been put into quicker methods. Reversed-phase high performance liquid chromatography (RP-HPLC) is such a 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,

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

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 very important, however, that the properties of the training set should be well matched to properties of the test set of compounds, otherwise incorrect values of log $P_{oct}$ will be calculated [8]. This arises because the solute factors that influence log $P_{oct}$ are quantitatively not quite the same [9] as those that influence log $k'$, or extrapolated log $k_w$ values [10,11].

Similar considerations could apply to other processes that might be useful models for water–octanol partitioning. Reversed-phase thin-layer chromatography (RP-TLC) has been suggested as a quick method for lipophilicity determination [12,13], and Dross et al. [13] have obtained a reasonable corelation of RP-TLC data with values of log $P_{oct}$ for 65 varied solutes,

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

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

Here, $RM_W$ refers to RM defined by Eq. (3) and extrapolated to 100% water; $n$ is the number of solutes, $\rho$ is the correlation coefficient, S.D. is the overall standard deviation, and $F$ is the $F$-statistic. Dross et al. [13] used commercial precoated TLC plates (RP-18 $F_{245S}$); solvents were various methanol–buffer mixtures with the latter at pH 7.4 and 0.1 mol $dm^{-3}$ ionic strength.

$$RM = \log((1/R_F) - 1) \quad (3)$$

Dross et al. [13] noted that substituted benzoic acids and especially salicylic acid and imidazoles were significant outliers on Eq. (2), but whether this is due to the RP-TLC system not being an exact model for log $P_{oct}$ is not known. One aim of the present work is to analyse the $RM_W$ values of Dross et al. [13] in order to deduce the solute factors that influence $RM_W$, and to compare them with the corresponding factors in log $P_{oct}$

There have been several analyses of RM values obtained by RP-TLC, but these have invariably been restricted to particular series of compounds, for example a series of nine aromatic alcohols [14], or fourteen phenols [15] or 29 alkanolamines [16]. With these data sets it is not possible to establish general chemical factors that influence RP-TLC. However, the 92 compounds studied by Dross et al. [13] include aromatic hydrocarbons, ketones, nitro compounds, chloro compounds, phenols, acids, amines and imidazoles, and so represent a wide and varied data set. It is this set that we shall analyse.

## 2. Methodology

Our method is based [17] on the general solvation equation,

$$\log SP = c + r \cdot R_2 + s \cdot \pi_2^H + a \cdot \Sigma\alpha_2^H + b \cdot \Sigma\beta_2 + v \cdot V_x \quad (4)$$

Here, SP is a property for a series of solutes in a fixed solvent system; in this work, SP will either be RM for solutes in a given RP-TLC system, or will be $P_{oct}$ values for a series of solutes. Eq. (4) is an example of a linear free energy relationship, or LFER. The explanatory variables in Eq. (4) are [17] solute descriptors as follows: $R_2$ is an excess molar refraction, $\pi_2^H$ 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 in units of $(cm^3 \cdot mol^{-1})/100$. There is a complication in that certain compounds such as anilines, pyridines and some heterocyclic amines have a variable basicity. For partition between water and solvents that contain little water at saturation, such as chloroform or cyclohexane, a general 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. In the present work, it is clear that for RP-HPLC and

RP-TLC, the $\Sigma\beta_2^O$ parameter should be used. Application of Eq. (4) to log $P_{oct}$ values [9] yields,

$$\log P_{oct} = 0.088 + 0.562R_2 - 1.054\pi_2^H + 0.034\Sigma\alpha_2^H - 3.460\Sigma\beta_2 + 3.841V_x \quad (5)$$

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

The coefficients in Eq. (4) can be used to characterize the system in question; thus in Eq. (5) they provide information on the difference in properties of octanol (or wet octanol) and water. The $r$-coefficient shows that solute polarizability favours octanol, and the $s$-coefficient that solute dipolarity/ polarizability favours water; hence octanol is itself more polarizable than water but water is more dipolar than octanol. The $a$-coefficient is a measure of the difference in hydrogen-bond basicity between octanol and water (because acidic solutes interact with basic solvents), and shows that the two solvents have almost exactly the same basicity. The $b$-coefficient indicates that water is much more acidic than octanol. Finally, the large positive $v$-coefficient shows that octanol will interact with lipophilic solutes to a much greater extent than will water.

When Eq. (4) was applied [11] to a set [18,19] of log $k'$ values for 126 varied solutes in a typical RP-HPLC system with 60% methanol–40% water as the mobile phase, we obtained the equation

$$\log k' = -0.322 + 0.252R_2 - 0.651\pi_2^H - 0.429\Sigma\alpha_2^H - 1.529\Sigma\beta_2^O + 1.773V_x \quad (6)$$

$n = 126$, $\rho = 0.992$, S.D. = 0.072, $F = 1408$

Since the ratios of coefficients in Eq. (6) differs from those in Eq. (5), it is clear that the particular RP-HPLC system cannot be an exact model for log $P_{oct}$. This is the basis for the more detailed analysis [8] of the relationship between log $k'$ and log $P_{oct}$.

## 3. Results and discussion

Of the 92 compounds studied by Dross et al. [13], we had, or were able to obtain, all the required descriptors for 83 of them; these are listed in Table 1. Application of Eq. (4) to the 83 $RM_W$ values led to the regression equation,

$$RM_W = -0.256 + 0.264R_2 - 0.312\pi_2^H - 0.551\Sigma\alpha_2^H - 3.396\Sigma\beta_2^O + 3.733V_x \quad (7)$$

$n = 83$, $\rho = 0.9805$, S.D. = 0.290, $F = 383$

Inspection of the regression equation revealed a number of solutes that were considerable outliers. Removal of these solutes gave the equation,

$$RM_W = 0.259 + 0.239R_2 - 0.662\pi_2^H - 0.666\Sigma\alpha_2^H - 3.006\Sigma\beta_2^O + 3.603V_x \quad (8)$$

$n = 76$, $\rho = 0.9891$, sd = 0.206, $F = 635$

which is much better. In Eq. (8), all the descriptors are significant at the 99.8% level at least, and the maximum covariance between the descriptors is $\rho = 0.646$ for $R_2/\pi_2^H$. The outlying solutes, together with the observed $RM_W$ values, and those calculated from Eq. (8) are in Table 2. It is noteworthy that using Eq. (2), Dross et al. [13] found that salicylic acid and a number of imidazoles were extreme outliers. Dross et al. [13] felt that some clarification was needed as to whether RP-TLC or the determination of partition coefficients provided "more precise" data as regards lipophilicity.

The outliers given in Table 2 are thus of considerable interest. Salicylic acid ($pK = 2.97$) is the strongest Bronsted acid in the data set, appreciably stronger than e.g. 4-nitrobenzoic acid ($pK = 3.41$). It is possible that salicylic acid is partially ionised in the mobile phases, especially those near 100% water; this would lead to a faster elution of salicylic acid than calculated, exactly as found (see Table 2). The imidazoles in Table 2 are also eluted faster than calculated, but this cannot be due to ionisation because Dross et al. [13] found that $RM_W$ values for the imidazoles were unaffected by a change in the buffer pH from 7 to 12. Neither can it be due to any "silanophilic effect", because any interaction of a solute with free silanol groups would lead to slower retention and not to faster retention. The only explanation we have rests on the observation of Dross et al. [13] who noted that plots of RM vs. methanol content of the solvent were linear over a much smaller range for imidazoles than for other

Table 1
Solute descriptors and $RM_W$ values with aqueous methanol mobile phase a

| Solute | log $P_{oct}$ | $R_2$ | $\pi_2^H$ | $\Sigma\alpha_2^H$ | $\Sigma\beta_2^O$ | $V_x$ | $RM_W$(obs) |
|---|---|---|---|---|---|---|---|
| Benzoic acid | 1.87 | 0.730 | 0.90 | 0.59 | 0.40 | 0.9320 | 1.649 |
| 2-Methylbenzoic acid | 2.46 | 0.730 | 0.90 | 0.60 | 0.34 | 1.0730 | 1.967 |
| 3-Methylbenzoic acid | 2.37 | 0.730 | 0.90 | 0.59 | 0.38 | 1.0730 | 2.208 |
| 4-Methylbenzoic acid | 2.27 | 0.730 | 0.90 | 0.60 | 0.40 | 1.0730 | 2.213 |
| 3,4-Dimethylbenzoic acid | 2.95‡ | 0.130 | 0.90 | 0.59 | 0.36 | 1.2140 | 2.668 |
| 3-Methoxybenzoic acid | 2.02 | 0.830 | 0.89 | 0.58 | 0.58 | 1.1310 | 1.804 |
| 4-Methoxybenzoic acid | 1.96 | 0.830 | 0.91 | 0.55 | 0.50 | 1.1310 | 1.954 |
| 3-Fluorobenzoic acid | 2.15 | 0.600 | 0.89 | 0.64 | 0.27 | 0.9410 | 1.763 |
| 4-Fluorobenzoic acid | 2.07 | 0.600 | 0.91 | 0.61 | 0.29 | 0.9410 | 1.797 |
| 3-Chlorobenzoic acid | 2.68 | 0.840 | 0.95 | 0.65 | 0.30 | 1.0540 | 2.106 |
| 4-Chlorobenzoic acid | 2.65 | 0.840 | 0.99 | 0.63 | 0.26 | 1.0540 | 2.190 |
| 3-Bromobenzoic acid | 2.86 | 1.000 | 1.04 | 0.65 | 0.27 | 1.1070 | 2.265 |
| 4-Bromobenzoic acid | 2.86 | 1.000 | 1.07 | 0.63 | 0.26 | 1.1070 | 2.368 |
| 3-Iodobenzoic acid | 3.13 | 1.310 | 1.13 | 0.66 | 0.31 | 1.1900 | 2.536 |
| 4-Iodobenzoic acid | 3.02 | 1.310 | 1.15 | 0.64 | 0.30 | 1.1900 | 2.628 |
| 4-Butylbenzoic acid | 3.97 | 0.730 | 0.90 | 0.60 | 0.40 | 1.4950 | 3.940 |
| 4-Pentylbenzoic acid | 4.50 | 0.730 | 0.90 | 0.60 | 0.39 | 1.6360 | 4.429 |
| 4-Heptylbenzoic acid | 5.56 | 0.730 | 0.90 | 0.60 | 0.38 | 1.9180 | 5.440 |
| 4-Hydroxybenzoic acid | 1.58 | 0.930 | 0.92 | 0.87 | 0.53 | 0.9900 | 1.068 |
| 3-Methylphenylacetic acid | 1.95 | 0.730 | 0.97 | 0.60 | 0.63 | 1.2140 | 2.049 |
| 3-Fluorophenylacetic acid | 1.95 | 0.600 | 0.96 | 0.61 | 0.56 | 1.0600 | 1.644 |
| 4-Fluorophenylacetic acid | 1.55 | 0.600 | 0.98 | 0.60 | 0.58 | 1.0900 | 1.649 |
| 4-Chlorophenylacetic acid | 2.12 | 0.840 | 1.06 | 0.61 | 0.55 | 1.1950 | 2.166 |
| 4-Bromophenylacetic acid | 2.31 | 1.000 | 1.14 | 0.61 | 0.56 | 1.2480 | 2.306 |
| 3-Phenylpropanoic acid | 1.84 | 0.730 | 1.20 | 0.60 | 0.58 | 1.2140 | 2.095 |
| 4-Phenylbutanoic acid | 2.42 | 0.730 | 1.20 | 0.55 | 0.58 | 1.3540 | 2.527 |
| Benzophenone | 3.18 | 1.447 | 1.50 | 0.00 | 0.50 | 1.4810 | 3.361 |
| 2,6-Dimethylbenzophenone | 3.65 | 1.450 | 1.50 | 0.00 | 0.69 | 1.7630 | 4.038 |
| 2,2′-Dimethylbenzophenone | 3.87 | 1.450 | 1.50 | 0.00 | 0.63 | 1.7630 | 4.121 |
| 2,6,2′,6′-Tetramethyl‘ | 4.69 | 1.450 | 1.50 | 0.00 | 0.70 | 2.0440 | 4.463 |
| 2,6,2′,6′-Tetraethyl‘ | 6.54 | 1.450 | 1.50 | 0.00 | 0.78 | 2.6080 | 6.131 |
| 4-Bromoacetophenone | 2.45 | 1.100 | 1.17 | 0.00 | 0.45 | 1.1890 | 2.938 |
| 2-Hydroxybenzamide | 1.28 | 1.140 | 1.50 | 0.59 | 0.52 | 1.0320 | 1.380 |
| 4-Hydroxybenzamide | 0.33 | 1.180 | 1.70 | 0.55 | 0.75 | 1.0320 | 0.460 |
| Phenol | 1.50 | 0.805 | 0.89 | 0.60 | 0.30 | 0.7750 | 1.278 |
| 4-Chlorophenol | 2.39 | 0.915 | 1.08 | 0.67 | 0.20 | 0.8980 | 2.031 |
| 4-Bromophenol | 2.59 | 1.080 | 1.17 | 0.67 | 0.20 | 0.9500 | 2.223 |
| 1-Naphthol | 2.92 | 1.520 | 1.05 | 0.60 | 0.37 | 1.1440 | 2.572 |
| 2-Naphthol | 2.78 | 1.520 | 1.08 | 0.61 | 0.40 | 1.1440 | 2.577 |
| 4-Methylbenzyl alcohol | 1.58 | 0.810 | 0.88 | 0.39 | 0.60 | 1.0570 | 1.916 |
| 4-Chlorobenzyl alcohol | 1.96 | 0.911 | 0.96 | 0.42 | 0.46 | 1.0380 | 2.120 |
| Imidazole | −0.08 | 0.710 | 0.85 | 0.42 | 0.50 | 0.5360 | −0.130 |
| 2-Methylimidazole | 0.24 | 0.710 | 0.82 | 0.42 | 0.57 | 0.6770 | 0.014 |
| Benzimidazole | 1.32 | 1.270 | 1.10 | 0.42 | 0.52 | 0.9050 | 0.821 |
| 4-Nitroaniline | 1.39 | 1.220 | 1.91 | 0.42 | 0.38 | 0.9900 | 1.415 |
| 4-Chloroaniline | 1.88 | 1.060 | 1.13 | 0.30 | 0.35 | 0.9390 | 1.692 |
| 4-Bromoaniline | 2.26 | 1.190 | 1.19 | 0.31 | 0.35 | 0.9910 | 1.989 |
| 2-Naphthylamine | 2.40 | 1.670 | 1.28 | 0.22 | 0.55 | 1.1850 | 2.201 |
| 1-Amino-4-bromonaphthylamine | 3.26 | 1.910 | 1.49 | 0.25 | 0.44 | 1.3600 | 3.341 |
| 2-Aminobiphenyl | 2.84 | 1.600 | 1.48 | 0.26 | 0.58 | 1.4240 | 2.988 |
| 2-Aminofluorene | 3.20‡ | 1.930 | 1.38 | 0.21 | 0.60 | 1.4560 | 3.421 |

Table 1. Continued

| Solute | log $P_{oct}$ | $R_2$ | $\pi_2^H$ | $\Sigma\alpha_2^H$ | $\Sigma\beta_2^O$ | $V_x$ | $RM_W$(obs) |
|---|---|---|---|---|---|---|---|
| 2-Amino-7-bromofluorene | 3.97‡ | 2.200 | 1.59 | 0.21 | 0.55 | 1.6310 | 4.110 |
| 1-Aminoanthracene | 3.26‡ | 2.630 | 1.69 | 0.21 | 0.63 | 1.5540 | 3.562 |
| Acridine | 3.40 | 2.356 | 1.32 | 0.00 | 0.58 | 1.4130 | 3.400 |
| 4-Nitrotoluene | 2.42 | 0.870 | 1.11 | 0.00 | 0.28 | 1.0320 | 2.605 |
| 1-Chloro-4-nitrobenzene | 2.39 | 0.980 | 1.18 | 0.00 | 0.20 | 1.0130 | 2.701 |
| 1-Bromo-4-nitrobenzene | 2.55 | 1.140 | 1.27 | 0.00 | 0.27 | 1.0660 | 2.760 |
| 1-Nitronaphthalene | 3.06 | 1.270 | 1.50 | 0.00 | 0.30 | 1.2600 | 3.248 |
| Pentamethylbenzene | 4.56 | 0.850 | 0.66 | 0.00 | 0.21 | 1.4210 | 4.352 |
| Biphenyl | 4.01 | 1.360 | 0.99 | 0.00 | 0.26 | 1.3240 | 3.920 |
| 1,2-Diphenylethane | 4.79 | 1.220 | 1.04 | 0.00 | 0.33 | 1.6060 | 4.676 |
| Naphthalene | 3.30 | 1.340 | 0.92 | 0.00 | 0.20 | 1.0850 | 3.168 |
| 2-Methylnaphthalene | 3.85 | 1.304 | 0.92 | 0.00 | 0.20 | 1.2260 | 3.747 |
| 2,6-Dimethylnaphthalene | 4.31 | 1.329 | 0.91 | 0.00 | 0.20 | 1.3670 | 4.290 |
| 1-Phenylnaphthalene | 5.20 | 1.950 | 1.20 | 0.00 | 0.34 | 1.6930 | 4.529 |
| Anthracene | 4.45 | 2.290 | 1.34 | 0.00 | 0.28 | 1.4540 | 4.228 |
| 2-Methylanthracene | 5.00 | 2.290 | 1.30 | 0.00 | 0.31 | 1.5950 | 4.623 |
| 9-Ethylanthracene | 5.52 | 2.290 | 1.30 | 0.00 | 0.31 | 1.7360 | 5.085 |
| 2-Chloroanthracene | 5.20 | 2.400 | 1.47 | 0.00 | 0.21 | 1.5770 | 4.750 |
| 9-Bromoanthracene | 5.31 | 2.560 | 1.55 | 0.00 | 0.23 | 1.6290 | 4.959 |
| 2-Methylphenanthrene | 5.24 | 2.055 | 1.25 | 0.00 | 0.29 | 1.5950 | 5.158 |
| 1,3,5-Trichlorobenzene | 4.19 | 0.980 | 0.73 | 0.00 | 0.00 | 1.0840 | 4.047 |
| 1,2,4,5-Tetrachlorobenzene | 4.60 | 1.160 | 0.86 | 0.00 | 0.00 | 1.2060 | 4.524 |
| Pentachlorobenzene | 5.18 | 1.330 | 0.96 | 0.00 | 0.00 | 1.3280 | 4.896 |
| Hexachlorobenzene | 5.37 | 1.490 | 0.93 | 0.00 | 0.00 | 1.4510 | 5.360 |
| 1,4-Dibromobenzene | 3.79 | 1.150 | 0.86 | 0.00 | 0.04 | 1.0660 | 3.877 |
| Salicylic acid | 2.26 | 0.890 | 0.70 | 0.72 | 0.41 | 0.9900 | 1.165 |
| 2-Ethylimidazole | 0.77 | 0.710 | 0.82 | 0.42 | 0.57 | 0.8180 | 0.155 |
| 2-Propylimidazole | 1.30 | 0.710 | 0.82 | 0.42 | 0.57 | 0.9590 | 0.309 |
| 2-Phenylimidazole | 1.88 | 1.320 | 1.37 | 0.50 | 0.54 | 1.1440 | 1.170 |
| 2-Methylbenzimidazole | 1.84 | 1.270 | 1.04 | 0.42 | 0.54 | 1.0460 | 0.917 |
| 3-Aminofluoranthene | 4.56‡ | 2.720 | 1.90 | 0.21 | 0.59 | 1.6840 | 4.588 |
| 1-Aminopyrene | 4.01‡ | 3.150 | 2.06 | 0.21 | 0.61 | 1.6840 | 4.661 |

[a] Values of log $P_{oct}$ marked ‡ have been calculated through Eq. (5)

compounds, see Fig. 1 in Ref. [13]. This might lead to a larger error than usual in the calculated $RM_W$ value, although it is hard to see how this could account for the large deviations shown in Table 2. Dross et al. [13] suggested that the deviations in Eq. (2) for salicylic acid and the imidazoles could be due to incorrect values of log $P_{oct}$ that arise through ionisation of solutes that are strong proton acids or strong proton bases. This is quite improbable; the log $P_{oct}$ value of 2.26 for salicylic acid ($pK_a = 2.97$) was determined [20] at a pH of 1.0, where the acid exists in the unionised form, and the log $P_{oct}$ values for the imidazoles were determined [20] at a pH of 9.0, again precluding ionisation. The remaining two outliers in Table 2 are the aromatic primary amines, 3-aminofluoranthene and 1-aminopyrene. The other aromatic amines shown in Table 1, viz the anilines and the six aromatic primary amines that are derivatives of polyaromatic hydrocarbons, all fit Eq. (8) and we can supply no explanation of the unusual behaviour of the particular aromatic primary amines

Table 2
Outlying solutes of Eq. (8)

| Compound | $RM_W$(obs) | $RM_W$(calc) |
|---|---|---|
| Salicylic acid | 1.165 | 1.863 |
| 2-Ethylimidazole | 0.155 | 0.840 |
| 2-Propylimidazole | 0.309 | 1.348 |
| 2-Phenylimidazole | 1.170 | 1.833 |
| 2-Methylbenzimidazole | 0.917 | 1.739 |
| 3-Aminofluoranthene | 4.588 | 3.804 |
| 1-Aminopyrene | 4.661 | 3.741 |

that are outliers. Our analysis suggests that the outliers in Table 2 are not due to any deficiencies in the log $P_{oct}$ determinations, but that there are complicating interactions with certain solutes (e.g. those in Table 2) in RP-TLC. Hence the RP-TLC method for lipophilicity determination is not valid for these solutes.

Inspection of Eq. (8) indicates that the solute effects governing the RP-TLC process are closely related to those that influence log $P_{oct}$ values. How well the RP-TLC process models the partitioning can be found from the ratio of the coefficients in Eq. (5) and Eq. (8) (as shown in Table 3). The quite close correspondences confirm that the RP-TLC system of Dross et al. [13] is indeed a good lipophilicity model. We have more log $P_{oct}$ values to hand than before [13], and for the 83 solutes in Eq. (7) we find,

$$RM_W = -0.162 + 1.004 \log P_{oct} \quad (9)$$

$n = 83$, $\rho = 0.9735$, S.D. = 0.329, $F = 1467$

Once again, salicylic acid and a number of nitrogen bases (2-propylimidazole, 2-phenylimidazole, 2-methylbenzimidazole and 1-aminopyrene) are outliers, and on leaving out these five solutes we obtain the equation,

$$RM_W = -0.040 + 0.974 \log P_{oct} \quad (10)$$

$n = 78$, $\rho = 0.9815$, S.D. = 0.267, $F = 1992$

which is good enough to estimate log $P_{oct}$ values to around 0.3 log units; compare the corresponding Eq. (2) of Dross et al. [13] that includes three of the outliers in Table 2. As noted above, however, the RP-TLC method with aqueous methanol mobile phases may not be valid for aromatic and heterocyclic nitrogen bases.

Dross et al. [13] also investigated the use of aqueous acetonitrile as the mobile phase for 22 compounds (fourteen benzoic acids, five alkyl benzophenones, pentamethylbenzene, biphenyl and naphthalene). The range of descriptors covering these compounds is not large enough to obtain a definitive correlation equation, but for the 22 $RM_W$ (MeCN) values obtained [13] we find,

$$RM_W(MeCN) = 1.092 - 0.036R_2 + 0.321\pi_2^H - 1.293\Sigma\alpha_2^H - 1.273\Sigma\beta_2^O + 1.391V_x \quad (11)$$

$n = 22$, $\rho = 0.9934$, S.D. = 0.107, $F = 241$

Not only does the magnitude of the coefficients in Eq. (11) differ markedly from those in Eq. (8), where aqueous methanol was used as the mobile phase, but the ratios of the coefficients differ also (see Table 3). Comparison of the coefficient ratios in Table 3 indicates that the solute factors governing $RM_W$(MeCN) values are not the same as those that influence log $P_{oct}$. Hence, as noted before [13], $RM_W$(MeCN) values cannot be used as a measure of solute lipophilicity. It is not obvious why this should be so. The $RM_W$ and $RM_W$(MeCN) values are obtained by extrapolation of RM values to zero methanol or zero acetonitrile concentrations, but since they are different, they both cannot refer to the same mobile phase of 100% water and to the same stationary phase. The limiting $RM_W$ and $RM_W$(MeCN) values must still include some influence of the particular organic modifier used.

En route to the $RM_W$ values, Dross et al. [13] determined RM values with various percentage methanol mobile phases, and showed that in plots of RM vs. log $P_{oct}$ the slope became much lower than unity, and the intercept became quite negative as the percentage methanol modifier was increased. Although this shows that the absolute values of RM

Table 3
Ratio of coefficients in the general solvation equation

| Equation | $r/v$ | $s/v$ | $a/v$ | $b/v$ | $v/v$ |
|---|---|---|---|---|---|
| Eq. (5), log $P_{oct}$ | 0.15 | −0.27 | 0.01 | −0.90 | 1 |
| Eq. (8), $RM_W$ | 0.07 | −0.18 | −0.18 | −0.83 | 1 |
| Eq. (11), $RM_W$(MeCN) | −0.02 | 0.23 | −0.90 | −0.92 | 1 |
| Table 5, 80%THF | 0.29 | −0.37 | −0.05 | −1.10 | 1 |

Table 4
Descriptors and RM values with aqueous THF mobile phase[a]

| Solute | $R_2$ | $\pi_2^H$ | $\Sigma\alpha_2^H$ | $\Sigma\beta_2^O$ | $V_x$ | RM(40%) | RM(50%) | RM(60%) | RM(70%) | RM(80%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Acetophenone | 0.818 | 1.01 | 0.00 | 0.48 | 1.0139 | −0.162 | 0.049 | 0.273 | 0.542 | 0.857 |
| Ethylphenylketone | 0.804 | 0.95 | 0.00 | 0.51 | 1.1548 | −0.017 | 0.239 | 0.530 | 0.882 | 1.317 |
| *n*-Propylphenyllketone | 0.797 | 0.95 | 0.00 | 0.51 | 1.2957 | 0.080 | 0.376 | 0.730 | 1.158 | 1.669 |
| *n*-Butylphenylketone | 0.795 | 0.95 | 0.00 | 0.50 | 1.4366 | 0.167 | 0.508 | 0.921 | 1.440 | 2.042 |
| Benzene | 0.610 | 0.52 | 0.00 | 0.14 | 0.7164 | 0.137 | 0.406 | 0.717 | 1.073 | 1.440 |
| Toluene | 0.601 | 0.52 | 0.00 | 0.14 | 0.8573 | 0.226 | 0.530 | 0.891 | 1.327 | 1.817 |
| Aniline | 0.955 | 0.96 | 0.26 | 0.50 | 0.8162 | −0.214 | −0.023 | 0.180 | 0.387 | 0.589 |
| Methylphenyl ether | 0.708 | 0.75 | 0.00 | 0.29 | 0.9160 | 0.049 | 0.310 | 0.619 | 0.989 | 1.392 |
| Benzaldehyde | 0.820 | 1.00 | 0.00 | 0.39 | 0.8730 | −0.142 | 0.064 | 0.294 | 0.552 | 0.837 |
| Benzamide | 0.990 | 1.50 | 0.49 | 0.67 | 0.9728 | −0.638 | −0.432 | −0.347 | −0.187 | 0.045 |
| Benzonitrile | 0.742 | 1.11 | 0.00 | 0.33 | 0.8711 | −0.131 | 0.101 | 0.360 | 0.659 | 0.984 |
| Bromobenzene | 0.882 | 0.73 | 0.00 | 0.09 | 0.8914 | 0.182 | 0.498 | 0.895 | 1.392 | 1.996 |
| Chlorobenzene | 0.718 | 0.65 | 0.00 | 0.07 | 0.8388 | 0.180 | 0.479 | 0.861 | 1.337 | 1.916 |
| N,N-Dimethylbenzamide | 0.950 | 1.40 | 0.98 | 0.98 | 1.2546 | −0.602 | −0.457 | −0.337 | −0.200 | 0.030 |
| N-Ethylaniline | 0.945 | 0.85 | 0.17 | 0.51 | 1.0980 | 0.084 | 0.376 | 0.717 | 1.091 | 1.440 |
| Fluorobenzene | 0.477 | 0.57 | 0.00 | 0.10 | 0.7341 | 0.114 | 0.395 | 0.730 | 1.137 | 1.557 |
| Methyl benzoate | 0.733 | 0.85 | 0.00 | 0.46 | 1.0726 | −0.056 | 0.191 | 0.479 | 0.837 | 1.270 |
| N-Methylbenzamide | 0.950 | 1.49 | 0.40 | 0.71 | 1.1137 | −0.602 | −0.457 | −0.302 | −0.149 | 0.098 |
| Nitrobenzene | 0.871 | 1.11 | 0.00 | 0.28 | 0.8906 | −0.040 | 0.226 | 0.542 | 0.921 | 1.307 |
| Phenol | 0.805 | 0.89 | 0.60 | 0.30 | 0.7751 | −0.207 | 0.042 | 0.315 | 0.627 | 0.949 |

[a] RM values calculated from data in [21]; The percentage water in the mobile phase is given.

Table 5
Coefficients with aqueous THF mobile phases; data from Ref. [21]

| %Aqueous | $c$ | $r$ | $s$ | $a$ | $b$ | $v$ | $\rho$ | S.D. | $F$ |
|---|---|---|---|---|---|---|---|---|---|
| 40 | −0.13 | 0.37 | −0.58 | −0.19 | −0.76 | 0.65 | 0.986 | 0.05 | 99 |
| 50 | −0.01 | 0.42 | −0.65 | −0.14 | −1.03 | 0.90 | 0.985 | 0.06 | 91 |
| 60 | 0.09 | 0.55 | −0.79 | −0.14 | −1.43 | 1.27 | 0.987 | 0.08 | 103 |
| 70 | 0.16 | 0.66 | −0.89 | −0.12 | −2.01 | 1.79 | 0.989 | 0.09 | 124 |
| 80 | 0.13 | 0.73 | −0.91 | −0.12 | −2.71 | 2.46 | 0.994 | 0.08 | 226 |

deviate more and more from log $P_{oct}$, it does not necessarily mean that equations on the lines of Eq. (2) or Eq. (10) cannot be used to estimate log $P_{oct}$ from RM. Dross et al. [13] gave no actual regression equations, so this point cannot be tested in their system. However, one of the few other sets of RP-TLC data that covers a variety of compound types are those of Podgorny and Kowalska [21], who listed $R_F$ values for 21 aromatic compounds with various aqueous tetrahydrofuran (THF) mobile phases, using exactly the same commercial precoated TLC plates (RP-18 $F_{254S}$) as did Dross et al. [13]. We have calculated the corresponding RM values through Eq. (3), and list these RM values and our descriptors in Table 4. For one compound, benzylsulfonamide, no descriptors were available, and so only twenty data points could be used. Although this is not enough for a definite correlation equation, it should suffice to show any general trends in coefficients or their ratios. A summary of the coefficients is given in Table 5, together with the percentage of water (v/v) in the mobile phase, and the goodness-of-fit ($\rho$, S.D. and $F$). The coefficients vary quite regularly with mobile phase composition. As expected, the $s$-, $b$- and $v$-coefficients become numerically larger as the water content increases, and the mobile phase becomes more dipolar, more acidic and less hydrophobic by comparison to the stationary phase.

In order to test the usefulness of RM/log $P_{oct}$ equations for estimation or prediction of log $P_{oct}$ values, it is more instructive to regress log $P_{oct}$ on RM, rather than vice versa. We therefore give in Table 6 a summary of Eq. (12), as applied to the twenty RM values with different percentage THF mobile phases.

$$\log P_{oct} = w + x \cdot \mathrm{RM} \qquad (12)$$

Exactly the same trend of $w$- and $x$-coefficients with the percentage organic modifier is found, as reported [13] for the aqueous methanol modifier system; note that the Dross et al. [13] coefficients refer to RM vs. log $P_{oct}$. However, the key statistical parameter is the sd value in log $P_{oct}$; the smaller this is, the more useful will the correlation be in the prediction of further log $P_{oct}$ values. Although the equations summarised in Table 6 refer to only twenty data points, and Eq. (8) to 76 data points, our analysis of the Podgorny and Kowalska [21] data suggests that it is not always necessary to determine the extrapolated $RM_W$ values. The RM values at 80% water–20% THF mobile phase, for example, are well correlated with log $P_{oct}$, and the ratios of coefficients for this system are quite close to those in Eq. (5) (see Tables 3 and 5).

Our conclusion is that the extrapolated $RM_W$ values with aqueous methanol obtained by Dross et al. [13] are well correlated with log $P_{oct}$, and that the ratio of coefficients in the LFER equations for $RM_W$ and log $P_{oct}$ are very close. The same is also true for the RM values with 80% water–20% THF mobile phases of the limited, but varied, data set of Podgorny and Kowalska [21]. However we feel that great care should be taken if correlations of TLC data with log $P_{oct}$ are used for the prediction of

Table 6
Summary of regression equation, Eq. (12), with aqueous THF mobile phases; data from Ref. [21]

| %Aqueous | $w$ | $x$ | $\rho$ | S.D. | $F$ |
|---|---|---|---|---|---|
| 40 | 2.140 | 2.689 | 0.918 | 0.32 | 96 |
| 50 | 1.530 | 2.313 | 0.935 | 0.29 | 91 |
| 60 | 1.095 | 1.832 | 0.947 | 0.26 | 155 |
| 70 | 0.768 | 1.464 | 0.961 | 0.22 | 217 |
| 80 | 0.479 | 1.229 | 0.981 | 0.16 | 453 |

further log $P_{oct}$ values for amines, especially heterocyclic amines.

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