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## APPLICABILITY OF GAS-LIQUID CHROMATOGRAPHY IN DETERMINING LIQUID-LIQUID PARTITION DATA

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### SUMMARY

Theoretical and practical possibilities for the applicability of gas-liquid chromatography (GLC) in determining liquid-liquid partition data have been investigated using correlation analysis. Literature data for 9 *s*-triazine, 13 aniline, 26 phenol, 13 pyridine, 9 benzene, 8 barbiturate and 24 O-alkyl-O-arylphenylphosphonothioate derivatives with several partition parameters ( $PP$ ), such as  $\log P$  and thin-layer chromatographic  $R_M$ , and GLC retention parameters ( $RP$ ), such as  $\log V_N$ ,  $\log k'$ ,  $\pi_{GLC}$  and  $I$ , were analysed. Forty-five equations of the forms  $PP = c_1(RP_1 - RP_2) + c_2$  (i.e.,  $PP \approx \Delta RP$ ) and  $PP = c_3 RP_1 - c_4 RP_2 + c_5$  (i.e.,  $PP \approx \Delta' RP$ ), where  $RP_1$  and  $RP_2$  represent GLC retention parameters obtained from stationary phases 1 and 2, respectively, were derived. It was found that the variation in partition parameters can generally be better accounted for by weighted differences,  $\Delta' RP$ , of retention parameters than simple differences,  $\Delta RP$ . The weighted difference,  $\Delta' I$ , of the GLC retention index is proposed for use as a hydrophobicity index, e.g., in studies of quantitative relationships between chemical structure and biological activity. Limitations of applicability are discussed.

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### INTRODUCTION

In studies of quantitative structure-activity relationships (QSAR), hydrophobicity is regarded as one of the most important factors influencing the biological activity of compounds<sup>1,2</sup>. The most widely used hydrophobicity indices are the logarithms of partition coefficients of compounds in the 1-octanol-water system ( $\log P_{o/w}$  or simply  $\log P$ ) and the  $\pi$  substituent constant derived from it<sup>2</sup>. A simple and rapid method for determining  $\log P$  is, therefore, of great importance.

The traditional shake-flask method is being increasingly replaced by chromatographic methods. Their advantages are that they are simple, rapid and less tedious, require little material, impurities generally do not affect the measurements, there is no

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need for specific quantitative analysis of the compounds and hydrophobic indices of molecules with very low or high  $\log P$  values can also be accurately determined.

Thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC) have already been successfully used<sup>3,4</sup> to determine partition data for QSAR studies. Gas-liquid chromatography (GLC) also has the general advantages of chromatographic methods and in certain instances it may be preferred to the other two<sup>7</sup> (e.g., when detection problems arise in TLC or HPLC, when volatile compounds are to be analysed or when retention data from different laboratories are to be compared).

According to Kaliszan's<sup>5</sup> recent review, GLC retention data are not related to the hydrophobic properties of the solute, because during the retention Van der Waals and polar forces are more significant than hydrophobic interactions. The lack of correlation has been shown by Steurbaut *et al.*<sup>6</sup> and Rittich and Dubský<sup>7</sup>. On the other hand, Sheehan and Langer<sup>8</sup> and Boček<sup>9</sup> have reported methods for obtaining liquid-liquid partition data by GLC. However, the aim of these methods is the precise measurement of true partition coefficients, which considerably limits their applicability. For example, Boček's method<sup>9</sup> is suitable only for highly volatile solutes and is complicated owing to the inevitability of adsorption processes, because water is applied as the stationary phase in order to obtain oleyl alcohol-water partition coefficients.

In this paper we attempt to elucidate the theoretical and practical possibilities for the applicability of GLC in determining liquid-liquid partition data. The applicability was tested by correlation analysis, GLC retention data being correlated with liquid-liquid partition data for a wide range of compounds, taken from the literature.

#### THEORETICAL

Consider the partition processes of the same solute in two different gas-liquid systems, and define the respective equilibrium constants,  $K_1$  and  $K_2$ , as

$$K_1 = \frac{c_{l1}}{c_{g1}} \quad (1a)$$

$$K_2 = \frac{c_{l2}}{c_{g2}} \quad (1b)$$

where the  $c_l$  and  $c_g$  terms represent the concentrations of the solute in the liquid and gas phases, respectively. If  $K_1$  and  $K_2$  are independent of the solute concentrations and both relate to the same temperature, then the liquid-liquid partition coefficient,  $P_{1/2}$ , for the solute can be obtained as

$$P_{1/2} = \frac{K_1}{K_2} \quad (2)$$

where the subscripts indicate the liquid phases.

Equilibrium constants,  $K$ , can be related to GLC retention data. If solute retention in GLC is governed only by a partition mechanism (*i.e.*, liquid interfacial

and solid support adsorption can be excluded), the relationship takes the well known form<sup>10</sup>

$$K = \frac{V_N}{V_L} \quad (3)$$

where  $V_N$  is net retention volume of the solute and  $V_L$  is volume of the stationary phase. Under constant gas chromatographic conditions, retention can be expressed by several terms, each being related to  $V_N$  as in eqn. 4a-d.

$$t_R = a V_N \quad (4a)$$

$$k' = b V_N \quad (4b)$$

$$\pi_{\text{GLC}} = \log \left( \frac{V_{N,X}}{V_{N,H}} \right) \quad (4c)$$

$$I = c \log V_N + d \quad (4d)$$

where  $t_R$  is net retention time,  $k'$  is capacity factor<sup>11</sup>,  $\pi_{\text{GLC}}$  is a substituent constant<sup>12</sup> analogous to the Hansch  $\pi$  parameter<sup>13</sup>,  $V_{N,X}$  and  $V_{N,H}$  are net retention volumes of a substituted and the unsubstituted compounds in a congeneric series, respectively,  $I$  is Kováts retention index<sup>14</sup> and  $a$ ,  $b$ ,  $c$  and  $d$  are constants depending on the conditions of the gas chromatographic measurements such as flow-rates of the gases and elution volumes of unretained solutes.

From eqns. 2-4 it follows that the partition coefficient,  $P_{1/2}$ , for a given solute can be expressed by the GLC retention data of the solute measured on stationary phases 1 and 2, respectively:

$$\log P_{1/2} = \log \left( \frac{V_{N1}}{V_{N2}} \right) + e \quad (5a)$$

$$\log P_{1/2} = \log \left( \frac{t_{R1}}{t_{R2}} \right) + f \quad (5b)$$

$$\log P_{1/2} = \log \left( \frac{k'_1}{k'_2} \right) + g \quad (5c)$$

$$\log P_{1/2} = \pi_{\text{GLC}1} - \pi_{\text{GLC}2} + h \quad (5d)$$

$$\log P_{1/2} = i I_1 - j I_2 + k \quad (5e)$$

where  $e$ ,  $f$ ,  $g$ ,  $h$ ,  $i$ ,  $j$  and  $k$  are constants. Of course, it is required that GLC retention data relate to the same temperature and be independent of solute concentrations<sup>15,16</sup> (this latter requirement is met in the case of symmetrical GLC peaks).

Eqn. 5a-e can be extended as follows. First, Collander<sup>17</sup> has found an extra-

thermodynamic relationship between the partition coefficients for a given solute set in two different solvent systems:

$$\log P_{3/4} = l \log P_{1/2} + m \quad (6)$$

where  $l$  and  $m$  are constants. Leo<sup>18</sup> has shown the limitations of eqn. 6, stating that a linear relationship between  $\log P$  values can exist only if the primary solvation forces in the two solvent systems, or the solutes being considered, are properly similar. It should be noted that this latter similarity can be assumed in the case of a homologous series of solutes and possibly also in the case of congeneric solutes. Second, it is well known<sup>3,4</sup> that the TLC or HPLC  $R_M$  value is linearly related to  $\log P$ , where  $P$  is the partition coefficient for the solute between the non-polar and polar phases of the chromatographic system. Thus, the relationship between partition parameters ( $PP$ ) ( $\log P$ , TLC  $R_M$  and HPLC  $R_M$ ) and GLC retention parameters ( $RP$ ) ( $\log V_N$ ,  $\log t_R$ ,  $\log k'$  and  $\pi_{GLC}$ ) can be written as

$$PP_{3/4} = c_1(RP_1 - RP_2) + c_2 \quad (7a)$$

(i.e.,  $PP \approx \Delta RP$ ), whereas with  $l$  as the GLC retention parameter it takes the form

$$PP_{3/4} = c_3 RP_1 - c_4 RP_2 + c_5 \quad (7b)$$

(i.e.,  $PP \approx \Delta' RP$ ), where  $c_1$ ,  $c_2$ ,  $c_3$ ,  $c_4$  and  $c_5$  are constants. Eqn. 7a and b show that, under certain conditions, the partition data for a given solute relating to a particular solvent system can be expressed by the GLC retention data of the solute obtained from two commonly used stationary phases.

The validity of eqn. 7a and b can be tested by means of linear regression analysis<sup>19</sup>. For this purpose, suitable compound series should first be selected.

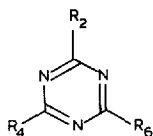
#### STARTING DATA

Seven congeneric series were selected with several partition parameters ( $\log P$  or TLC  $R_M$ ) and at least two GLC retention parameters ( $\log V_N$ ,  $\log k'$ ,  $\pi_{GLC}$  or  $l$ ) available. The selected compounds were of basic, acidic and neutral character, several of them being biologically active. The data for two compound series (O-alkyl-O-arylphenylphosphonothioates<sup>6</sup> and barbiturates<sup>7</sup>) seemed to be particularly suitable for our purposes, because they have already been subjected to a similar but unsuccessful analysis. The partition and retention data of the compounds are given in Tables I–IV.

#### RESULTS AND DISCUSSION

Starting from eqn. 7a and b, linear regression analysis was performed on the data in Tables I–IV, the partition parameters being regarded as dependent variables and the GLC retention parameters as independent variables. The equations so obtained (eqns. 8–30) are given in Table V. Although most of eqns. 8–30 are significant at a level of at least 5%, only one of them can be stated to have excellent statistical

TABLE I  
PARTITION AND GLC RETENTION DATA FOR *s*-TRIAZINES



Compound			Partition data*	GLC retention data**	
$R_2$	$R_4$	$R_6$	$\log P_{cy/w}$	$t_{463^\circ K}^{Carbowax\ 20M}$	$t_{463^\circ K}^{OV-101}$
Cl	$N(C_2H_5)_2$	$NHiC_3H_7$	3.15	2475.1	1763.3
Cl	$N(C_2H_5)_2$	$NHC_2H_5$	2.43	2559.3	1760.5
Cl	$NHiC_3H_7$	$NHiC_3H_7$	1.54	2659.1	1733.1
$SCH_3$	$NHC_2H_5$	$NHC_2H_5$	0.99	2937.1	1878.1
$SCH_3$	$NHCH_3$	$NHiC_3H_7$	0.92	2888.9	1847.9
$SCH_3$	$NHC_2H_5$	$NHiC_3H_7$	1.76	2859.3	1882.5
Cl	$NHC_2H_5$	$NHC_2H_5$	0.21	2833.9	1723.1
$SCH_3$	$NHiC_3H_7$	$NHiC_3H_7$	2.45	2779.6	1887.7
Cl	$NHC_2H_5$	$NHiC_3H_7$	0.81	2747.3	1726.5

\* From ref. 2. Subscript cy/w denotes cyclohexane-water solvent system.

\*\* From ref. 20 ( $P_{cy/w}$  values were available for only nine of the twelve reported compounds).

characteristics (eqn. 8 calculated for nine *s*-triazines; measured and calculated  $PP$  values are compared in Fig. 1a). The reason may be that some of the assumptions made when deriving eqn. 7a and b are not valid. Thus, it appears that the partition coefficients of solutes related to stationary phase pairs are often not correlated with those measured in 1-octanol-water ( $P_{o/w}$ ), cyclohexane-water ( $P_{cy/w}$ ) or chloroform-water ( $P_{ch/w}$ ) systems. Further, it is to be expected that adsorption mechanisms in solute retention can only rarely be neglected.

Nevertheless, several interesting conclusions can be drawn from eqns. 8-30. The excellent quality of eqn. 8 concerning *s*-triazines can be explained as follows. First, for these compounds there seems to exist a Collander-type relationship between the  $P_{cy/w}$  and  $P_{OV-101/Carbowax\ 20M}$  values. Second, a glass capillary column was employed, in which adsorption processes can mostly be neglected. Third, the Kováts retention index, the most suitable retention parameter for comparison of different GLC retentions, was used. At this point, we should mention our experience concerning the relationships between the partition parameters and GLC retention parameters of pyrido[1,2-*a*]pyrimidine derivatives, where great care was taken to avoid adsorp-

Comparison of the equations where  $\log P_{o/w}$ ,  $\log P_{cy/w}$  or  $\log P_{ch/w}$  were used as excellent correlation was obtained<sup>22</sup>.

Comparison of the equations where  $\log P_{o/w}$ ,  $\log P_{cy/w}$  or  $\log P_{ch/w}$  were used as partition parameters offers another interesting conclusion. Table V shows that with anilines, phenols and barbiturates the equations calculated using the latter two partition parameters are significantly better than those calculated using  $\log P_{o/w}$  (compare eqns. 10 and 9, 12 and 11, 20 and 17, and 21 and 18), whereas with benzene derivatives there is no significant difference between the equations (see eqns. 14 and 15). It appears that with solutes acting as hydrogen bond donors, GLC stationary

TABLE II

PARTITION AND GLC RETENTION DATA FOR ANILINE, PHENOL, PYRIDINE AND BENZENE DERIVATIVES

Compound	Partition data*		GLC retention data**	
	Log $P_{o/w}$	Log $P_{cy/w}$	Log $V_{N 479}^{PEG}$	Log $V_{N 479}^{Apiezon}$
Aniline	0.98	0.05	2.017	1.574
Aniline:				
<i>o</i> -CH <sub>3</sub>	1.32	0.61	2.089	1.783
<i>o</i> -Cl	1.92	1.25	2.277	1.902
<i>o</i> -OCH <sub>3</sub>	0.95	0.52	2.292	1.926
<i>o</i> -NO <sub>2</sub>	1.79	-0.70	3.116	2.364
<i>m</i> -CH <sub>3</sub>	1.43	0.58	2.140	1.776
<i>m</i> -Cl	1.90	0.89	2.586	2.007
<i>m</i> -OCH <sub>3</sub>	0.93	-0.13	2.605	2.039
<i>m</i> -NO <sub>2</sub>	1.37	-0.42	3.439	2.467
<i>p</i> -CH <sub>3</sub>	1.41	0.55	2.112	1.766
<i>p</i> -Cl	1.83	0.69	2.574	2.002
<i>p</i> -OCH <sub>3</sub>	0.95	-0.41	2.504	2.006
<i>p</i> -NO <sub>2</sub>	1.39	-1.00	3.862	2.671
Phenol	1.48	-0.81	2.314	1.437
Phenol:				
<i>o</i> -CH <sub>3</sub>	1.95	0.00	2.302	1.644
<i>o</i> -C <sub>2</sub> H <sub>5</sub>	2.47	0.83	2.388	1.805
<i>o</i> -F	1.71	-0.30	2.005	1.292
<i>o</i> -Cl	2.19	0.86	2.115	1.644
<i>o</i> -Br	2.35	1.16	2.285	1.845
<i>o</i> -I	2.65	1.26	2.624	2.112
<i>o</i> -OCH <sub>3</sub>	1.32	0.48	2.164	1.761
<i>o</i> -CN	1.61	-1.70	3.087	1.819
<i>o</i> -NO <sub>2</sub>	1.73	1.45	2.175	1.930
<i>m</i> -CH <sub>3</sub>	2.01	-0.34	2.420	1.684
<i>m</i> -C <sub>2</sub> H <sub>5</sub>	2.40	0.43	2.549	1.844
<i>m</i> -F	1.93	-0.70	2.473	1.460
<i>m</i> -Cl	2.47	0.08	2.887	1.906
<i>m</i> -Br	2.63	-0.52	3.106	2.091
<i>m</i> -I	2.93	-0.10	3.350	2.357
<i>m</i> -NO <sub>2</sub>	2.00	-1.52	3.770	2.341
<i>p</i> -CH <sub>3</sub>	1.92	-0.35	2.418	1.654
<i>p</i> -C <sub>2</sub> H <sub>5</sub>	2.26	0.37	2.542	1.833
<i>p</i> -F	1.77	-1.00	2.439	1.458
<i>p</i> -Cl	2.44	-0.30	2.884	1.883
<i>p</i> -Br	2.59	-0.09	3.097	2.082
<i>p</i> -I	2.91	0.21	3.349	2.344
<i>p</i> -OCH <sub>3</sub>	1.34	-1.08	2.830	1.918
<i>p</i> -CN	1.60	-2.14	3.717	2.206
<i>p</i> -NO <sub>2</sub>	1.91	-1.79	3.984	2.469
Pyridine	0.65	-	1.297	1.115
Pyridine:				
<i>o</i> -CH <sub>3</sub>	1.11	-	1.310	1.265
<i>o</i> -C <sub>2</sub> H <sub>5</sub>	1.69	-	1.399	1.433
<i>o</i> -Cl	1.45	-	1.738	1.523
<i>o</i> -Br	1.42	-	1.956	1.737
<i>o</i> -CN	0.50	-	2.282	1.670
<i>m</i> -CH <sub>3</sub>	1.20	-	1.448	1.366

TABLE II (continued)

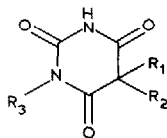
Compound	Partition data*		GLC retention data**	
	Log $P_{o/w}$	Log $P_{cy/w}$	Log $V_{N 479^\circ K}^{PEG}$	Log $V_{N 479^\circ K}^{Apiezon}$
<i>m</i> -Cl	1.43	—	1.534	1.454
<i>m</i> -Br	1.60	—	1.746	1.667
<i>m</i> -CN	0.36	—	2.050	1.571
<i>p</i> -CH <sub>3</sub>	1.22	—	1.457	1.368
<i>p</i> -Cl	1.28	—	1.539	1.441
<i>p</i> -CN	0.46	—	1.964	1.512
Benzene	2.15	2.80	0.913	1.004
Benzene: CH <sub>3</sub>	2.69	3.41	1.064	1.221
C <sub>2</sub> H <sub>5</sub>	3.15	3.68	1.182	1.402
F	2.27	2.85	0.942	0.971
Cl	2.84	3.46	1.336	1.408
OCH <sub>3</sub>	2.11	3.12	1.485	1.470
CN	1.56	2.71	1.891	1.560
NO <sub>2</sub>	1.88	2.93	2.070	1.804
Br	2.99	3.61	1.539	1.607

\* From ref. 2. Subscripts o/w and cy/w denote 1-octanol-water and cyclohexane-water solvent systems, respectively.

\*\* From ref. 21 ( $P_{o/w}$  and  $P_{cy/w}$  values were available for only 13 of the 28 reported anilines, 26 of the 28 reported phenols, 13 of the 18 reported pyridines and 9 of the 10 reported benzenes).

TABLE III

## PARTITION AND GLC RETENTION DATA FOR BARBITURATES



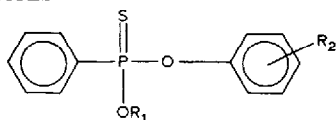
Compound			Partition data*		GLC retention data**		
$R_1$	$R_2$	$R_3$	Log $P_{o/w}$	Log $P_{ch/w}$	Log $k'_{473^\circ K}^{NPGS}$	Log $k'_{473^\circ K}^{OV-17}$	Log $k'_{473^\circ K}^{OV-1}$
CH <sub>2</sub> CH=CH <sub>2</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	1.05	0.48	0.895	0.885	0.487
C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H	2.07	1.30	0.879	1.028	0.565
C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	0.65	-0.10	0.586	0.669	0.000
C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub>	H	1.65	1.00	0.827	0.985	0.367
C <sub>2</sub> H <sub>5</sub>		H	1.86	0.13	1.507	1.616	1.054
CH <sub>3</sub>		CH <sub>3</sub>	1.92	2.50	0.845	1.404	0.845
C <sub>2</sub> H <sub>5</sub>	CH(CH <sub>3</sub> )C <sub>3</sub> H <sub>7</sub>	H	2.03	1.41	0.981	1.091	0.636
C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	1.42	0.65	1.710	1.693	1.054

\* From refs. 2 ( $P_{ch/w}$ ) and 7 ( $P_{o/w}$ ). Subscripts o/w and ch/w denote 1-octanol-water and chloroform-water solvent systems, respectively.

\*\* From ref. 7 ( $P_{o/w}$  and  $P_{ch/w}$  values were available for only eight of the nine reported compounds).

TABLE IV

PARTITION AND GLC RETENTION DATA FOR O-ALKYL-O-ARYLPHENYLPHOSPHONOTHIOATES



Compound		Partition data*			GLC retention data**		
$R_1$	$R_2$	$R_{M1}$	$R_{M2}$	$R_{M3}$	$\pi_{GLC 493^\circ K}^{OV-101}$	$\pi_{GLC 493^\circ K}^{OV-225}$	$\pi_{GLC 493^\circ K}^{DEGS}$
C <sub>2</sub> H <sub>5</sub>	H	0.059	-0.503	0.259	0.000	0.000	0.000
C <sub>2</sub> H <sub>5</sub>	2-CH <sub>3</sub>	0.182	-0.599	0.319	0.111	0.061	0.000
C <sub>2</sub> H <sub>5</sub>	3-CH <sub>3</sub>	0.151	-0.525	0.325	0.111	0.104	0.049
C <sub>2</sub> H <sub>5</sub>	4-CH <sub>3</sub>	0.154	-0.547	0.380	0.155	0.158	0.117
C <sub>2</sub> H <sub>5</sub>	2-OCH <sub>3</sub>	-0.026	-0.244	0.151	0.246	0.384	0.378
C <sub>2</sub> H <sub>5</sub>	3-OCH <sub>3</sub>	0.033	-0.335	0.193	0.305	0.427	0.439
C <sub>2</sub> H <sub>5</sub>	4-OCH <sub>3</sub>	0.019	-0.284	0.231	0.364	0.511	0.530
C <sub>2</sub> H <sub>5</sub>	2-Cl	0.156	-0.404	0.378	0.210	0.233	0.215
C <sub>2</sub> H <sub>5</sub>	3-Cl	0.273	-0.523	0.454	0.230	0.225	0.190
C <sub>2</sub> H <sub>5</sub>	4-Cl	0.259	-0.525	0.491	0.260	0.279	0.267
C <sub>2</sub> H <sub>5</sub>	2-CN	-0.103	-0.003	0.094	0.312	0.574	0.589
C <sub>2</sub> H <sub>5</sub>	3-CN	-0.014	0.028	0.154	0.367	0.664	0.683
C <sub>2</sub> H <sub>5</sub>	4-CN	-0.040	0.124	0.226	0.431	0.763	0.826
C <sub>2</sub> H <sub>5</sub>	2-NO <sub>2</sub>	-0.043	0.007	0.162	0.422	0.712	0.749
C <sub>2</sub> H <sub>5</sub>	3-NO <sub>2</sub>	0.098	-0.030	0.319	0.526	0.799	0.816
C <sub>2</sub> H <sub>5</sub>	4-NO <sub>2</sub>	0.126	0.024	0.406	0.606	0.919	0.964
C <sub>2</sub> H <sub>5</sub>	4-F	0.103	-0.439	0.279	-0.032	-0.061	-0.041
C <sub>2</sub> H <sub>5</sub>	4-Br	0.306	-0.508	0.581	0.410	0.459	0.455
C <sub>2</sub> H <sub>5</sub>	4-I	0.370	-0.383	0.676	0.572	0.699	0.694
C <sub>2</sub> H <sub>5</sub>	4-C <sub>2</sub> H <sub>5</sub>	0.294	-0.621	0.486	0.290	0.270	0.190
C <sub>2</sub> H <sub>5</sub>	4-C <sub>3</sub> H <sub>7</sub>	0.432	-0.704	0.608	0.418	0.375	0.246
C <sub>2</sub> H <sub>5</sub>	2,5-di-Cl-4-Br	0.562	-0.479	0.891	0.736	0.763	0.717
CH <sub>3</sub>	4-CN	-0.117	2.374	0.160	0.439	0.757	0.873
C <sub>3</sub> H <sub>7</sub>	4-CN	0.094	0.003	0.325	0.548	0.852	0.843

\* From ref. 6.  $R_{M1}$  denotes  $R_M$  values obtained from reversed-phase TLC, acetone-water (6:4).  $R_{M2}$  denotes  $R_M$  values obtained from polyamide TLC, *n*-hexane-acetic acid (95:5).  $R_{M3}$  denotes  $R_M$  values obtained from polyamide TLC, acetone-water (6:4).

\*\* From ref. 6.

phase pairs can model the cyclohexane-water or chloroform-water systems to a greater extent than the 1-octanol-water system where hydrogen bonding can occur in the organic phase between the solute and the solvent.

With barbiturates it can also be observed that no significant equations will be obtained if the polarities of the stationary phases do not differ from each other sufficiently (OV-1 and OV-17; see eqns. 16 and 19). It is obvious that the 1-octanol-water or chloroform-water systems cannot be modelled by a stationary phase pair that hardly differ in polarity.

In view of the above, it can be stated that in most instances partition parameters cannot be described sufficiently well by simple differences of GLC retention parameters ( $\Delta RP$ ). However, an attempt might be made to use weighted differences



TABLE V  
RELATIONSHIPS BETWEEN PARTITION (PP) AND GLC RETENTION (RP) PARAMETERS, OF THE FORMS  $PP = c_1(RP_1 - RP_2) + c_2$  AND  $PP = c_3RP_1 - c_4RP_2 + c_5$

C*	N**	PP***	RP <sub>1</sub>	RP <sub>2</sub>	c <sub>1</sub>	c <sub>2</sub>	R <sup>§</sup>	F <sup>§</sup>	s <sup>§</sup>	Eqn. No.	c <sub>3</sub>	c <sub>4</sub>	c <sub>5</sub>	R <sup>§</sup>	F <sup>§</sup>	s <sup>§</sup>	Eqn. No.
1	9	Log P <sub>cy/w</sub>	Carbowax 20M	f <sup>OV-101</sup>	-	-	-	-	-	-	-0.007	0.011	1.945	0.995	278.7 <sup>§§§</sup>	0.113	8
2	13	Log P <sub>o/w</sub>	Log V <sup>PEG</sup>	Log V <sup>Apiezon</sup>	0.176	1.298	0.125	0.2 <sup>§§</sup>	0.386	9	-0.646	1.403	0.231	0.259	0.4 <sup>§§</sup>	0.394	31
2	13	Log P <sub>ey/w</sub>	Log V <sup>PEG</sup>	Log V <sup>Apiezon</sup>	-1.924	1.276	0.754	14.6 <sup>†</sup>	0.465	10	-2.021	2.111	1.149	0.754	6.6 <sup>††</sup>	0.487	32
3	26	Log P <sub>o/w</sub>	Log V <sup>PEG</sup>	Log V <sup>Apiezon</sup>	-0.054	2.145	0.039	0.0 <sup>§§</sup>	0.471	11	-0.435	1.326	0.801	0.529	4.5 <sup>††</sup>	0.409	33
3	26	Log P <sub>ey/w</sub>	Log V <sup>PEG</sup>	Log V <sup>Apiezon</sup>	-2.586	2.018	0.897	99.1 <sup>§§§</sup>	0.431	12	-3.025	4.053	0.467	0.944	94.6 <sup>§§§</sup>	0.328	34
4	13	Log P <sub>o/w</sub>	Log V <sup>PEG</sup>	Log V <sup>Apiezon</sup>	-1.925	1.490	0.821	22.9 <sup>§§§</sup>	0.272	13	-2.507	3.997	-0.584	0.963	64.4 <sup>§§§</sup>	0.134	35
5	9	Log P <sub>o/w</sub>	Log V <sup>PEG</sup>	Log V <sup>Apiezon</sup>	-2.483	2.398	0.849	18.1 <sup>†</sup>	0.304	14	-3.287	4.271	1.034	0.948	26.5 <sup>†</sup>	0.198	36
5	9	Log P <sub>ey/w</sub>	Log V <sup>PEG</sup>	Log V <sup>Apiezon</sup>	-1.374	3.171	0.682	6.1 <sup>††</sup>	0.291	15	-2.273	3.373	1.647	0.965	40.1 <sup>§§§</sup>	0.110	37
6	8	Log P <sub>o/w</sub>	Log k <sup>OV-17</sup>	Log k <sup>OV-1</sup>	-2.033	2.565	0.359	0.9 <sup>§§</sup>	0.556	16	-1.529	2.316	1.923	0.648	1.8 <sup>§§</sup>	0.458	38
6	8	Log P <sub>o/w</sub>	Log k <sup>NPGS</sup>	Log k <sup>OV-1</sup>	-1.633	2.114	0.589	3.2 <sup>§§</sup>	0.482	17	-1.238	1.945	1.637	0.750	3.2 <sup>§§</sup>	0.398	39
6	8	Log P <sub>o/w</sub>	Log k <sup>NPGS</sup>	Log k <sup>OV-17</sup>	-1.390	1.258	0.455	1.6 <sup>§§</sup>	0.531	18	-1.058	1.650	0.737	0.606	1.5 <sup>§§</sup>	0.479	40
6	8	Log P <sub>ch/w</sub>	Log k <sup>NPGS</sup>	Log k <sup>OV-1</sup>	-2.226	2.135	0.261	0.4 <sup>§§</sup>	0.865	19	-2.043	2.611	1.680	0.358	0.4 <sup>§§</sup>	0.916	41
6	8	Log P <sub>ch/w</sub>	Log k <sup>NPGS</sup>	Log k <sup>OV-17</sup>	-3.578	2.362	0.858	16.7 <sup>†</sup>	0.460	20	-3.490	3.781	2.145	0.867	7.6 <sup>††</sup>	0.489	42
6	8	Log P <sub>ch/w</sub>	Log k <sup>NPGS</sup>	Log k <sup>OV-17</sup>	-3.695	0.394	0.804	11.0 <sup>††</sup>	0.533	21	-3.646	3.804	0.216	0.807	4.7 <sup>§§</sup>	0.580	43
7	24	R <sub>M1</sub>	π <sup>OV-225</sup>	π <sup>OV-101</sup>	-0.777	0.232	0.631	14.6 <sup>†</sup>	0.136	22	-1.385	2.180	0.039	0.965	140.7 <sup>§§§</sup>	0.047	44
7	24	R <sub>M1</sub>	π <sup>BEGS</sup>	π <sup>GLC</sup>	-0.653	0.214	0.685	19.5 <sup>§§§</sup>	0.128	23	-1.008	1.698	0.023	0.957	114.8 <sup>§§§</sup>	0.052	45
7	24	R <sub>M1</sub>	π <sup>BEGS</sup>	π <sup>OV-225</sup>	-2.451	0.125	0.711	22.5 <sup>§§§</sup>	0.124	24	-2.903	3.062	0.050	0.749	13.4 <sup>§§§</sup>	0.119	46
7	24	R <sub>M2</sub>	π <sup>GLC</sup>	π <sup>OV-101</sup>	2.856	-0.556	0.660	17.0 <sup>§§§</sup>	0.465	25	3.156	-3.549	-0.461	0.668	8.4 <sup>†</sup>	0.472	47
7	24	R <sub>M2</sub>	π <sup>BEGS</sup>	π <sup>GLC</sup>	2.413	-0.489	0.720	23.7 <sup>§§§</sup>	0.429	26	2.553	-2.825	-0.414	0.724	11.6 <sup>§§§</sup>	0.437	48
7	24	R <sub>M2</sub>	π <sup>BEGS</sup>	π <sup>OV-225</sup>	9.171	-0.161	0.756	29.4 <sup>§§§</sup>	0.405	27	8.143	-7.782	-0.331	0.772	15.5 <sup>§§§</sup>	0.403	49
7	24	R <sub>M3</sub>	π <sup>GLC</sup>	π <sup>OV-101</sup>	-0.671	0.437	0.486	6.8 <sup>††</sup>	0.173	28	-1.432	2.426	0.195	0.948	93.1 <sup>§§§</sup>	0.064	50
7	24	R <sub>M3</sub>	π <sup>BEGS</sup>	π <sup>OV-225</sup>	-0.564	0.421	0.528	8.5 <sup>†</sup>	0.168	29	-1.013	1.886	0.180	0.920	58.0 <sup>§§§</sup>	0.079	51
7	24	R <sub>M3</sub>	π <sup>GLC</sup>	π <sup>GLC</sup>	-2.118	0.344	0.548	9.4 <sup>†</sup>	0.165	30	-2.844	3.099	0.226	0.644	7.4 <sup>†</sup>	0.155	52

\* C, Compound series; 1, s-triazines; 2, anilines; 3, phenols; 4, pyridines; 5, benzenes; 6, barbiturates; 7, O-alkyl-O-aryphenylphosphonothioates.

\*\* N, Number of compounds.

\*\*\* For abbreviations o/w, cy/w, ch/w, R<sub>M1</sub>, R<sub>M2</sub>, R<sub>M3</sub>, see the first footnote in each of Tables I-IV.

§ R, simple or multiple correlation coefficient; F, overall Fisher-test value; s, standard error of the estimate.

§§ Non-significant F value.

§§§ F value significant at a level of 0.1%.

† F value significant at a level of 1%.

†† F value significant at a level of 5%.

( $\Delta'RP$ ) instead, in order to counterbalance the unjustified neglects applied when deriving eqn. 7a and b. This means that the three-parameter model (eqn. 7b) is suggested instead of the two-parameter model (eqn. 7a) for  $\log V_N$ ,  $\log t_R$ ,  $\log k'$  and  $\pi_{GLC}$ , also.

Using the three-parameter model, the data in Tables II–IV were subjected to a repeated regression analysis that yielded eqns. 31–52, several of which are statistically satisfactory (eqns. 34–37, 44, 45, 50 and 51; see Table V). Concerning some of the satisfactory equations, measured and calculated  $PP$  values are compared in Fig. 1b–e.

The validity of our hypothesis is supported by the fact that the signs of the weighting coefficients ( $c_3$  and  $-c_4$ ) are different with each equation [a liquid–liquid partition can, after all, be described only by the difference of two (logarithmically transformed) gas–liquid partition parameters]. Table V shows that with anilines, phenols and barbiturates the statistical improvement of the equations is not significant (compare eqns. 9 and 10 with 31 and 32, 11 and 12 with 33 and 34, and 16–21 with 38–43). However, a significant improvement has been found for pyridine and benzene derivatives where the three-parameter equations obtained are statistically nearly as reliable as the equation obtained for *s*-triazines (compare eqns. 13–15 with 35–37). With *O*-alkyl-*O*-arylphenylphosphonothioates, some of the three-parameter equations are significantly better than the corresponding two-parameter equations (compare eqns. 22 and 23 and eqns. 28 and 29 with eqns. 44 and 45 and 50 and 51, respectively). However, no significant improvement has been obtained in the equations where the polarity of the stationary phases was not sufficiently different (DEGS and OV-225; compare eqns. 24 and 30 with 46 and 52), and where an acidic

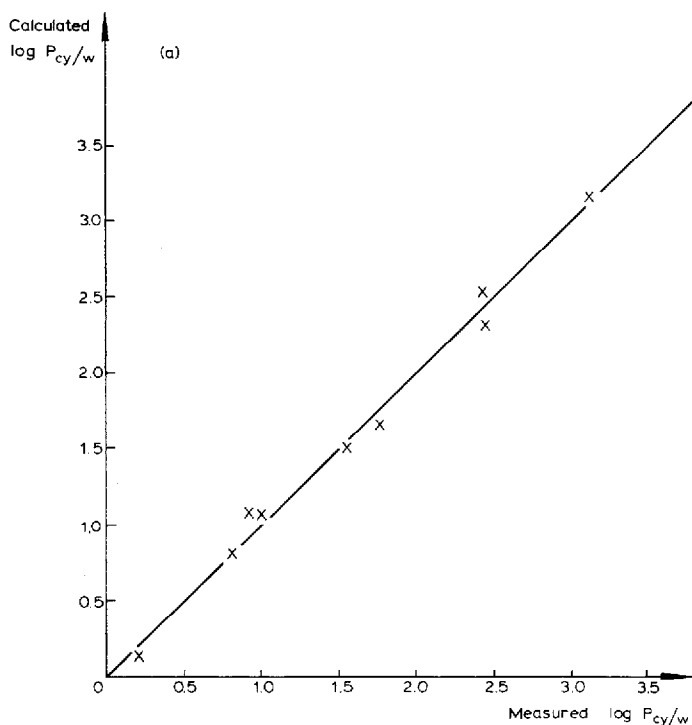


Fig. 1.

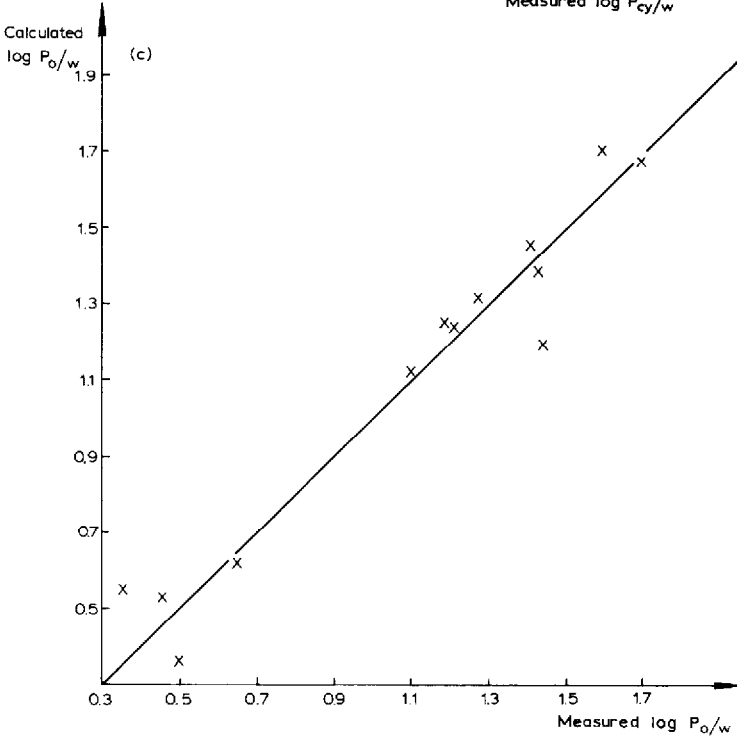
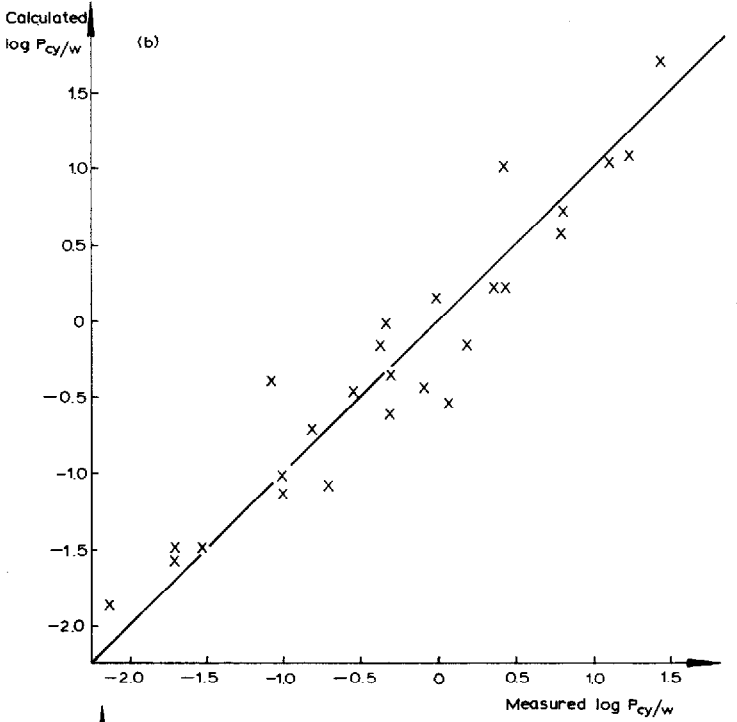


Fig. 1.

(Continued on p. 88)

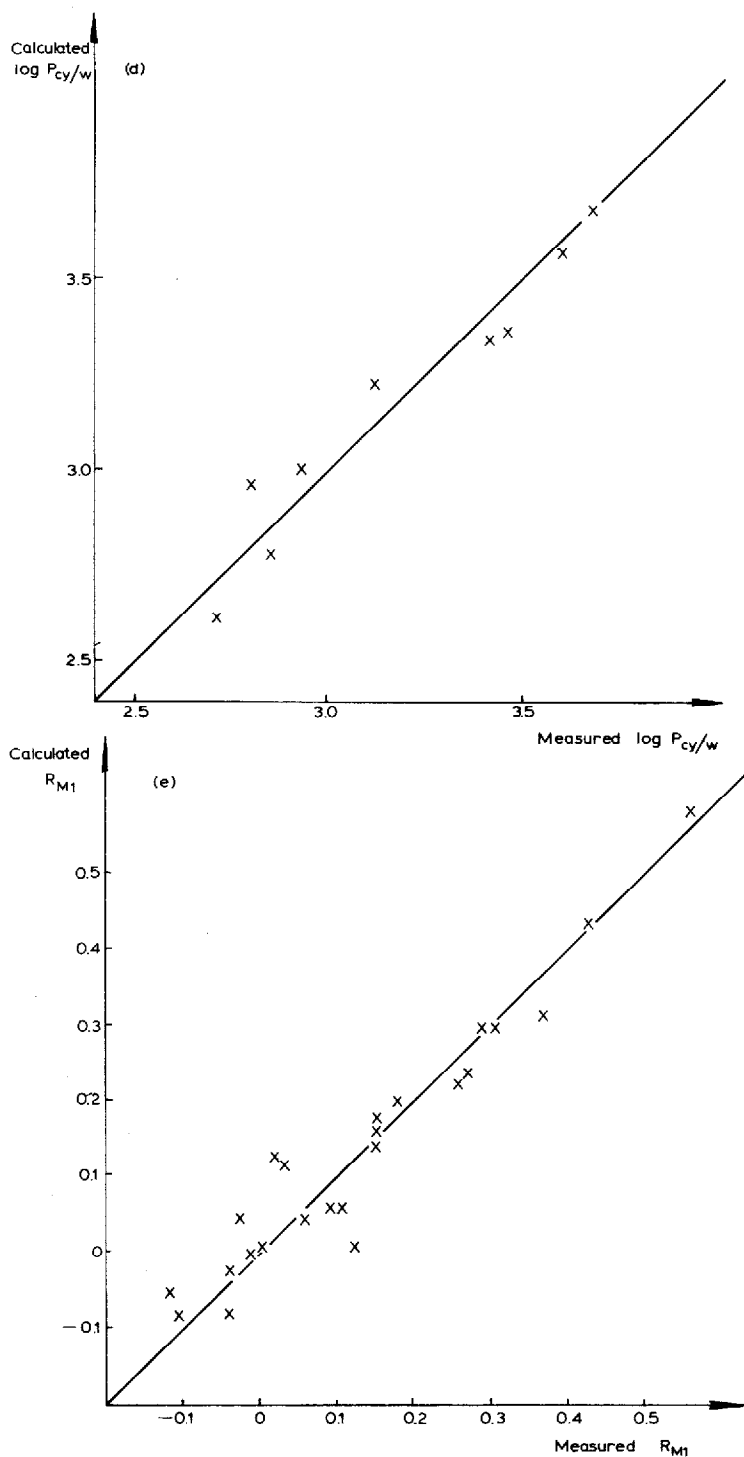


Fig. 1. Comparison of experimental  $PP$  values with those calculated using (a) eqn. 8 (*s*-triazines), (b) eqn. 34 (phenols), (c) eqn. 35 (pyridines), (d) eqn. 37 (benzenes) and (e) eqn. 44 (O-alkyl-O-arylphenylphosphothioates).

medium was used in the TLC measurements to obtain  $R_{M2}$  values<sup>6</sup> (see the first footnote in Table IV; compare eqns. 25-27 with 47-49).

From the above, it appears that the use of  $\Delta'RP$  instead of  $\Delta RP$  in the search for relationships between partition parameters and GLC retention parameters counterbalances mainly the influence of adsorption mechanisms in solute retention. The introduction of the third parameter does not result in a significant improvement in the equations where the stationary phase pair cannot model the solvent system. This is the case with stationary phases that do not differ sufficiently in polarity, with an acidic medium in TLC measurements yielding the  $R_M$  values and with solutes acting as hydrogen bond donors (particularly when hydrogen bonds can form between the solute and the solvent in the organic phase of the solvent system). The question of how to select the most suitable stationary phase pairs is currently under study.

## CONCLUSIONS

It is generally accepted that GLC retention is governed by Van der Waals, polar and, to a lesser extent, hydrophobic interactions between the solute and the stationary phase<sup>5</sup>. In view of the above results, however, it can be stated that the simple or weighted differences ( $\Delta RP$  or  $\Delta'RP$ , respectively) of the properly transformed GLC retention parameters such as  $\log V_N$ ,  $\log t_R$ ,  $\log k'$ ,  $\pi_{GLC}$  and  $I$  are, in many instances, determined only by hydrophobic interactions. Accordingly, our results suggest that these differences (preferably the weighted difference,  $\Delta'I$ , of Kováts retention indices) should be used as hydrophobicity indices in QSAR studies. Hence GLC, like TLC and HPLC, can also be a useful technique in quantitative drug design.

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