SELECTION OF GAS CHROMATOGRAPHIC STATIONARY PHASE PAIRS FOR CHARACTERIZATION OF THE 1-OCTANOL–WATER PARTITION COEFFICIENT

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SUMMARY

Stationary phase pairs are recommended for the gas chromatographic estimation of log K values for the partition of organic compounds in 1-octanol–water. These pairs model the solute–solvent interactions in 1-octanol and water. The applicability of EPON 1001 as a polar and OV-1 as a non-polar phase was tested experimentally by measuring the retention indices of eight compounds with known log K values. The standard error in the log K determination was less than ± 0.16. The suggested method seems to be appropriate for the estimation of log K values without resorting to a large reference series.

INTRODUCTION

In studies of quantitative structure–activity relationships (QSARs)[1] the hydrophobic properties of compounds are expressed in terms of the logarithm of their 1-octanol–water partition coefficients, log K. Accurate, fast and inexpensive methods for determining log K are of great importance in drug design.

The calculation of log K values using substituent or fragmental constants[2,3] is widely used in QSAR studies. These methods imply that the contributions of the substituents or fragments to the log K value of the whole molecule are additive. In many cases where the functional groups interact sterically with each other this assumption is invalid and, therefore, experimental measurements of log K values are preferred.

The traditional shaken-flask method for measuring log K is gradually being replaced by chromatographic procedures, *e.g.*, reversed-phase high-performance liquid chromatography (RP-HPLC)[4] and thin-layer chromatography (RP-TLC)[5].

The advantages of such methods are that they are simple, rapid and less laborious, require little material, are not disturbed by impurities and the hydrophobic indices of molecules with very low or high log K values can also be measured accurately. Gas–liquid chromatography (GLC) has similar advantages and in certain instances is preferred, *e.g.*, when detection problems arise in TLC or HPLC, when volatile compounds are to be analyzed, such as narcotic gases, etc.

Some attempts have already been made to apply GLC to log K determination. Patte *et al.*[6] predicted log K values on the basis of a multiparameter empirical approach by analyzing the retention data of 240 compounds on 207 stationary phases. Boček's[7] method is suitable only for highly volatile compounds because of the use of water and 1-octanol as the stationary phase pair.

The applicability of all methods which do not use 1-octanol and water but other solvents is based on the linear relationship between log K values measured in two partition systems[8]. Leo[9] pointed out the limitations of such relationships in an investigation of the partition coefficients of about 300 compounds in 12 partition systems. A good correlation of log K values measured in two different solvent systems was found only when either the partitioning solvents or the compounds examined were similar in properties. Thus, it can be assumed that chromatographic methods can be applied to log K determination when either a closely related series of compounds is tested or the partition system is similar to 1-octanol–water.

The principle of the gas chromatographic method for log K determination proposed by us earlier[10,11] is based on the hypothesis that the ratio of two gas–liquid partition coefficients is equal to the liquid–liquid partition coefficient. As the retention index, I, of a compound measured on a given stationary phase changes with the logarithm of its gas–liquid partition coefficient, it follows that the weighted difference between the retention indices of a compound measured on two stationary phases, $aI_1 - bI_2 = \Delta'I$, is directly related to the log K values of that compound

$$\log K = aI_1 - bI_2 + c \tag{1}$$

where a, b and c are regression coefficients which can be calculated by the least squares method. In order to make eqn. 1 suitable for the practical determination of log K, one should use an optimum gas chromatographic stationary phase pair, *i.e.*, one that models best the 1-octanol–water partition system. The aim of this paper is to recommend such phase pairs and to present a preliminary test of their applicability.

THEORETICAL AND EXPERIMENTAL

The McReynolds[12] constants of the 61 stationary phases listed in Table I were used for the calculation of the retention indices at 120°C on a 15% coated column of the compounds benzene, *n*-butanol, 2-pentanone, nitropropane, pyridine, 2-methyl-2-pentanol and 2-octyne. These compounds were selected by McReynolds in order to characterize the most typical interactions between solutes and stationary phases.

The log K values shown in Table II of five of these seven compounds were taken from Hansch and Leo's compilation[2], and the log K values of 2-methyl-2-pentanol and octyne were calculated using Rekker's method[3] (see also the footnote to Table II).

TABLE I

STATIONARY PHASES CONSIDERED IN THE CALCULATIONS

1	Squalane	31	UCON 50 HB 280X
2	Apiezon M	32	Tricresyl phosphate
3	Apiezon L	33	QF-1
4	SE-30	34	SP 2401
5	OV-1	35	OV-210
6	UC-W982	36	Igepal CO-630
7	DC-200	37	UCON 50 HB 2000
8	OV-101	38	UCON 50 HB 5100
9	SP 2100	39	XE-60
10	DC-11	40	OV-225
11	SE-52	41	Igepal CO-880
12	Kel-F wax	42	Triton X-305
13	DC-550	43	Neopentyl glycol succinate
14	Di(2-ethylhexyl) sebacate	44	Carbowax 20M
15	DC-703	45	Carbowax 20M (tph.a.t.)*
16	SP 1200	46	EPON 1001
17	Diisooctyl adipate	47	Carbowax 6000
18	Diisodecyl phthalate	48	Silar 5CP
19	Dinonyl phthalate	49	Butanediol succinate
20	DC-710	50	Phenyldiethanolamine succinate
21	Di(2-ethylhexyl) phthalate	51	Diethylene glycol adipate
22	Dioctyl phthalate	52	Carbowax 1540
23	Poly I-110	53	Hyprose SP-80
24	Hallcomid M-18	54	Diethylene glycol succinate
25	OV-17	55	Silar 10C
26	UCON LB 550X	56	Ethylene glycol succinate
27	Didecyl phthalate	57	1,2,3-Tris(2-cyanoethoxy)propane
28	OV-25	58	Bis(2-cyanoethyl)formamide
29	Poly(phenyl ether) (5 rings)	59	LAC-1-R
30	Poly(phenyl ether) (6 rings)	60	LAC-3-R
		61	SF-96

* tph.a.t. = Terephthalic acid terminated.

TABLE II

LOGARITHMS OF 1-OCTANOL–WATER PARTITION COEFFICIENTS, log K, OF THE SEVEN McREYNOLDS COMPOUNDS

Compound	log K
Benzene	2.15
n-Butanol	0.88
2-Pentanone	0.91
Nitropropane	0.87
Pyridine	0.65
2-Octyne	3.97*
2-Methyl-2-pentanol	1.91*

* The log K value was not available in the literature[2], therefore it was calculated as follows: log K values of the seven compounds were calculated by Rekker's method[3]; on the basis of the linear relationship between the measured and the calculated log K values of the first five compounds, the corresponding values of the remaining two compounds were estimated.

The basis of the selection of the stationary phase pair was eqn. 1. Thus the log K values of the seven model compounds and their retention indices (measured by McReynolds on two arbitrary stationary phases) were introduced into eqn. 1. The correlation coefficient of eqn. 1 was regarded as a measure of the suitability of a given stationary phase pair for modelling the 1-octanol–water system.

The retention indices of the seven McReynolds compounds measured on the 61 stationary phases were substituted into eqn. 1 as I_1, giving a total of 7×61 values. With the aid of a computer program using Draper and Smith's algorithm[13] for stepwise linear regression analysis, the retention indices measured on another stationary phase, I_2, were selected as a second variable in eqn. 1, which led to an equation with a correlation coefficient $r \geqslant 0.95$. In this way the explicit calculation of the 1830 equations covering all combinations of the 61 stationary phases could be avoided and the best equations were not lost.

To support the results of these calculations the retention indices of further eight compounds (see Tables III and IV), similar to McReynolds' model compounds, were measured on 15% OV-1 (Merck, Darmstadt) and 15% EPON 1001 (Supelco) columns prepared by us. Six-feet glass columns and Gas-Chrom Q as support were used. Retention index measurements were carried out at 120°C in a HP-5710A gas chromatograph with a flame ionization detector.

TABLE III

RETENTION INDICES OF THE SEVEN McREYNOLDS COMPOUNDS ON OV-1 AND EPON 1001 CALCULATED FROM McREYNOLDS CONSTANTS

Compound	I^{OV-1}	$I^{EPON\,1001}$
Benzene	669	937
n-Butanol	645	1079
2-Pentanone	671	1033
Nitropropane	717	1191
Pyridine	741	1300
2-Methyl-2-pentanol	722	1068
2-Octyne	864	1048

TABLE IV

MEASURED RETENTION INDICES ON OV-1 AND EPON 1001 AND log K VALUES

Log K values were taken from ref. 2.

Compound	I^{OV-1}	$I^{EPON\,1001}$	log K
Toluene	771	1068	2.69
n-Pentanol	749	1199	1.48
Cyclohexanone	883	1318	0.81
Isobutyl methyl ketone	726	1076	1.38
4-Methylpyridine	860	1468	1.22
2-Ethylpyridine	895	1397	1.69
Isopentanol	718	1152	1.29
3-Methyl-1-pentin-3-ol	690	1133	1.36*

    * Calculated by Rekker's method[3].

RESULTS AND DISCUSSION

The results of the correlation analysis are summarized in Fig. 1. The highest correlation coefficient was obtained when Poly I-110 and diethylene glycol succinate were used

$$\log K = 0.0157 \, I_1 - 0.008 \, I_2 - 0.771 \tag{2}$$
$$n = 7, \, r = 0.987, \, s = 0.231, \, F_{(2,4)} = 76.9, \, F_{(2,4 \, p=0.95)} = 6.9$$

where n is the number of compounds, r is the correlation coefficient, F is the value of the Fischer test, s is the standard error of the estimates 2,4 indicates the degrees of freedom and p means probability.

The relationships with the ten highest correlation coefficients are listed in Table
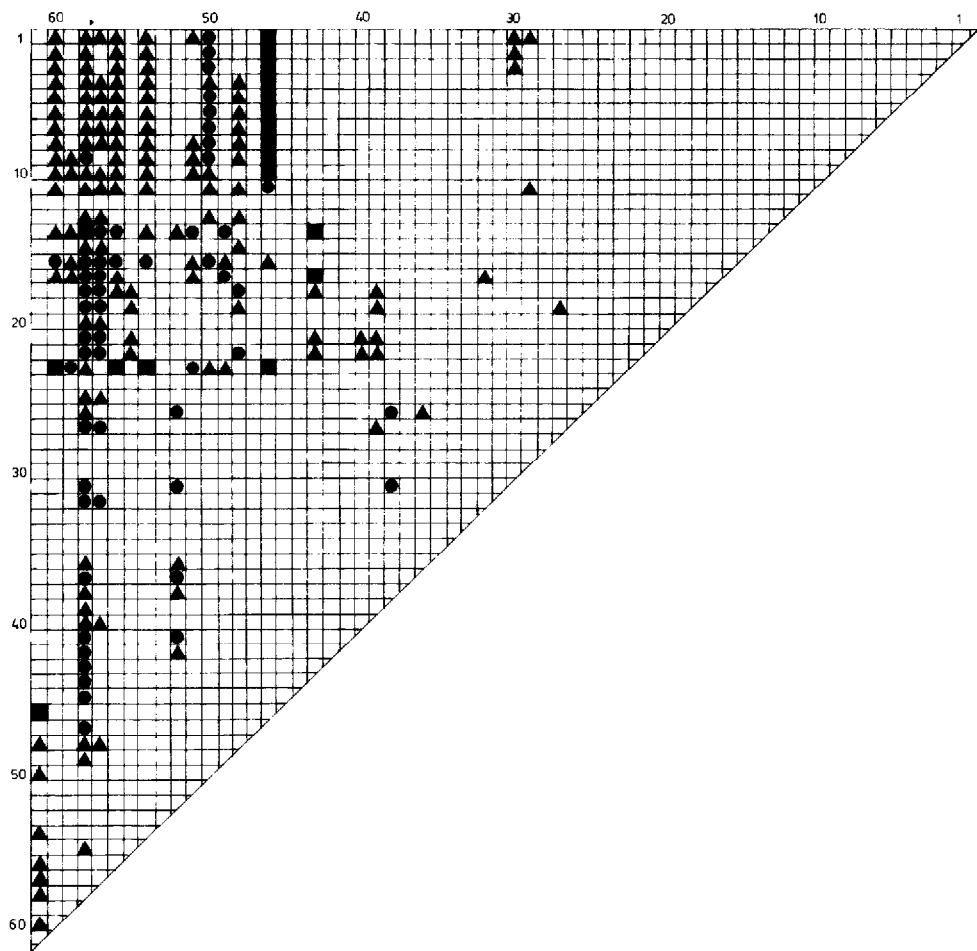

Fig. 1. Results of the correlation analysis according to eqn. 1. Figures on the horizontal and vertical axes are the stationary phases listed in Table I. The squares are marked according to the values of the correlation coefficients obtained when the index values on the two stationary phases were used in eqn. 1: ■, $r > 0.98$; ●, $0.98 \geqslant r > 0.97$; ▲, $0.97 \geqslant r > 0.96$.

TABLE V

BEST STATIONARY PHASE PAIRS AND REGRESSION EQUATIONS

$\log K = aI_1 - bI_2 + c \ (n = 7)$

	I_1	I_2	a	b	c	r	s
1	Poly I-110	Diethylene glycol succinate	0.0157	0.0080	-0.7713	0.987	0.231
2	DC-11	EPON 1001	0.0152	0.0072	-1.5899	0.986	0.242
3	Di(2-ethylhexyl) sebacate	Neopentylglycol succinate	0.0202	0.0127	-1.0665	0.985	0.253
4	Squalane	EPON 1001	0.0125	0.0054	-1.0205	0.984	0.258
5	SP 2100 (methyl)	EPON 1001	0.0142	0.0067	-1.3364	0.983	0.267
6	OV-101 (methyl)	EPON 1001	0.0142	0.0066	-1.2989	0.983	0.268
7	OV-1	EPON 1001	0.0134	0.0056	-1.2711	0.983	0.270
8	DC-200	EPON 1001	0.0141	0.0067	-1.2697	0.983	0.270
9	UC-W982	EPON 1001	0.0142	0.0066	-1.3150	0.982	0.275
10	SE-30	EPON 1001	0.0140	0.0066	-1.2136	0.981	0.278

V. The McReynolds constants of stationary phases included in the best ten phase pairs are shown in Table VI. Only three stationary phases are suitable for replacing the water phase in the 1-octanol–water system, diethylene glycol succinate (DEGS), neopentyl glycol succinate (NPGS) and EPON 1001. All contain many ether and ester moieties. It is noticeable that to the polar stationary phases DEGS and NPGS only two less polar stationary phases Poly I-110 and di(2-ethylhexyl) sebacate were suitable.

However, many less polar paraffin-type or methylsilicon polymer stationary phases can be paired with EPON 1001 as polar phase. These less polar stationary phases, which have nearly the same McReynolds constants, are frequently used over a wide range of operating temperatures. Thus, EPON 1001 seems to have the greatest practical importance.

Eqn. 3, calculated with the data on EPON 1001 and OV-1 as stationary phases (Table III), yielded almost the same statistical characteristics as eqn. 2:

$$\log K = 0.014 \, I_1 - 0.0066 \, I_2 - 1.244 \tag{3}$$
$$n = 7, \, r = 0.983, \, s = 0.269, \, F_{(2,4)} = 56.3, \, F_{(2,4 \ p=0.95)} = 6.9$$

By repeating the calculations and including the measured retention indices and log K data of the further eight compounds (Table IV), eqn. 4 was obtained:

$$\log K = 0.011 \, I_1 - 0.0065 \, I_2 + 0.764 \tag{4}$$
$$n = 15, \, r = 0.868, \, s = 0.466, \, F_{(2,12)} = 18.4, \, F_{(2,12 \ p=0.95)} = 3.9$$

The deviations, Δ, between the measured and calculated log K values (Table VII) suggest that cyclohexanone is probably an "outlier", its Δ value being higher

TABLE VI

McREYNOLDS CONSTANTS OF THE SELECTED STATIONARY PHASES USED IN THE CALCULATIONS OF THE EQUATIONS IN TABLE V

Stationary phase	Model compound						
	1	2	3	4	5	6	7
SE-30	15	53	44	64	41	31	22
OV-1	16	55	44	65	42	32	23
UC-W982	16	55	45	66	42	34	21
OV-101	17	57	45	67	43	33	23
SP 2100	17	57	45	67	43	34	22
DC-11	17	86	48	69	56	36	23
Di(2-ethylhexyl)sebacate	72	168	108	180	125	132	49
Poly I-110	115	194	122	204	202	152	55
Neopentylglycol succinate	272	469	366	539	474	371	184
EPON 1001	284	489	406	539	601	378	207
Diethylene glycol succinate	499	751	593	840	860	595	323
Squalane*	653	590	627	652	699	690	841

* Retention indices of the seven model compounds are given on squalane. (1 = Benzene; 2 = n-butanol; 3 = 2-pentanone; 4 = nitropropane; 5 = pyridine; 6 = 2-methyl-2-pentanol; 7 = octyne.) The respective retention indices were added to the corresponding McReynolds constants to get retention indices of the model compounds on the given stationary phase.

TABLE VII

MEASURED AND CALCULATED log K VALUES USING EQN. 4 AND THEIR DIFFERENCES, Δ

Compound	log K		Δ
	Measured	Calculated	
Toluene	2.69	2.35	0.34
n-Pentanol	1.48	1.26	0.22
Cyclohexanone	0.81	1.97	−1.16*
Isobutyl methyl ketone	1.38	1.81	−0.43*
4-Methylpyridine	1.22	0.75	0.47
2-Ethylpyridine	1.69	1.59	0.10
Isopentanol	1.29	1.23	0.06
3-Methyl-1-pentin-3-ol	1.36	1.04	0.32
Benzene	2.15	2.08	0.07
n-Butanol	0.88	0.89	−0.01
2-Pentanone	0.91	1.48	−0.57*
Nitropropane	0.87	0.96	−0.09
Pyridine	0.65	0.52	0.13
2-Methyl-2-pentanol	1.91	1.81	0.10
2-Octyne	3.97	3.51	0.46

* Compound omitted from further calculations because of the great difference between measured and calculated log K values. The omission of only the data for cyclohexanone made 2-pentanone a significant outlier. Omission of the data for 2-pentanone as well resulted in isobutyl methyl ketone becoming a significant outlier.

than $2s$ of eqn. 4. When cyclohexanone was omitted, 2-pentanone became an "outlier" in the new relationship, and in the next step isobutyl methyl ketone, the third oxo-compound of the series, should be omitted for the same reason. This observation suggests that the electron donor–acceptor interactions of oxo groups during partition processes cannot be modelled by the OV-1 and the EPON 1001 stationary phase pair. By omitting the data of the three oxo compounds from the calculations, the following equation was obtained:

$$\log K = 0.0127\, I_1 - 0.0068\, I_2 + 0.058 \qquad (5)$$
$$n = 12,\ r = 0.988,\ s = 0.159,\ F_{(2,9)} = 181.0,\ F_{(2,9\ p=0.95)} = 4.3$$

The significant improvement in the fit in comparison to eqn. 4 and the good agreement between the measured and calculated data (Fig. 2) suggest that the OV-1 and EPON 1001 stationary phase pair is suitable for estimating log K values of aromatic, alcoholic and basic compounds but not for ketones, or perhaps for other compounds with high dipole moments. Nevertheless, the constancy of the regression constants in eqns. 3–5 allows one to determine at least an approximate log K value for a new compound.

This estimation does not require additional GLC measurements with a congeneric series as references. Reducing the determination of log K to a single GLC measurement thus results in a considerable saving in both manpower and time, and is the main advantage of the proposed method. The extension of eqn. 5 to a larger
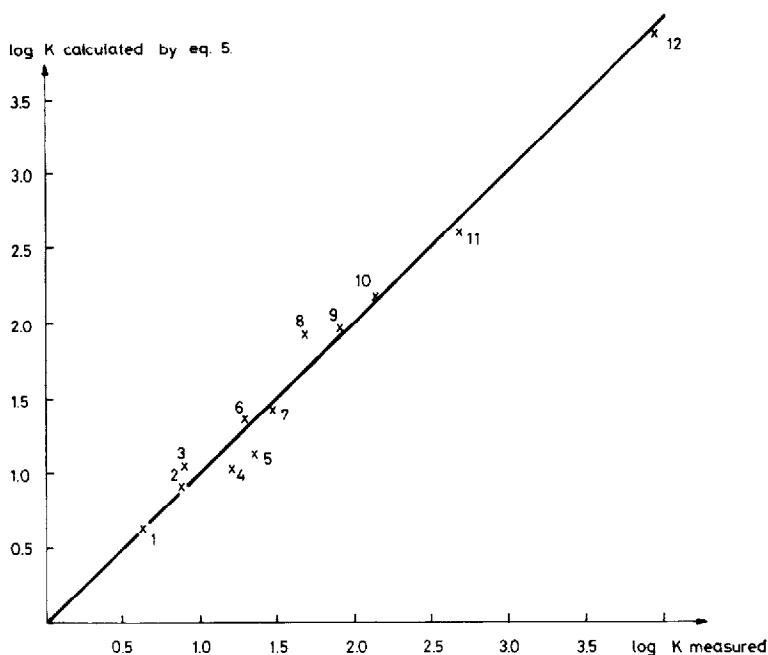
Fig. 2. Fit of measured and calculated log *K* values by using eqn. 5. Compounds: 1 = pyridine; 2 = *n*-butanol; 3 = nitropropane; 4 = 4-methylpyridine; 5 = 3-methyl-pent-1-in-3-ol; 6 = isopentanol; 7 = *n*-pentanol; 8 = 2-ethylpyridine; 9 = 2-methyl-2-pentanol; 10 = benzene; 11 = toluene; 12 = 2-octyne.

series of compounds and the effects of temperature form the subjects of a further study, which should reduce the error in this estimation of log *K*.

It seems reasonable to select more than one stationary phase pair since this allows a larger temperature range for GLC analysis. Thus, the stationary phase pairs listed in Table V are also recommended for log *K* determination.

In conclusion, a method has been described for the selection of the best stationary phase pairs for characterizing gas chromatographically the 1-octanol–water partition system. On the basis of the results obtained the log *K* values of compounds can be estimated according to eqn. 5 by measuring the retention indices on OV-1 and EPON 1001 as stationary phases under the given chromatographic conditions.

ACKNOWLEDGEMENTS

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