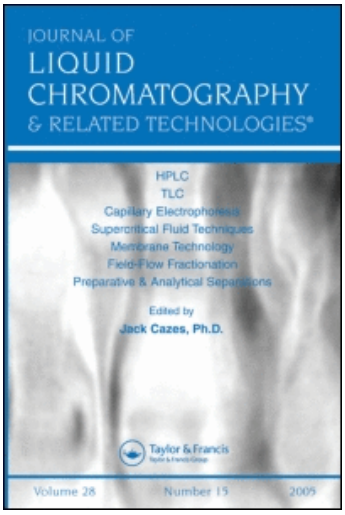

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RAPID METHOD FOR ESTIMATING OCTANOL-WATER PARTITION COEFFICIENT (LOG P_{OCT}) FROM ISOCRATIC RP-HPLC AND A HYDROGEN BOND ACIDITY TERM (A)

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ABSTRACT

The linear solvation equation approach has been used to describe the octanol/water lipophilicity scale ($logP_{oct}$) and the isocratic retention factors (log k) obtained using reversed phase HPLC with acetonitrile. Both the octanol/water partition coefficients and the RP-HPLC retention data obtained from the literature, showed good correlation with the molecular descriptors such as size, excess molar refractivity, H-bond acidity/basicity, and polarity/dipolarity. However, the impact of the H-bond acidity term was very different on the two lipophilicity scales.

The H-bond acidity term was not significant in describing the octanol/water lipophilicity, while the H-bond acidity of the mole-

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cules decreased significantly their RP-HPLC retention. As the other terms had very similar impact on the two lipophilicity scales, it made it possible to convert one scale to the other by incorporating only the H-bond acidity of the compounds as is shown by the equation below, where A is the compound H-bond acidity.

$\log P_{oct} = 2.067(\pm 0.04) \log k_{40} + 1.094(\pm 0.08) A + 0.517(\pm 0.05)$
$n = 111 \qquad r = 0.982 \qquad rms = 0.189$

Using the simpler hydrogen bond donor counts (HBC) also helped to align the two lipophilicity scales to each other.

$\log P_{oct} = 1.913(\pm 0.07) \log k_{40} + 0.367(\pm 0.07) HBC + 0.720(\pm 0.08)$
$n = 111 \qquad r = 0.962 \qquad rms = 0.272$

The validity of the above equations was tested using a test set of 41 drug compounds with our measured data. The log P_{oct} values were estimated from isocratic RP-HPLC retention data with the H-bond acidity term and counts, with an error of 0.284 and 0.325 log unit, respectively.

INTRODUCTION

Lipophilicity of a solute is an important parameter in structure activity relationship studies. Lipophilicity is most often characterised by the partition coefficient of a solute between an aqueous and an immiscible organic phase. In particular, partition measurements in octanol and water, log P_{oct}, are often used following the work of Hansch, Fujita, and Leo,[1-3] who showed that the partition coefficient can model many biological systems. However, the shake flask method for partitioning measurement is slow, it requires the solute to be pure and with adequate solubility in the aqueous phase. Insolubility often means that hydrophobic compounds may not be determined accurately. Therefore, there is great value in finding alternative methods for estimating log P_{oct}.

The most popular method of choice is reversed-phase high performance liquid chromatography (RP-HPLC),[4-7] simply because it is faster; there is no need for concentration determination as the solute retention can be directly related to lipophilicity. More importantly, the measurement of RP-HPLC retention data can be automated and with very little sample preparation time.

The chromatographic retention factors, log k, and log k_W (a measure of a series of log k at different organic modifier concentration values extrapolated back to 100% aqueous phase) have been used as chromatographic measures of

lipophilicity.[8-11] Measurements are usually carried out on an octyldecyl silica (ODS) column eluted with mixtures of water and organic modifiers, such as acetonitrile or methanol,[12-16] with methanol being the preferred solvent. Although linear relationships between log of the capacity factor, k, and logP_{oct} have been found,[17-18] these are restricted to particular chemical series. Other alternative stationary phases were octadecylpolyvinyl-alcohol copolymer (ODP), polystyrene-divinylbenzene copolymer (PLRP-S),[19-21] and immobilized artificial membrane phosphatidycholine (IAM).[22]

Terada et al[23] obtained capacity factors for various compounds, using an octadecylsilica (ODS) and gly-CPG (glyceryl-coated controlled-pore glass) with different percentages of methanol in the mobile phase, and found that the correlation of log k with log P_{oct} significantly improved when a hydrogen-bond term was added.

With ODS stationary phase, the hydrogen-bond term was significant as the percentage of methanol reached zero. The significance of the hydrogen bond term in the capacity factor to estimate octanol/water partition can be explained by the general solvation equation, equation 1.

$$SP = c + eE + sS + aA + bB + vV \quad (1)$$

Here, SP is a solute property, e.g. logarithm of partition coefficients, log P, chromatographic retention parameters; log k, and log k_w. The explanatory variables are solute descriptors, as follows: E is an excess molar refraction that can be obtained from a compound's measured refractive index or can be calculated easily, S is the solute dipolarity/dipolarisability, A and B are the solute overall or effective hydrogen-bond acidity and basicity, and V is the McGowan characteristic volume (in cm^3/100 mol) that can be calculated for any solute simply from molecular structure using a table of atomic constants.[24]

The equation constants are c, e, s, a, b, and v, that describe a measure of difference in properties of the two phases of the system. The r constant gives a measure of the propensity of the solvent to interact with solute π- and n-electron pairs, the s constant is a measure of the dipolarity/polarisability, the a constant measures the hydrogen-bond basicity (because an acidic solute will interact with the basic phase), the b constant measures hydrogen-bond acidity, and v is a measure of the hydrophobicity.

The constants in equation (1) can be obtained by multiple linear regression analysis for a set of experimental data[25] of the solute property, SP. To be statistically valid, a set of known solute properties should be varied widely to probe all the interaction parameters in equation (1), and there should be sufficient data points. The molecular descriptors of more than 4000 compounds are currently in the database.[26] A calculation method for the solute descriptors has been developed by Platts et al.,[27] and commercial software (ABSOLV) for the descriptor calculation is available from Sirius. (Analytical Instruments Ltd., Forest Row, East Sussex, UK.)

Abraham et al.[28] obtained a solvation equation for octanol and water partition, log P_{oct}, equation 2.

$$\log P_{oct} = 0.088 + 0.562E - 1.054S + 0.034A - 3.460B + 3.841V \quad (2)$$
$$n = 613 \qquad r = 0.997 \qquad sd = 0.116$$

The coefficients in the equation are all significant except for the hydrogen bond acidity, where it is almost zero (a = 0.034). The solvation equations obtained for RP-HPLC are quite different to that of equation 2, in particular the hydrogen bond acidity term (A) which is significant.[29] This means that compounds with hydrogen bond acidity will have lower $\log P_{oct}$ equivalent value when determined by chromatography compared to the flask method.

We showed previously, that the isocratic retention determined on an ODS stationary phase correlated significantly with gradient elution retention. On analysis using the solvation equation, it was found that both methods of elution lead to almost the same equation.[29] Furthermore, the only significant difference between the solvation equations obtained by the chromatographic method and that of partition is the solute hydrogen bond acidity. Based on the results found in this study we show, that by adding a solute hydrogen-bond acidity term, the correlation of log k with log P_{oct} could be improved significantly.

EXPERIMENTAL

Reagents

The compounds investigated in this study were all commercially available. Samples were prepared by dissolving the solute in acetonitrile (Rathburn, Walkerburn, UK) and 50 mM ammonium acetate (Fisons, Loughborough, UK), pH 7.4 solution (0.1mg/mL). The solution (5 μL) was injected into the HPLC system.

The HPLC organic modifier was HPLC grade acetonitrile and the aqueous mobile phase was 50 mM ammonium acetate adjusted to pH 7.4 and pH 10.5 by addition of concentrated ammonia solution. For a pH 2 solution, phosphoric acid solution (0.1M) was prepared.

Chromatography

A Hewlett Packard 1100 series high performance liquid chromatograph was used. Data acquisition and processing were performed on a Hewlett Packard

PC with HP Chemstation software (Hewlett-Packard, Amsterdam, Netherlands). The stationary phase was a Luna octadecyl (C18) column with dimensions of 150 x 4.6 mm (Phenomenex, Macclesfield, UK).

Isocratic Measurements of log k

The dead time (t_0) of the system was determined by measuring the retention time of a sodium nitrate solution. The mobile phase flow rate was 1.00 mL/min.

$$\log k = \log [(t_R - t_0) / t_0].$$

where log k is the logged retention factor, t_R and t_0 are the retention times, respectively.

Octanol/Water Partition Coefficients (log P_{oct})

The measured log P_{oct} values were retrieved from Medicinal Chemistry Database, Pomona, CA., using Daylight software.

Calculations

The data analysis was carried out by using Microsoft Excel 5 software package. The multiple linear regression analysis was carried out by using a JMP statistical software.

RESULTS AND DISCUSSION

Analysis using the solvation equation (1) on the set of isocratic retention values on an octyldecyl stationary phase with acetonitrile measured by Smith et al.[30] showed excellent correlation with the molecular descriptors, which had previously been carried out before by Abraham et al.[31] The results are set out in Table 1. Comparing the coefficients of the solvation equation given in Table 1 and the coefficients of equation 2 for log P_{oct}, it is clear that they are different.

Direct comparison of the coefficients cannot be made as the scales are quite different, but one obvious term stands out, the redundancy of the hydrogen bond acidity term (aA) in octanol/water partition. The relationship between the two lipophilicities can be represented by a plot of log k at 40% acetonitrile concentration vs log P_{oct}, see Figure 1.

Table 1. The Regression Coefficients and Their Statistical Analysis of the Solvation Equation for log k in ODS with Different Acetonitrile Concentrations

	c	r	s	a	b	v	n	r	Rms
log k_{30}	−0.141	0.354	−0.673	−0.596	−2.004	2.33	105	0.991	0.095
	±0.074	±0.068	±0.047	±0.043	±0.057	±0.068			
log k_{40}	−0.141	0.311	−0.579	−0.51	−1.581	1.787	111	0.990	0.080
	±0.058	±0.052	±0.039	±0.035	±0.046	±0.053			
log k_{50}	−0.135	0.21	−0.479	−0.503	−1.275	1.371	127	0.988	0.072
	±0.05	±0.04	±0.03	±0.027	±0.04	±0.043			
log k_{60}	−0.25	0.193	−0.4	−0.448	−1.059	1.121	127	0.988	0.061
	±0.04	±0.04	±0.026	±0.023	±0.033	±0.037			
log k_{70}	−0.324	0.157	−0.381	−0.424	−0.828	0.917	126	0.985	0.060
	±0.04	±0.0	±0.027	±0.02	±0.03	±0.04	125	0.980	0.060
log k_{80}	−0.463	0.116	−0.334	−0.354	−0.726	0.822			
	±0.04	±0.037	±0.026	±0.032	±0.036	±0.036			

A very reasonable correlation was obtained, but the difference in the hydrogen bond acidity term (A) is clearly emphasised by a series of compounds that deviate from the main line. Compounds that lie separately from the main line have much lower estimated log P_{oct} value, and they are identified as having strong hydrogen bond acidity, e.g., phenols.

Table 2 gives the coefficient for the correlation of log k at 30-80% acetonitrile compositions and their statistics. It is obvious, therefore, that adding a term for solute hydrogen bond acidity (A) could improve the correlation between the

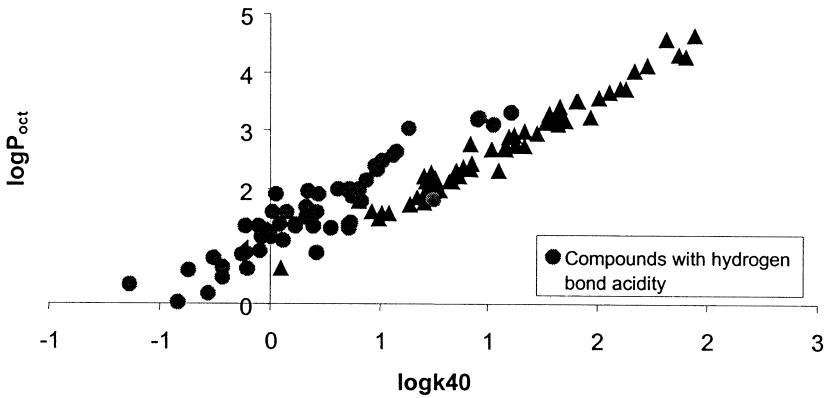

Figure 1. Plot of log P_{oct} with log k_{40} on the Smith data[30] set.

Table 2. The Regression Coefficients and Their Statistical Analysis When Correlated log k Values for the Training Set of Compounds with log P_{oct} [a]

	x	c	n	r	rms
log k_{30}	1.300 ±0.04	0.897 ±0.04	105	0.956	0.286
log k_{40}	1.626 ±0.05	1.102 ±0.05	111	0.951	0.308
log k_{50}	1.892 ±0.07	1.477 ±0.04	127	0.935	0.34
log k_{60}	2.246 ±0.08	1.840 ±0.03	127	0.930	0.351
log k_{70}	2.512 ±0.10	2.311 ±0.04	126	0.908	0.399
log k_{80}	2.860 ±0.12	2.811 ±0.04	125	0.907	0.402

[a] $\log P_{oct} = x \log k + c$

lipophilicities. A representative correlation of estimated log P_{oct} from log k_{40} with the hydrogen-bond acidity (A) term with log P_{oct} is given in equation 3.

$$\log P_{oct} = 1.626(\pm 0.05) \log k_{40} + 1.102(\pm 0.05) \quad (3)$$
$$n = 111 \qquad r = 0.951 \qquad rms = 0.308$$

$$\log P_{oct} = 2.067(\pm 0.04) \log k_{40} + 1.094(\pm 0.08)\, A + 0.517(\pm 0.05) \quad (4)$$
$$n = 111 \qquad r = 0.982 \qquad rms = 0.189$$

Here, log P_{oct} is the partition of solute in octanol/water, log k_{40} is the retention factor at 40% acetonitrile, log P_{oct} is the equivalent log P_{oct} estimated from isocratic measurement and corrected with a hydrogen bond acidity term (A).

The correlation markedly improved and the estimation of log P_{oct} is within 0.2 log unit, as in Figure 2. The same correlation was carried out at other acetonitrile concentrations, and are given in Table 3. The hydrogen bonding donor ability of a compound is an important factor in identifying the difference between log k and log P_{oct}.

Using a much simpler hydrogen bond donor count (HBC), log P_{oct}, instead of the hydrogen bond acidity, the relationship between log k and log P_{oct} also significantly improved; equation 5, with an error of 0.272 log unit. The relationship is shown in Figure 3. A summary of the results for other acetonitrile compositions is given in Table 4. The hydrogen bond count here shows the number of

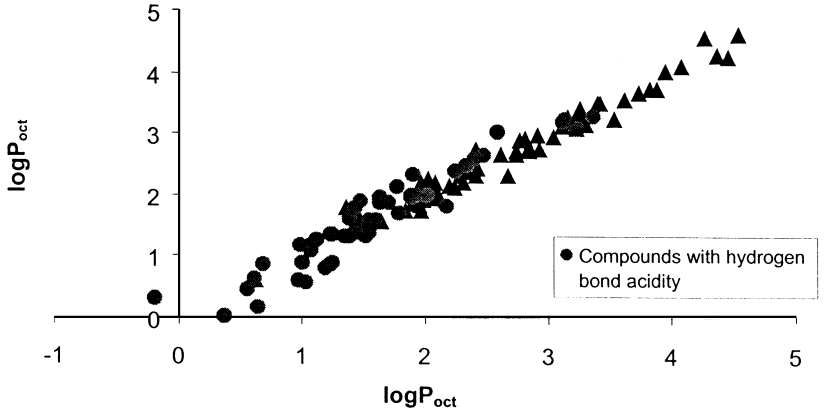

Figure 2. Plot of estimated log P_{oct} determined from log k at 40% acetonitrile and a hydrogen bond acidity term (A) vs. log P_{oct}.

hydrogen bond donor group that a molecule possess, regardless of the strength of the hydrogen bond strength, e.g., $-NH_2$, -OH.

$$\log P_{oct} = 1.913(\pm 0.07) \log k_{40} + 0.367(\pm 0.07)\ HBC + 0.720(\pm 0.08) \quad (5)$$
$$n = 111 \qquad r = 0.963 \qquad rms = 0.272$$

Table 3. The Regression Coefficients and Their Statistical Analysis When Linearly Correlated log k Values for the Smith Data Set (30) and Hydrogen Bond Acidity Term (A) with log P_{oct} [a]

	x	a	c	n	r	rms
log k_{30}	1.651	1.03	0.274	105	0.983	0.176
	±0.04	±0.08	±0.06			
log k_{40}	2.067	1.094	0.517	111	0.982	0.189
	±0.05	±0.08	±0.05			
log k_{50}	2.529	1.285	0.890	127	0.974	0.212
	±0.06	±0.09	±0.05			
log k_{60}	3.048	1.366	1.348	127	0.975	0.212
	±0.07	±0.09	±0.04			
log k_{70}	3.583	1.540	1.948	126	0.962	0.259
	±0.11	±0.12	±0.04			
log k_{80}	3.977	1.423	2.667	125	0.954	0.285
	±0.13	±0.13	±0.03			

[a] $\log P_{oct} = x \log k + aA + c$

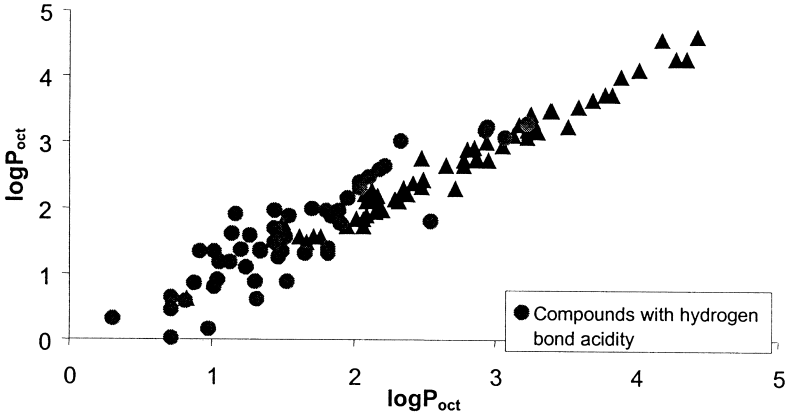

Figure 3. Plot of estimated log P_{oct} determined from log k at 40% acetonitrile and a hydrogen bond count term (HBC) vs. log P_{oct}.

Here, log P_{oct} is the equivalent partition value in octanol/water estimated from chromatographic isocratic measurement corrected by the hydrogen bond count (HBC). The hydrogen bond acidity (A) term gave a better estimation of log P_{oct} than the simpler hydrogen bond count. The latter does not account for the dif-

Table 4. The Regression Coefficients and Their Statistical Analysis When Linearly Correlated log k Values for the Smith Data Set [30] and Hydrogen Bond Count (HBC) Against log P_{oct} [a]

	x	H	c	n	r	rms
log k_{30}	1.529	0.347	0.489	105	0.965	0.254
	±0.06	±0.07	±0.09			
log k_{40}	1.912	0.367	0.720	111	0.962	0.272
	±0.07	±0.07	±0.08			
log k_{50}	2.301	0.421	1.089	127	0.949	0.301
	±0.09	±0.07	±0.07			
log k_{60}	2.688	0.393	1.555	127	0.943	0.317
	±0.11	±0.07	±0.06			
log k_{70}	3.007	0.380	2.126	126	0.921	0.372
	±0.15	±0.09	±0.05			
log k_{80}	3.356	0.338	2.734	125	0.918	0.381
	±0.16	±0.09	±0.04			

[a] log P_{oct} = x log k + h HBC + c

ferent strengths of hydrogen bonding ability in the different functional groups, as does the hydrogen bond acidity term (A).

Methanol, as the organic modifier, is the preferred choice of solvent, because of its similarity to octanol water partition values. However, analysis of log k_w (extrapolated to 0% methanol) using the solvation equation[32] shows that log k_w (equation 6) is very similar to equation 2, except for the hydrogen bond acid term (A).

$$\log k_w = 0.023 + 0.375\ (\pm 0.15)\ E - 0.78\ (\pm 0.19)\ S - 0.248\ (\pm 0.18)\ A - 3.746\ (\pm 0.23)\ B + 3.975\ (\pm 0.18)\ V \quad (6)$$

$$n = 84 \qquad r = 0.995 \qquad sd = 0.162$$

It seems reasonable to add a hydrogen bond acceptor term to the above equation to improve correlation with log P_{oct}. We also obtain the solvation equations for log k values with methanol organic modifier[33] on the same data set by Smith et al.,[30] Table 5. It can be seen, that log k measured in methanol differs from log P_{oct}, not only in the hydrogen bond acidity term (A), but in all other terms in the equation. Therefore, to match the log k measured in methanol to that of log P_{oct}, corrections for other terms must be made.

To test the general applicability of equations 4 and 5 in estimating log P_{oct} for a diverse set of compounds, log k was measured at 40% acetonitrile concentration. The data are shown in Table 6, together with log P_{oct} values. The plot of the estimated log P_{oct}, using equations 4 and 5 and clog P values vs. log P_{oct} values, gave errors of 0.284, 0.325, and 0.529, respectively, Figures 4 - 6. For this

Table 5. The Regression Coefficients and Their Statistical Analysis of the Solvation Equation for log k in ODS with Different Methanol Concentrations[a]

	c	r	s	a	b	v	n	r	sd
log k_{40}	−0.415	0.33	−0.795	−0.515	−1.969	2.720	120	0.991	0.095
	±0.069	±0.065	±0.044	±0.039	±0.052	±0.058			
log k_{50}	−0.293	0.254	−0.709	−0.470	−1.767	2.175	135	0.988	0.101
	±0.065	±0.057	±0.043	±0.038	±0.053	±0.055			
log k_{60}	−0.385	0.268	−0.668	−0.463	−1.456	1.807	146	0.986	0.096
	±0.061	±0.053	±0.038	±0.034	±0.047	±0.050			
log k_{70}	−0.409	0.252	−0.553	−0.442	−1.200	1.380	142	0.986	0.078
	±0.049	±0.044	±0.032	±0.029	±0.041	±0.041			
log k_{80}	−0.497	0.241	−0.509	−0.392	−0.866	1.050	142	0.980	0.075
	±0.048	±0.04	±0.031	±0.028	±0.039	±0.039			

[a] $\log k = c + eE + sS + aA + bB + vV$

Table 6. A Test Set of Compounds with Their Variables, log k, log P_{oct} and log P_{oct} Equivalent Values

Name	A	HBC	clog P	log k_{40}	logP_{oct} (eqn. 4)	logP_{oct} (eqn. 5)	logP_{oct}
2-Pyrazine-carboxamide*	0.45	1	−0.71	−0.60	−0.23	−0.02	−0.6
2,6-Dimethyl-1,4-benzoquinone*	0	0	1.26	0.54	1.63	1.76	1.22
Betahistamine*	0.09	0	−0.07	0.002	0.62	0.73	0.68
Quinazoline-2,4-dione*	0.51	1	0.54	−0.34	0.37	0.47	0.77
Methylstyryketone	0	0	2.07	0.76	2.09	2.17	2.07
Podofilox*	0.35	1	−0.05	0.56	2.06	2.18	2.01
3,3-Dibenzo [18]crown [6]ether*	0	0	3.21	1.08	1.90	2.78	2.2
Mefenamicacid*	0.69	2	4.66	1.63	4.64	4.61	5.12
Renanolone*	0.35	1	2.02	1.01	2.99	3.04	3.28
3,4-Dichlorophenol	0.85	2	4.75	0.93	3.37	3.28	3.33
Colchicine*	0.37	1	0.32	−0.04	0.84	1.04	1.03
Diphenhydramine*	0	0	3.36	1.45	3.51	3.49	3.27
Propranolol	0.1	1	2.75	0.99	2.67	3.00	2.98
5,6-Dehydrois-androsterone*	0.35	1	3.07	1.00	2.97	3.02	3.23
Benzotriazole-2-hydroxy*	0.55	1	0.69	−0.29	0.52	0.57	0.69
Fenbufen*	0.59	1	3.14	0.98	3.19	2.98	3.2
Spironolactone*	0	0	3.19	1.15	2.05	2.92	2.26
Azobenzene	0	0	3.85	1.66	3.95	3.88	3.82
Phenothiazine*	0.2	1	4.06	1.54	3.92	4.05	4.15
Acetanilide	0.5	1	1.16	0.12	1.31	1.35	1.16
Theophylline	0.54	1	−0.06	−0.44	0.21	0.29	−0.02
Caffeine	0	0	−0.06	−0.28	−0.07	0.19	−0.07
Hydrocortisone	0.71	3	0.54	0.19	1.69	2.26	1.55
Cortisone-21-Acetate	0.21	2	1.07	0.49	1.76	2.44	2.1
Progesterone	0	0	3.78	1.43	3.47	3.45	3.7
Butabarbital	0.47	2	1.58	0.27	1.59	2.02	1.89
Procaine	0.32	1	2.38	0.46	1.82	2.00	1.89
Nicotine	0	0	1.32	0.45	1.44	1.58	1.17
Estratriol	0.88	2	2.55	0.60	2.72	2.65	2.69
Furoxemide*	1.36	2	1.24	0.31	2.65	2.10	2.03
Lidocaine	0.11	1	1.98	1.05	2.80	3.11	2.26

(continued)

Table 6. Continued

Name	A	HBC	clog P	log k_{40}	$logP_{oct}$ (eqn. 4)	$logP_{oct}$ (eqn. 5)	$logP_{oct}$
Metropol*	0.1	1	1.20	0.39	1.43	1.86	1.88
Pindolol*	0.47	2	1.67	0.25	1.54	1.98	1.75
Atenolol*	0.55	2	−0.11	−0.48	0.12	0.59	0.16
Alprenolol*	0.1	1	2.65	0.93	2.55	2.89	2.89
Oxprenolol HCl*	0.1	1	1.69	0.59	1.84	2.24	2.1
Nadolol*	0.7	3	0.23	−0.16	0.95	1.59	0.71
Diazepam*	0	0	3.29	0.92	2.41	2.47	2.99
Cimetidine	0.67	2	0.35	−0.50	0.21	0.55	0.4
Trimitoprim*	0.5	2	0.80	−0.24	0.58	1.06	0.91
Phenacetin	0.48	1	1.77	0.19	1.43	1.48	1.58

* The hydrogen bond acidity (A) was calculated using ABSOLV.

test set of compounds, estimated log P_{oct} gave better results than from clog P calculation. If the two outliers, betahistamine and podofilox are removed, error in clog P is reduced to 0.384; there were no error messages for the two outliers.

Our test set was measured on a Luna C_{18} stationary phase, which is different to that used by Smith et al.[30] from which the equations were derived, and so some slight differences in results might be expected. We recommend that you set up your own equations for equation 4 and 5 on a carefully chosen set of training compounds, because log k values are usually not inter-laboratory comparable.

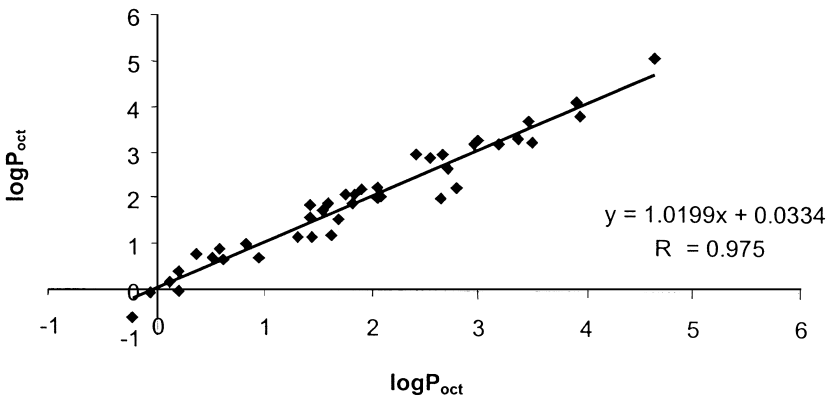

Figure 4. Plot of estimated log P_{oct} using equation 4 with log P_{oct} values on a test set of compounds in Table 6.

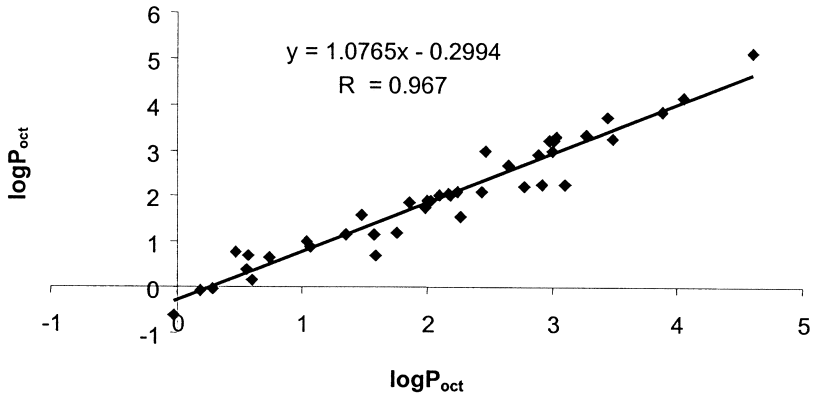

Figure 5. Plot of estimated $logP_{oct}$ using equation 5 with log P_{oct} values on a test set of compounds in Table 6.

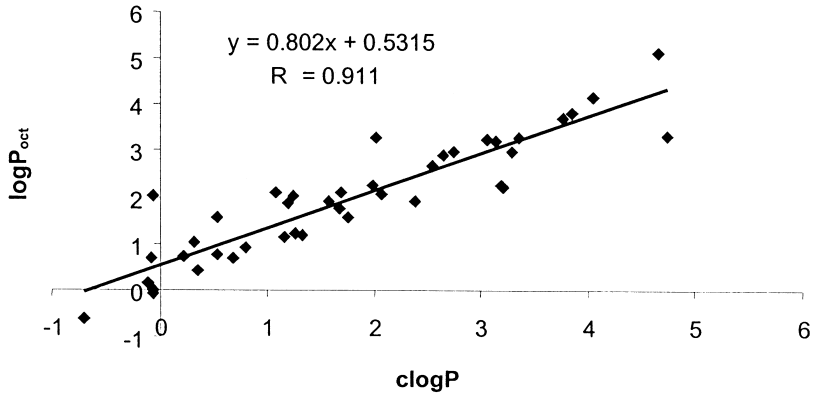

Figure 6. Plot of clog P with log P_{oct} values for the same test set of compounds.

In conclusion, our estimation of log P_{oct} using isocratic measurements and an added hydrogen bond acidity term (A) gave excellent agreement with the measured log P_{oct} values. With the ease of automation of HPLC, the high pH stability of this C18 stationary phase allows measurements to be made for both acid and basic compounds, and the calculable hydrogen bond acidity term (A) provides a rapid means for determining log P_{oct}.

Additionally, the chromatographic method allows very hydrophobic compounds to be measured by a simple correction to the organic concentration at which the compound elutes. We thus show, that our equations to estimate log P_{oct} can be generally applied to any drug molecule and are not restricted to any chemical series.

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