Solvatochromic analysis of di-*n*-butyl ether/water partition coefficients as compared to other solvent systems

Alessandra Pagliara,[a] Giulia Caron,[a] Giuseppe Lisa,[a] Weizheng Fan,[a] Patrick Gaillard,[a] Pierre-Alain Carrupt,[a] Bernard Testa *[,a] and Michael H. Abraham[b]

[a] *Institut de Chimie Thérapeutique, Section de Pharmacie, Université de Lausanne, CH-1015 Lausanne-Dorigny, Switzerland*
[b] *Chemistry Department, University College London, 20 Gordon St., London, UK WC1H 0AJ*

In order to assess the molecular parameters controlling partition coefficients in the di-*n*-butyl ether/water system, a set of 43 solutes has been selected. Centrifugal partition chromatography and the pH-metric method have been used to measure log P_{dbe} values. Using linear solvation Gibbs-energy relationship analyses, the balance of intermolecular forces governing the di-*n*-butyl ether partition coefficient has been identified, indicating that the partitioning of H-bond acceptors is less important in the di-*n*-butyl ether/water system than in the *n*-octanol/water system. The di-*n*-butyl ether/water system appears to be a valuable substitute to propyleneglycol dipelargolate/water in the detailed characterisation of intermolecular interactions of complex compounds using the 'critical quarter' methodology.

Introduction

To reach its site of action, a drug must cross several biological membranes such as the intestine, the skin and the blood-brain barrier (BBB), depending on the route of administration and on its site of action.[1–3] The lipophilicity of solutes, as expressed by their partition coefficient, has often been considered to be a key parameter to model passive diffusion, as unambiguously demonstrated in numerous quantitative structure–permeability relationship (QSPR) studies.[4]

For complex compounds such as most drugs, the traditional *n*-octanol/water partition coefficient is not always a good indicator of their biodistribution.[5–7] Taking into account the fact that all cell membranes do not possess the same biophysical characteristics, more complex approaches to QSPRs have been proposed. Thus, four types of solvent systems have been found to be sufficient to model the partitioning of solutes into membranes.[8,9] These four solvents form the 'critical quartet' composed of an amphiprotic solvent such as *n*-octanol, an inert one (*n*-alkane), a hydrogen-bond donor such as chloroform, and a hydrogen-bond acceptor such as propyleneglycol dipelargolate (PGDP).[10]

While PGDP appears satisfactory as a hydrogen-bond acceptor solvent, its use is limited by some experimental disadvantages, *e.g.* a marked UV absorption, a great viscosity inducing problems with the separation of phases, and the impossibility of quantifying the solute in the organic phase. Thus, an alternative solvent to PGDP might be of interest, but the choice is limited by such problems as high water content, high volatility, or too long a hydrocarbon chain.[11]

In this study, di-*n*-butyl ether was examined as a putative standard hydrogen-bond acceptor solvent because of its low volatility compared to diethyl ether, its low water content at saturation (0.2 wt% compared to 1.5 wt% for diethyl ether), its chemical stability and its structural isomerism with *n*-octanol. To unravel the structural determinants governing the partitioning of organic solutes in the di-*n*-butyl ether/water system, we used the linear solvation Gibbs-energy relationships approach (LSERs) based on the solvatochromic parameters extensively used by Taft, Kamlet, Abraham and co-workers.[12–14] Using a balanced set of solutes, a solvatochromic equation for di-*n*-butyl ether/water partition coefficients was developed and is discussed in comparison with other biphasic solvent systems.

Experimental

All solutes were obtained from commercial sources (Merck, Darmstadt, Germany; Fluka, Buchs, Switzerland; Janssen, Beerse, Belgium; Aldrich, Steinheim, Germany) in the highest available purity. Analytical grade di-*n*-butyl ether was purchased from Fluka and orthophosphoric acid and its sodium salts for buffer preparations from Merck and Fluka. Deionized water was used throughout.

The partition coefficients of solutes belonging to the training set and test set (Tables 1 and 2) were measured using one of the following techniques: centrifugal partition chromatography (CPC),[15,16] the shake-flask method,[17] the pH-metric two-phase titration,[18,19] or the indirect method of Abraham.[20] The detailed experimental procedures and the instrumental aspects can be found in the references cited above.

Directly determined partition coefficients for the olive oil/water system were taken from the literature[21–24] and from the Medchem database.[25] Indirectly determined values were calculated from the gas/olive oil partition coefficients at 37 °C obtained by a gas-chromatographic method with olive oil as the stationary phase together with gas/water partition coefficients at 37 °C.[26] The partition coefficient in the propyleneglycol dipelargolate (PGDP)/water system were taken from the work of Leahy *et al.*[9,11]

The LSER approach allows us to quantify the intermolecular forces governing the partition of neutral organic solutes using four structural parameters, namely the calculated van der Waals volume (V_{w}) and the so-called solvatochromic parameters (dipolarity/polarizability π^*, hydrogen-bond donor acidity α and hydrogen-bond acceptor basicity β).[12] The linear eqn. (1)

$$\log P = vV_{\mathrm{w}} + p\pi^* + a\alpha + b\beta + c \qquad (1)$$

reflects a differential solvation model constructed with an endergonic factor (*i.e.* the volume term accounting for solvophobic/hydrophobic and dispersive forces) and exergonic factors (*i.e.* the polar interactions between solute and solvents represented by π^*, α and β).

In this equation, v, p, a and b are the regression coefficients which reflect the contribution of each solute parameter to the analysed partition coefficient (log P).

Table 1 Partition coefficients of compounds in the optimal set (training set)

No.	Solute	log P_{dbe}	log P_{oct} ^{a}	log P_{dce} ^{b}	log P_{oil}	log P_{PGDP}
1	Dichloromethane	1.39^{c}	1.15		1.28	
2	1,2-Dichloroethane	1.74^{c}	1.48		1.60	
3	1-Chlorobutane	2.89^{c}	2.64		2.53	
4	Butyl acetate	2.26^{d}	1.82	2.48	1.52	
5	Acetonitrile	−0.50^{d}	−0.34	0.30		
6	*N*,*N*-Dimethylacetamide	−2.04^{d}	−0.77	−0.43		
7	Ethanol	−1.30^{c}	−0.25	−1.00	−1.35	
8	Propan-1-ol	−0.42^{d}	0.28	−0.38	−0.67	
9	2-Methylpropan-2-ol	−0.40^{d}	0.36		−0.64	
10	Formic acid	−1.27^{e}	−0.54	−2.02		
11	Acetic acid	−0.97^{f}	−0.24	−1.50		
12	Butanoic acid	0.14^{f}	0.79	−0.19	−0.28	
13	Pentanoic acid	0.77^{f}	1.39	0.26	0.45	
14	1-Nitrobutane	1.59^{d}	1.47	2.61		
15	Toluene	3.19^{c}	2.69		2.73	2.89
16	Acetophenone	1.61^{d}	1.58	2.38		1.63
17	Nitrobenzene	2.27^{d}	1.85	3.13		2.16
18	Methyl phenyl ether	2.63^{d}	2.11			2.41
19	Ethyl benzoate	3.10^{d}	2.64			2.84
20	Ethyl phenyl ketone	2.43^{d}	2.20			
21	1-Chloro-2-nitrobenzene	2.52^{d}	2.24	3.31		
22	Phenylacetonitrile	1.53^{d}	1.56	3.40		
23	Benzyl methyl ketone	1.35^{d}	1.44	2.49		1.59
24	2-Phenylethyl acetate	2.54^{d}	2.30	3.25		2.57
25	Pyridine	0.20^{d}	0.65	0.72	0.09	0.08
26	1-Naphthoic acid	2.25^{f}	3.10	2.05		
27	2-Naphthylamine	2.32^{d}	2.28	3.08		
28	Aniline	0.71^{d}	0.90	1.45		0.95
29	*N*-Ethylaniline	2.30^{d}	2.16	3.00		
30	2-Chloroaniline	1.98^{d}	1.91	2.54		
31	2-Aminobiphenyl	2.80^{f}	2.84	3.45		
32	4-Nitroaniline	0.74^{d}	1.39	1.70		
33	Phenol	1.01^{d}	1.49	0.61	0.78	1.17
34	3-Chlorophenol	2.35^{d}	2.49	1.22		2.24
35	3-Methylbenzoic acid	2.41^{d}	2.37	1.33		
36	Phenylacetic acid	0.76^{f}	1.46	0.60		0.59
37	3-Chlorophenylacetic acid	1.60^{f}	2.09	1.24		
38	4-Phenylbutanoic acid	1.79^{f}	2.42	1.74		
39	Benzyl alcohol	0.60^{d}	1.08	0.79	0.29	0.61
40	4-Chlorobenzyl alcohol	1.29^{d}	1.96	1.57		
41	4-Nitrophenol	1.19^{d}	1.92	0.79		1.42
42	Trimethylamine	−0.36^{e}	0.22			
43	*N*,*N*-Dimethylbenzylamine	1.81^{f}	1.91	2.46		

[a] *n*-Octanol/water partition coefficients taken from Medchem 95.[25] [b] 1,2-Dichloroethane/water partition coefficient taken from ref. 34. [c] Indirect method.[20] [d] Measured by CPC (neutral form). [e] Taken from Medchem 95.[25] [f] Measured by the pH-metric two-phase titration.

The original solvatochromic parameters (α, β, π^*) were collected from the literature,[12] molecular volumes were expressed by van der Waals volumes (V_{w}) calculated with the standard software MOLSV (QCPE N° 509) and the atomic radii of Gavezzotti.[27] The geometries used to generate van der Waals volumes were optimized with the Tripos force field.[28]

The solvation parameters used in eqns. (9)–(12) were taken from the work of Abraham and co-workers.[13] V_{X} is McGowan's characteristic volume, R_2 the excess molar refraction, $\Sigma\alpha_2^{\mathrm{H}}$ the solute hydrogen-bond acidity and $\Sigma\beta_2^{\mathrm{X}}$ the solute hydrogen-bond basicity.

The complete datasets used in this study are available as Excel files upon request directly to the authors.

The LSER models were generated by multivariate regression or stepwise regression analyses using both the TSAR program[29] and the QSAR module of the Sybyl software[30] running on Silicon Graphics Indy R4400 workstations. The relative contribution of each variable to the LSER model was obtained by standardization.[31]

Results and discussion

Selection of an optimal set of compounds

In order to avoid statistical artifacts which can arise by comparing solvatochromic equations resulting from different and/or biased sets of compounds, an optimal set of 80 compounds, selected by cluster analysis from an original set of 248 solutes, was chosen.[32] Due to some experimental limitations the optimal set had to be reduced to a training set of 43 compounds (Table 1). To ascertain that the reduced optimal set retained the distribution of the explored properties space, the LSER of log P_{oct} was used to test the relevance of the data reduction process.

The optimal set of 80 compounds was characterized by the LSER model of eqn. (2) with a relative contribution of 54% for V_{w}, 37% for β, 9% for π^* and 1% for α calculated by the standardization procedure.[31] The minor or negligible influence of π^* and α of the solutes on their *n*-octanol/water partitioning is well known.[12]

$$\log P_{\mathrm{oct}} = 3.10 \times 10^{-2}(\pm 0.16 \times 10^{-2})V_{\mathrm{w}} - 0.58(\pm 0.15)\pi^* + 0.19(\pm 0.15)\alpha - 4.15(\pm 0.23)\beta + 0.22(\pm 0.19) \quad (2)$$

$$n = 80;\ q^2 = 0.98;\ r^2 = 0.98;\ s = 0.20;\ F = 1070$$

In the above and following equations, 95% confidence limits are given in parentheses, n is the number of compounds, q^2 the cross-validated correlation coefficient,[33] r^2 the squared correlation coefficient, s the standard deviation and F the test of Fischer.

For the final set of 43 compounds, the LSER model gives eqn. (3).

Table 2 Partition coefficients of compounds belonging to the test set*

No.	Solute	log P_{dbe}	log $P_{oct}{}^{a}$	log P_{oil}	log P_{PGDP}
44	1,1,1-Trichloroethane	2.76^{c}	2.49	2.50	
45	Propanone	-0.60^{d}	−0.24	−0.68	
46	Butanone	0.01^{c}	0.29	−0.05	
47	Nitromethane	-0.36^{c}	−0.34	−0.21	
48	*N*,*N*-Dimethylformamide	-2.05^{d}	−1.01		
49	Propanoic acid	-0.43^{e}	0.30	−0.82	
50	Methanol	-1.75^{d}	−0.70	−1.96	
51	Propan-2-ol	-0.90^{d}	0.13	−0.93	
52	Fluorobenzene	3.42^{d}	2.27		2.50
53	Benzaldehyde	1.53^{d}	1.48		1.57
54	Benzonitrile	1.69^{d}	1.56		1.66
55	4-Chloroaniline	1.72^{d}	1.83		
56	*N*,*N*-Dimethylaniline	2.62^{d}	2.28	2.42	2.52
57	1-Naphthylamine	1.88^{d}	2.24		
58	Benzoic acid	1.86^{d}	1.95	0.60	1.15
59	3-Bromobenzoic acid	2.30^{f}	2.37		
60	3-Methylphenol	1.59^{d}	1.96		
61	4-Methylphenol	1.57^{d}	1.94		
62	4-Chlorophenol	2.11^{d}	2.45		2.13
63	3-Bromophenol	2.18^{d}	2.63		
64	4-Bromophenol	2.40^{d}	2.59		
65	1-Naphthol	3.27^{d}	2.91		
66	2-Naphthol	2.97^{d}	2.81		
67	2-Phenylethanol	1.51^{d}	1.36		0.74
68	3-Phenylpropan-1-ol	1.88^{d}	1.88		
69	4-Methylpyridine	0.53^{e}	1.22	0.51	
70	4-Chlorobenzoic acid	2.81^{d}	2.65		

* For footnotes *a*–*f*, see Table 1.

$$\log P_{oct} = 3.30 \times 10^{-2}(\pm 0.20 \times 10^{-2})V_w - 0.66(\pm 0.25)\pi^* + 0.18(\pm 0.19)\alpha - 3.99(\pm 0.49)\beta + 0.07(\pm 0.24) \quad (3)$$

$$n = 43;\ q^2 = 0.97;\ r^2 = 0.98;\ s = 0.15;\ F = 421.5$$

Eqns. (2) and (3) have similar regression coefficients and the relative contribution of variables (57% for V_w, 31% for β, 10% for π^* and 2% for α). Thus, the smaller set of 43 compounds yields a LSER model with the correct balance of intermolecular forces governing *n*-octanol/water partitioning, the broadening of the 95% confidence limits being the main effect of the reduction in the number of compounds. We conclude that the reduced set of 43 compounds retains properties similar to those of the optimal set of 80 compounds selected by cluster analysis, the loss of apparent precision being compensated by the lower number of measurements needed to obtain a reliable answer.

Solvatochromic analysis of log P_{dbe}

The log P_{dbe} values for the training set are reported in Table 1. Values of log *P* in other solvent systems are also reported and will be used below to examine intermolecular forces encoded in partition coefficients.

The linear solvation Gibbs-energy relationships (LSERs) for the di-*n*-butyl ether/water partitioning of the neutral organic compounds in Table 1 is given in eqn. (4).

$$\log P_{dbe} = 4.02 \times 10^{-2}(\pm 0.56 \times 10^{-2})V_w - 0.86(\pm 0.42)\pi^* - 0.80(\pm 0.45)\alpha - 5.89(\pm 1.10)\beta + 0.24(\pm 0.42) \quad (4)$$

$$n = 43;\ q^2 = 0.93;\ r^2 = 0.95;\ s = 0.31;\ F = 175$$

Standardization[31] of eqn. (4) yields the following relative contributions of each variable to the LSER model: 50% for V_w, 8% for π^*, 9% for α and 33% for β.

A test set of 26 compounds (Table 2) was used to validate the predictive power of eqn. (4). For a lipophilicity range from −2.05 to 3.42 log P_{dbe} is well predicted by the model, as shown by eqn. (5) and Fig. 1.

$$\log P_{dbe} = 1.13(\pm 0.07) \log P_{pred} - 0.12(\pm 0.14) \quad (5)$$

$$n = 27;\ q^2 = 0.97;\ r^2 = 0.97;\ s = 0.26;\ F = 821$$

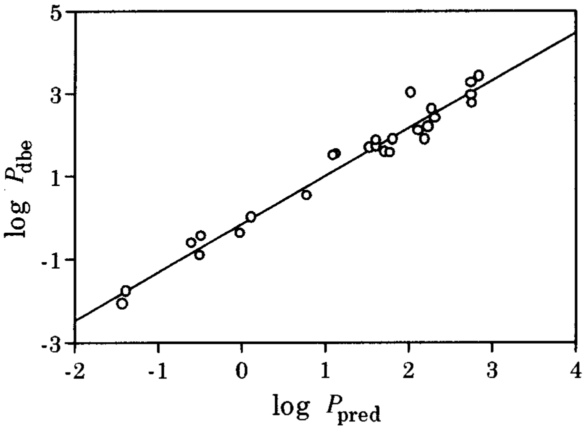

Fig. 1 Prediction of di-*n*-butyl ether/water partition coefficients for the compounds in the test set using eqn. (4). The regression line is represented.

Intermolecular forces encoded in partition coefficients

We have recently demonstrated that 1,2-dichloroethane/water (DCE/water) partition coefficients encode the same contribution from H-bonding as alkane/water partition coefficients.[34] Because DCE has a much better solvent capacity than alkanes towards polar solutes, DCE/water appears to be a promising substitute to alkane/water in the 'critical quarter' as the reference inert solvent/water system. To position similarly the di-*n*-butyl ether/water system relative to the 'critical quartet' without statistical bias coming from different data sets of solutes, one would have to compare solvatochromic equations for log P_{dbe} [eqn. (4)], log P_{oct} [eqn. (3)], log P_{dce} [eqn. (6)] and log P_{chl} obtained from the same training set of 43 compounds.

Table 3 Compilation of regression coefficients (±95% CL). $\log P = vV_w + p\pi^* + a\alpha + b\beta + c$.

Partition coefficients	10^{-2} *v*	*p*	*a*	*b*	Eqn. no.
$\log P_{dbe}$	3.90 (±0.60)	−0.77 (±0.46)	−0.75 (±0.48)	−5.69 (±1.22)	4
$\log P_{oct}$	3.30 (±0.20)	−0.66 (±0.25)	+0.18 (±0.19)	−3.99 (±0.49)	3
$\log P_{dce}$	3.70 (±0.40)	—	−2.89 (±0.46)	−5.32 (±1.22)	6
$\log P_{chl}$	3.50 (±0.60)	+0.16 (±0.82)	−3.20 (±0.82)	−2.87 (±0.28)	7

$$\log P_{dce} = 3.70 \times 10^{-2}(\pm 0.40 \times 10^{-2})V_w - 2.89(\pm 0.46)\alpha - 5.32(\pm 1.22)\beta + 0.50(\pm 0.60) \quad (6)$$

$$n = 34;\ q^2 = 0.93;\ r^2 = 0.94;\ s = 0.37;\ F = 161$$

For 1,2-dichloroethane, the decrease in the number of solutes did not affect the statistical quality of eqn. (6). However, the low number of compounds of the training set measured in chloroform/water did not allow a statistically significant equation. Thus, the previously published set of solutes[35] was used to derive eqn. (7).

$$\log P_{chl} = 3.50 \times 10^{-2}(\pm 0.60 \times 10^{-2})V_w - 3.20(\pm 0.82)\alpha - 2.87(\pm 0.28)\beta + 0.16(\pm 0.82) \quad (7)$$

$$n = 60;\ q^2 = 0.94;\ r^2 = 0.95;\ s = 0.29;\ F = 369$$

The regression coefficients are summarized in Table 3. The regression coefficient for V_w is very similar for the four solvent systems. The coefficients for the polarizability term π^* are also similar and very small.

Moreover, the similarity of coefficients for the α term between chloroform/water and 1,2-dichloroethane/water indicates a similar partitioning of H-bond donors solutes. In contrast, the partitioning of H-bond acceptors into the organic phase is enhanced in chloroform/water with respect to di-*n*-butyl ether/water (smaller coefficients for the β term), a behaviour resulting from the pure H-bond donor characteristics of chloroform.

The di-*n*-butyl ether/water system is comparable to DCE/water (and, seemingly, also chloroform/water) for the partitioning of H-bond acceptors (comparable coefficients for the β term). In contrast, the di-*n*-butyl ether/water system favours the partitioning of H-bond donors in the organic phase (smaller coefficient for the α term). The pure H-bond acceptor characteristics of di-*n*-butyl ether is responsible for this difference.

Finally, the *n*-octanol/water system favours the partitioning of both H-bond donors and acceptors in the organic phase with respect to the 1,2-dichloroethane/water system (smaller coefficients for both the α and the β terms) as a result of the dual nature (H-bond donor and H-bond acceptor) of the wet *n*-octanol.[35]

These results can be compared to analyses of the 'critical quartet',[10] although they were obtained with another set of compounds and two other biphasic systems ($\log P_{dbe}$ and $\log P_{dce}$). They confirm that the intermolecular forces governing the partitioning in di-*n*-butyl ether/water are similar to those governing the partitioning in PGDP/water. Thus, the di-*n*-butyl ether/water system could indeed offer a promising alternative to PGDP/water whose systematic use is rendered cumbersome by experimental problems.

To help understand better the di-*n*-butyl ether/water system, we also note the satisfactory correlation existing between $\log P_{oct}$ and $\log P_{dbe}$ values for all compounds in Tables 1 and 2 [eqn. (8)].

$$\log P_{oct} = 0.73(\pm 0.05)\log P_{oct} + 0.56(\pm 0.08) \quad (8)$$

$$n = 70;\ q^2 = 0.92;\ r^2 = 0.92;\ s = 0.29;\ F = 819$$

However, a plot of $\log P_{oct}$ *versus* $\log P_{bde}$ (Fig. 2) reveals the importance of the H-bonding factor. Indeed, the non-H-bonding solutes and the pure H-bond acceptors have $\log P_{dbe}$ values equal or slightly higher than their $\log P_{oct}$ values. In contrast, the H-bond donors have $\log P_{dbe}$ values smaller than their $\log P_{oct}$ values. The difference in the regression coefficient of the α term in eqn. (3) and eqn. (4) accounts for this behaviour, illustrating that *n*-octanol remains a better acceptor of H-bonds than di-*n*-butyl ether. A similar behaviour was described for PGDP.[10]

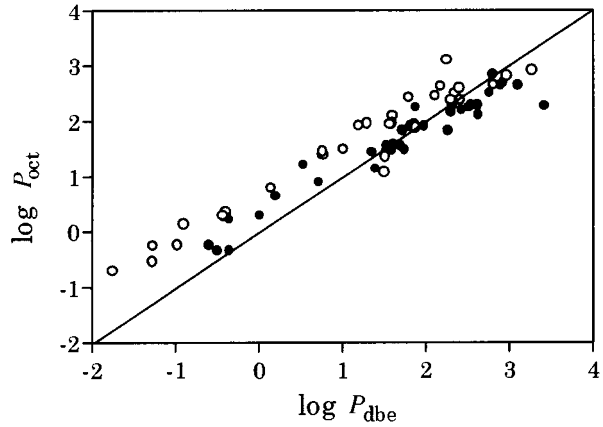

Fig. 2 Partition coefficients measured in *n*-octanol/water ($\log P_{oct}$) *versus* di-*n*-butyl ether/water ($\log P_{dbe}$). (○): solutes with $\alpha > 0$; (●): solutes with $\alpha = 0$. The ideal line of slope 1 and intercept 0 is represented.

The similarity of the intermolecular forces encoded in $\log P_{dbe}$ and $\log P_{PGDP}$ is confirmed by additional LSER analyses using other sets of solutes and other solvation parameters. Taking together all compounds described in Tables 1, 2 and 4 and recently developed solvation parameters,[13] eqn. (9) was obtained for di-*n*-butyl ether.

$$\log P_{dbe} = 4.69(\pm 0.28)V_X + 0.82(\pm 0.26)R_2 - 1.50(\pm 0.24)\Sigma\pi_2^H - 0.83(\pm 0.22)\Sigma\alpha_2^H - 5.09(\pm 0.31)\Sigma\beta_2^O + 0.18(\pm 0.22) \quad (9)$$

$$n = 98;\ q^2 = 0.96;\ r^2 = 0.96;\ s = 0.29;\ F = 525$$

The solvation analysis derived using only the training set described in Table 1 is described by eqn. (10).

$$\log P_{dbe} = 4.67(\pm 0.51)V_X + 0.72(\pm 0.40)R_2 - 1.35(\pm 0.38)\Sigma\pi_2^H - 0.84(\pm 0.29)\Sigma\alpha_2^H - 5.28(\pm 0.55)\Sigma\beta_2^O + 0.20(\pm 0.35) \quad (10)$$

$$n = 43;\ q^2 = 0.96;\ r^2 = 0.97;\ s = 0.23;\ F = 255$$

Comparing eqns. (9) and (10) confirms that the reduction of compounds to an optimal and well-balanced set by cluster analysis does not result in loss of information on intermolecular forces responsible for partitioning.

Additional solutes allow us to derive eqns. (11) and (12).

$$\log P_{PGDP} = 4.18(\pm 0.16)V_X + 0.37(\pm 0.12)R_2 - 0.62(\pm 0.13)\Sigma\pi_2^H - 1.02(\pm 0.12)\Sigma\alpha_2^H - 4.91(\pm 0.14)\Sigma\beta_2^H + 0.13(\pm 0.12) \quad (11)$$

$$n = 100;\ q^2 = 0.99;\ r^2 = 0.99;\ s = 0.14;\ F = 1925$$

Table 4 Partition coefficients of additional compounds used to derive eqns. (9), (11) and (12)*

No.	Solute	log P_{dbe}	log P_{oil}	log P_{PGDP}
71	Hydrogen	0.68^{c}	0.42	
72	Oxygen	0.94^{c}	0.69	
73	Nitrogen	1.12^{c}	0.72	
74	Butane	3.31^{c}	2.94	
75	*n*-Octane	5.95^{c}	5.35	
76	Cyclohexane	3.91^{c}	3.56	
77	1-Chloropentane	3.46^{c}	3.15	
78	Dibutyl ether	3.33^{c}	2.99	
79	1,4-Dioxane	-0.56^{c}	−0.52	
80	Dimethylamine	-0.56^{c}		
81	Butan-2-ol	-0.15^{d}	−0.60	
82	*N*-Methylaniline	1.25^{d}		1.87
83	Benzamide	-1.08^{d}	−0.51	−0.36
84	Acetanilide	-0.22^{d}	0.00	0.40
85	2-Methylphenol	1.79^{d}		
86	3,5-Dimethylphenol	2.41^{d}		
87	2-Chlorophenol	1.82^{d}		
88	4-Iodophenol	2.42^{d}		
89	4-Cyanophenol	0.70^{d}		
90	3-Aminophenol	-0.90^{d}		
91	4-Aminophenol	-1.30^{d}		
92	2-Nitrophenol	2.19^{d}		2.17
93	3-Nitrophenol	1.46^{d}		
94	Hydroquinone	-0.77^{d}		
95	Resorcinol	-0.48^{d}		
96	4-Phenylbutan-1-ol	2.65^{d}		
97	5-Phenylpentan-1-ol	2.57^{d}		
98	Methyl phenyl sulfoxide	-0.86^{d}		−0.41

* For footnotes *c* and *d*, see Table 1.

$$\log P_{\text{Oil}} = 4.17(\pm 0.08)V_{\text{X}} + 0.58(\pm 0.11)R_2 - 0.80(\pm 0.11)\Sigma\pi_2^{\text{H}} - 1.47(\pm 0.11)\Sigma\alpha_2^{\text{H}} - 4.92(\pm 0.12)\Sigma\beta_2^{\text{H}} + 0.01(\pm 0.6) \quad (12)$$

$$n = 174;\ q^2 = 0.99;\ r^2 = 0.99;\ s = 0.15;\ F = 5841$$

These solvation analyses reveal that the intermolecular forces responsible for the partitioning are similar for the PGDP/water and olive oil/water systems.

Moreover, eqns. (9) and (11) are quite similar, except for the coefficient of $\Sigma\pi^{\text{H}}_2$ which is less negative in eqn. (11), due to the higher dipolarity of PGDP relative to di-*n*-butyl ether, as expected for an ester compared to an ether.

Conclusions

The greater H-bond acceptor capacity of di-*n*-butyl ether allows it to attract H-bond donating solutes more than does 1,2-dichloroethane, as demonstrated by LSER models. Moreover, these models underline the similarity between partition coefficients in di-*n*-butyl ether/water and in PGDP/water. Thus, a good amount of information on intermolecular forces can be obtained with four solvent systems with good dissolving capabilities, namely *n*-octanol, 1,2-dichloroethane, chloroform and di-*n*-butyl ether.

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References

1 J. W. Wiechers, *Pharmac. Weekblad Sci. Ed.*, 1989, **11**, 185.

2 E. Rechthand, Q. R. Smith and S. I. Rapoport, *Am. J. Physiol.*, 1988, **255**, R317.

3 E. M. Cornford, *Mol. Physiol.*, 1985, **7**, 219.

4 H. van de Waterbeemd and B. Testa, in *Advances in Drug Research*, ed. B. Testa, Academic Press, London, 1987, p. 87.

5 M. S. Roberts, W. J. Pugh, J. Hadgraft and A. C. Watkinson, *Int. J. Pharm.*, 1955, **126**, 219.

6 M. S. Roberts, W. J. Pugh and J. Hadgraft, *Int. J. Pharm.*, 1996, **132**, 23.

7 W. J. Pugh, M. S. Roberts and J. Hadgraft, *Int. J. Pharm.*, 1966, **138**, 149.

8 O. J. M. Bos, M. J. E. Fischer, J. Wilting and L. H. M. Janssen, *Biochim. Biophys. Acta*, 1988, **953**, 37.

9 D. E. Leahy, J. J. Morris, P. J. Taylor and A. R. Wait, *J. Chem. Soc., Perkin Trans. 2*, 1992, 723.

10 D. E. Leahy, J. J. Morris, P. J. Taylor and A. R. Wait, *J. Chem. Soc., Perkin Trans. 2*, 1992, 705.

11 D. E. Leahy, P. J. Taylor and A. R. Wait, *Quant. Struct. -Act. Relat.*, 1989, **8**, 17.

12 M. J. Kamlet, R. M. Doherty, M. H. Abraham, Y. Marcus and R. W. Taft, *J. Phys. Chem.*, 1988, **92**, 5244.

13 M. H. Abraham, *Chem. Soc. Rev.*, 1993, 73.

14 M. H. Abraham and H. S. Chadha, in *Lipophilicity in Drug Action and Toxicology*, eds. V. Pliska, B. Testa and H. van de Waterbeemd, VCH, Weinheim, 1996, p. 311.

15 R. S. Tsai, P. A. Carrupt and B. Testa, in *ACS Symposium Series 593. Modern Contercurrent Chromatography*, eds. W. D. Conway and P. J. Petroski, American Chemical Society, Washington DC, 1995, p. 143.

16 R. S. Tsai, G. Lisa, P. A. Carrupt and B. Testa, in *Lipophilicity in Drug Action and Toxicology*, eds. V. Pliska, B. Testa and H. van de Waterbeemd, VCH, Weinheim, 1996, p. 89.

17 A. K. Mitra and T. J. Mikkelson, *J. Pharm. Sci.*, 1988, **77**, 771.

18 A. Avdeef, *Quant. Struct. -Act. Relat.*, 1992, **11**, 510.

19 A. Avdeef, *J. Pharm. Sci.*, 1993, **82**, 183.

20 M. H. Abraham, J. Andonian-Haftvan, J. P. Osei-Owusu, P. Sakellariou, J. S. Urieta, M. C. Lopez and R. Fuchs, *J. Chem. Soc., Perkin Trans. 2*, 1993, 299.

21 N. Bindslev and E. M. Wright, *J. Membrane Biol.*, 1976, **29**, 265.

22 R. Collander and H. Barlund, *Acta Botanica Fennica II*, 1933, **11**, 1.

23 R. Collander, *Physiologia Plantarum*, 1954, **7**, 420.

24 R. Macy, *J. Indust. Hygiene Toxicol.*, 1948, **30**, 140.

25 Medchem95 database. Medchem95. Daylight Chemical Information System, Inc., Irvine, California, 1995.

26 M. H. Abraham, P. L. Grellier and R. A. McGill, *J. Chem. Soc., Perkin Trans. 2*, 1987, 797.

27 A. Gavezzotti, *J. Am. Chem. Soc.*, 1983, **105**, 5220.

28 M. Clark, R. D. Cramer III and N. Van Opdenbosch, *J. Comput. Chem.*, 1989, **10**, 982.

29 Tsar2.4. Oxford Molecular Ltd., Oxford, UK, 1995.

30 SYBYL6.2. Tripos Associates, Inc., St-Louis, Missouri, 1995.

31 H. Mager and A. Barth, *Pharmazie*, 1979, **34**, 557.

32 A. Pagliara, E. Khamis, A. Trinh, P. A. Carrupt, R. S. Tsai and B. Testa, *J. Liq. Chromatogr.*, 1995, **18**, 1721.

33 M. Baroni, G. Costantino, G. Cruciani, D. Riganelli, R. Valigi and S. Clementi, *Quant. Struct. Act. Relat.*, 1993, **12**, 9.

34 G. Steyaert, G. Lisa, P. Gaillard, G. Boss, F. Reymond, H. H. Girault, P. A. Carrupt and B. Testa, *J. Chem. Soc., Faraday Trans.*, 1997, **93**, 401.

35 N. El Tayar, R. S. Tsai, B. Testa, P. A. Carrupt and A. Leo, *J. Pharm. Sci.*, 1991, **80**, 590.

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