PREDICTION OF RETENTION TIMES IN REVERSED-PHASE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY FROM THE CHEMICAL STRUCTURE

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SUMMARY

The capacity factor, k', on a Zorbax ODS column in methanol–water solvents was determined for alcohols and ethers with positional and geometric isomers by high-performance liquid chromatography. These log k' values are almost linearly correlated with the molecular cavity surface area, S, various molecular connectivity indices, *e.g.*, the first-order index, $^1\chi$, the logarithm of the octanol–water partition coefficient, P, and the logarithm of the aqueous solubility. The three parameters S, $^1\chi$ and log P are best correlated with log k'. The advantages and disadvantages of these parameters in the correlation with log k' are considered. The present log k' data can be used for prediction of log P and log k' for other compounds including amino acids.

INTRODUCTION

If we can predict the chromatographic retention time of a compound from its chemical structure, this will be useful for identification of the compound and optimization of elution conditions. In gas–liquid chromatography (GLC), the Kováts retention index has been successfully correlated with chemical structure[1]. However, in high-performance liquid chromatography (HPLC) such relationships are not well established, probably since the solute–solvent interactions are rather complicated.

On reversed-phase HPLC columns, such as ODS columns, hydrophobicity is known to be the most important factor for the retention time[2]; the logarithm of the HPLC capacity factor, k', shows a roughly linear relationship with the logarithm of octanol–water partition coefficient, P, for a wide variety of solutes[3–9]. For aromatic hydrocarbons[10] and aliphatic acids, alcohols and alkanes[11], log k' values varied linearly with the number of carbon atoms of the solutes in methanol–water solvents. The k' values for peptides have been predicted from the amino acid composition[12]. For alkylbenzenes, polycyclic aromatic hydrocarbons[7] and amino acids[13], log k' values were well correlated with the molecular surface areas, which were calculated additively from group surface-area increments given by Bondi[14]. Cavity surface

areas, S, were well correlated with the solubilities, C_w, of hydrocarbons in water, regardless of the hydrocarbons are linear, branched or cyclic[15,16], and a similar correlation has been reported for C_w of acyclic alcohols[17] and for P of ethers[18] and oligoethylene glycol diethers[19]. Therefore, the S^5 and C_w[6,20] values are expected to be correlated with k'. Various molecular connectivity indices have been used for correlation with a number of molecular properties[21] including GLC retention times[22]. The first-order molecular connectivity index, $^1\chi$, was used for correlation with k' of some acyclic alcohols[20] and polycyclic aromatic hydrocarbons[7], and the second-order valence connectivity index, $^2\chi^v$, was also used for substituted aromatic hydrocarbons[23]. The solubility parameter[24], hydrophobic fragmental constant[23,25], Bondi van der Waals volume[7] and the observed molar volume[18] were used for a variety of compounds (including some alcohols[24]) and substituted aromatic hydrocarbons[7,23,24].

The P values of solutes are used as an index of hydrophobicity in many studies of quantitative structure–activity relationships for drugs[3,4,8,9]. Since the flask-shake method used for the measurement of P has the disadvantage of slowness, HPLC is being explored for estimation of P[3,4,8,9].

In this work, we measured the HPLC retention times of 30 alcohols and 10 ethers including positional and geometric isomers on an ODS column in methanol–water solvents, and investigated the quantitative relationships between log k' and S, log C_w, log P and six connectivity indices.

EXPERIMENTAL

Materials

Most alcohols and ethers were obtained from Tokyo Kasei Organic Chemicals. 2,2-Dimethylpropanol-1 was purchased from Nakarai Chemicals and 2,5-dimethyltetrahydrofuran from Aldrich Chemical Co. The ion-exchanged water was twice distilled before use. 4-*tert.*-Butylcyclohexanol was a mixture of 37% *cis* and 62% *trans* as determined with a Shimadzu GC-3BT gas chromatograph (silicone DC550 column). 2-Methylcyclohexanol was a mixture of 22% *cis* and 76% *trans* and 2,6-dimethylcyclohexanol a mixture of 12% 1e, 2e, 6a-, 61% 1a, 2e, 6e- and 25% 1e, 2e, 6e-conformers (where e is equatorial and a axial) (GLC on an N,N,N′,N′-tetrahydroxyethylethylenediamine column). Similar contents of the three geometric isomers of 2,6-dimethylcyclohexanol were obtained by HPLC. A sample of 2,5-dimethyltetrahydrofuran was a mixture of 44% *cis* and 56% *trans* as determined by GLC. The geometric isomers of 2-methylcyclohexanol[26], 4-*tert.*-butylcyclohexanol[27], 2,6-dimethylcyclohexanol[28] and 2,5-dimethyltetrahydrofuran were identified by GLC.

Chromatography

A Shimadzu LC-3A liquid chromatograph with a Shimadzu RID-2A refractive index detector was used. A commercial Zorbax ODS column [15 cm × 4.6 mm I.D., particle size 5 μm, carbon content 20% (w/w) per g silica] was used. Isocratic elution was carried out with a mixture of methanol and water. Since the chromatogram peaks were generally symmetrical, the retention time, t, was evaluated from the distance between the injection point and the peak maximum on the chromatogram by using a Shimadzu Chromatopack C-R1B analyzer. Although chromatograms for

very hydrophobic compounds in highly water-rich solvents showed some tailing, t was measured from the peak maximum. The mobile phase hold-up times were measured by injecting sodium nitrate and the retention time of the first small peak was taken as t_0[13]. The sample was introduced by using a 10-μl Type A high-pressure injection syringe (Scientific Glass Engineering PTY). The mobile phase flow-rate depended on the eluent: 1 ml/min in most cases, 0.5 ml/min in the case of 80% (v/v) methanol and 2 ml/min in the case of water. The column was equilibrated with the appropriate mobile phase until a stable baseline was obtained.

Measurement of S

The cavity surface area, S, for a molecule in water is defined as the area of the surface traced out by the centre of a water molecule rolling over the van der Waals surface of the solute molecule[15]. Therefore, this area is suitable for consideration of solute–solvent interactions[15–19], in contrast to the Bondi surface area[14]. In fact, a Corey–Pauling–Koltun (CPK) molecular model of the solute was constructed; Styrofoam balls representing water molecules (corresponding to a radius of 1 Å) were glued onto the model and packed as tightly as possible. The balls were then counted, and the number was multiplied by 3.99 to convert into an absolute surface area[16]. For each solute the S value reported is the average of four or five values.

RESULTS AND DISCUSSION

Values of S and χ

The S value depends on the molecular conformation of the solute. Although *tert.*-butanol has only one stable conformation, most alcohols can have a number of conformations with different angles of internal rotation around the C–O and C–C axes. In regard to rotation around the C–O axis, for primary alcohols, R_1CH_2OH, we assumed that the R_1 group and alcoholic H atom are in *trans* position and for secondary alcohols, R_1R_2CHOH, we assumed that the methine and alcoholic H atoms are in *trans* position. Though two or three rotamers of an alcohol coexist, the difference in S among these is less than 4 Å^2 per molecule for the alcohols shown in Table I. In regard to rotation around the C–C axis, we assumed the most extended (all-*trans*) conformation. The presence of one *gauche* conformation in the C–C bond reduces S by about 4 Å^2 per molecule[16]. As the alkyl chain becomes longer, therefore, the difference between the maximum (shown in Table I) and minimum S values increases. As regards the inversion of the cyclohexane ring, we assumed the predominant conformation shown in the footnotes to Table I. The uncertainty in S for the cyclic alcohols shown in Table I is small, probably less than 2 Å^2 per molecule. The S values for ethers have been reported[18].

A molecule may be regarded as a graph, the atoms, forming the vertices and the bonds the edges of this graph. The simple connectivity value, δ_i, of a vertex i is the number of other vertices to which it is joined. The first-order (one-bond) connectivity index, $^1\chi$, is defined by

$$^1\chi = \sum_{s=1}^{n} (\delta_i\delta_j)_s^{-1/2} \tag{1}$$

TABLE I

CAPACITY FACTORS (50% METHANOL AND 45°C), OCTANOL-WATER PARTITION COEF-
FICIENTS (25°C), AQUEOUS SOLUBILITIES (25°C), FIRST-ORDER MOLECULAR CONNEC-
TIVITY INDICES AND MOLECULAR SURFACE AREAS FOR ALCOHOLS AND ETHERS

No.	Compound[a]	$\log k'$	$\log P$	$\log C_w$[b]	$^1\chi$	$S(\text{Å}^2$ per molecule)
1	Ethanol	−0.548	−0.32[c]		1.414	136
2	Propanol-1	−0.240	0.34[c]		1.914	160
3	Propanol-2	−0.297	0.14[d]		1.732	156
4	Butanol-1	0.077	0.88[c]	0.003	2.414	184
5	Butanol-2	0.011	0.61[c]	0.029	2.270	178
6	2-Methylpropanol-1	0.061	0.65[c]	0.010	2.270	180
7	tert.-Butanol	−0.053	0.39[d]		2.000	176
8	Pentanol-1	0.391	1.40[c]	−0.585	2.914	207
9	Pentanol-2	0.322	1.19[d]	−0.276	2.770	204
10	Pentanol-3	0.314	1.09[d]	−0.211	2.808	200
11	3-Methylbutanol-1	0.359	1.16[d]	−0.507	2.770	202
12	2,2-Dimethylpropanol-1	0.353	1.31[d]	−0.386	2.561	196
13	2-Methylbutanol-2	0.241	0.89[c]	−0.147	2.561	190
14	Hexanol-1	0.740	2.03[d]	−1.212	3.414	231
15	Hexanol-2	0.641	1.76[d]	−0.866	3.270	228
16	Hexanol-3	0.631	1.65[d]	−0.796	3.308	223
17	Heptanol-1	1.070	2.60[d]	−1.810	3.914	255
18	Heptanol-4	0.970	2.13[d]	−1.388	3.808	247
19	Octanol-1	1.401	3.15[c]	−2.346	4.414	279
20	Octanol-2	1.296	2.90[d]		4.270	275
21	Octanol-4	1.286	2.68[d]		4.308	271
22	CycC$_6$OH	0.355	1.23[c]	−0.417	2.894	200[e]
23	cis-2-MeCycC$_6$OH	0.701	1.84[d]		3.305	216[f]
24	trans-2-MeCycC$_6$OH	0.653	1.82[d]		3.305	216[f]
25	2e,6a-Me$_2$CycC$_6$OH-1e	0.942	2.10[d]		3.715	229[g]
26	2e,6e-Me$_2$CycC$_6$OH-1a	1.064	2.38[d]		3.715	235[g]
27	2e,6e-Me$_2$CycC$_6$OH-1e	0.981	2.37[d]		3.715	235[g]
28	cis-4-tert.-BuCycC$_6$OH	1.440	3.02[d]		4.499	263[h]
29	trans-4-tert.-BuCycC$_6$OH	1.489	3.09[d]		4.499	267[h]
30	Benzyl alcohol	0.093	1.10[c]		2.971	207
31	Diethyl ether	0.295	0.83[c]		2.414	188[i]
32	tert.-Butyl methyl ether	0.485	0.94[i]		2.561	191[i]
33	Dipropyl ether	1.024	2.03[c]		3.414	235[i]
34	Diisopropyl ether	0.809	1.52[i]		3.126	215[i]
35	Dibutyl ether	1.791	3.21[i]		4.414	284[i]
36	CycC$_4$O	0.033	0.22[i]		2.000	164[i]
37	CycC$_5$O	0.347	0.64[i]		2.500	180[i]
38	2-MeCycC$_4$O	0.269	0.71[i]		2.394	184[i]
39	cis-2,5-Me$_2$CycC$_4$O	0.521	1.22[i]		2.788	203[i]
40	trans-2,5-Me$_2$CycC$_4$O	0.558	1.38[i]		2.788	209[i]

[a] Abbreviations: tert. = tertiary; Me = methyl; Bu = butyl; CycC$_6$OH = cyclohexanol; CycC$_4$O =
tetrahydrofuran; CycC$_5$O = tetrahydropyran.
[b] From ref. 17.
[c] From ref. 30.
[d] In preparation.
[e] Same as for the 1a-OH and 1e-OH conformations. Cyclohexanol is present as a mixture of 77% 1e and
23% 1a in C^{2}HCl$_3$[26].
[f] For the cis-form, the 1a,2e-conformer ($S = 216$ Å^2) is predominant over the 1e,2a-conformer ($S = 214$

TABLE II

PARAMETERS FOR THE EQUATION, LOG $k'_{40,45°} = \alpha x + \beta$, FOR ALCOHOLS (A) AND ETHERS (E)

n = Number of data.

x	Compound (n)	α	β	$r^\star$	S.D.**
log P	A(26)	0.677	−0.224	0.9942	0.063
−log C_w	A(15)	0.664	−0.323	0.9834	0.070
S	A(26)	0.0165	−2.706	0.9871	0.094
$^0\chi$	A(26)	0.509	−1.909	0.9797	0.118
$^0\chi^v$	A(26)	0.509	−1.627	0.9797	0.118
$^1\chi$	A(26)	0.736	−1.443	0.9950	0.059
$^1\chi^v$	A(26)	0.726	−1.167	0.9940	0.064
$^2\chi$	A(26)	0.617	−0.701	0.7569	0.383
$^2\chi^v$	A(26)	0.690	−0.580	0.8161	0.339
log P	E(9)	0.612	0.071	0.9755	0.080
S	E(9)	0.0156	−2.347	0.9737	0.078
$^1\chi$	E(9)	0.802	−1.421	0.9936	0.041
$^1\chi^v$	E(9)	0.766	−1.022	0.9841	0.065
log P	A+E(35)	0.643	−0.120	0.9743	0.119
S	A+E(35)	0.0160	−2.555	0.9749	0.118
$^1\chi$	A+E(35)	0.717	−1.339	0.9804	0.104
$^1\chi^v$	A+E(35)	0.697	−1.034	0.9733	0.121
log $k'_{50,45°}$	A+E(36)***	1.160	0.186	0.9992	0.021
log $k'_{0,45°}$	A+E(16)§	0.633	−0.480	0.9956	0.030

* Correlation coefficient.
** Standard deviation.
*** Benzyl alcohol is included herein.
§ These compounds are listed in Table III.

where s identifies a subgraph and δ_i and δ_j are the connectivity values at each end of the graph[21]. For a heteroatom, a valence delta, δ^v, may be useful; e.g., δ^v for the −OH group is 5 and δ^v for the −O− group is 6. From eqn. 1, when δ is replaced by δ^v, we can calculate $^1\chi^v$ for the molecule. For cyclic compounds, we made a correction of −0.500 for $^1\chi$ and $^1\chi^{v}$[21]. Other connectivity indices $^0\chi$, $^0\chi^v$, $^2\chi$ and $^2\chi^v$ are defined as for $^1\chi$ and $^1\chi^{v}$[21]. Among these indices, only $^1\chi$ values are included in Table I.

Structure–retention relationships

The capacity factor, $k' = (t - t_0)/t_0$, is proportional to the coefficient of partition of the solute between the stationary and mobile phases[2,29]. We compared

Å^2); 80% in C^2HCl_3[26] and 83% in dimethyl sulphoxide (DMSO)[31]. For the *trans*-form, the 1e,2e-conformer (S = 216 Å^2) is predominant over the 1a,2a-conformer (S = 210 Å^2); 100% in C^2HCl_3[26] and 99% in DMSO[31].
$^{\text{s}}$ The 1e,2e,6a-conformer (S = 229 Å^2) is predominant over the 1a,2a,6e-conformer (S = 227 Å^2); 100% in C^2HCl_3[26] and 70% in DMSO[31]. The 1a,2e,6e-conformer (S = 235 Å^2) is predominant over the 1e,2a,6e-conformer; 97% in C^2HCl_3[26] and 100% in DMSO[31]. The 1e,2e,6e-conformer (S = 235 Å^2) is predominant over the 1a,2a,6e-conformer; 100% in C^2HCl_3[26] and in DMSO[31].
$^{\text{h}}$ The *cis*-form has about 100% of the 1a,4e-conformation and the *trans*-form about 100% of the 1e,4e-conformation[27].
$^{\text{i}}$ From ref. 18.

the logarithm of k', obtained in 40% methanol and at 45°C (abbreviated as $k'_{40,45°}$), with a number of parameters, as shown in Table II. The methanol content, 40%, was chosen so that we could determine the k' values for alcohols and ethers having a wide range of hydrophobicity: increases in the methanol content led to overlap of the peaks of some compounds, whereas increases in water content led difficulties in the detection of some hydrophobic compounds. The peaks of these hydrophobic compounds were so broad as to be lost in the baseline.

The log $k'_{40,45°}$ values for alcohols and ethers are plotted against S in Fig. 1, log P in Fig. 2, and $^1\chi$ in Fig. 3. Linear correlations among the log k' values obtained under different contents of methanol are generally very good (Table II). An exceptionally bad correlation was obtained with log $k'_{0,45°}$ values. Even these data are better correlated than with the other molecular parameters, as shown in Table II. Therefore, correlations of log $k'_{40,45°}$ with these molecular parameters (Table II and Figs. 1–3) can generally be applied to other log k' data. These correlations reflect the effects of the structural features, such as alcohols or ethers, cyclization and branching (Figs. 1–3).

As Fig. 1 shows, S is very well correlated with log k'. The parameter S accounts well for the effects of the position of the hydroxy group and the branched methyl group and the differences among some geometric isomers. Cyclic alcohols deviate positively from acyclic ones. The molecular conformations of the ethers used are well defined[18], but those of alcohols, particularly acyclic alcohols, are roughly presumed to be in their most extended conformations. The actual S values for acyclic alcohols should, therefore, be smaller than those shown in Table I. This conformational de-
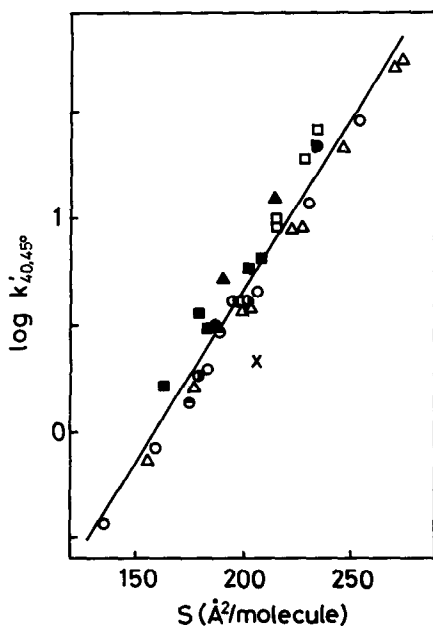

Fig. 1. Log k' values at 40% methanol and 45°C plotted against S for alcohols and ethers. Symbols: O, linear primary alcohols; △, secondary alcohols; ◑, branched primary alcohols; ◒, tertiary alcohols; □, cyclic alcohols; ×, benzyl alcohol; ●, linear ethers; ▲, branched ethers; ■, cyclic ethers.

pendence of S has the merit of providing the possibility of estimating molecular conformations[18,19] but also the disadvantage of requiring detailed knowledge of the molecular conformations. As Fig. 1 shows, the ethers generally have larger log k' values than the alcohols and benzyl alcohol has a smaller value than the other aliphatic alcohols. Alkanes have larger log k' values than carboxylic acids[11], when compared at the same S value. Similar deviations were reported for the solubilities of alkanes and alkylbenzenes in water[15]. These facts show the necessity for fragmentation of S into group surface areas[17]. The molecular surface area can be calculated from group surface areas[14,16], but it should be noted that this additivity rule overestimates the molecular surface areas for very crowded molecules[18,19]. Computed S values for alcohols[17] show an excellent linearity with ours. Since the slope of log k' vs. S plots is a quantity related to interfacial tensions, we can predict the dependence of log k' on the eluent[13,32], e.g., on the methanol content. This is a merit of the S approach.

The parameter P is best correlated with log k' for a wide variety of compounds[3-9]. However, the log k' values for the ethers are slightly larger than those for the alcohols, when compared at the same P value (Fig. 2 and Table II). The order of log k' for all geometric isomers is correctly predicted by P (Fig. 2 and Table I), as is that for all positional isomers, possessing an hydroxy or the methyl group at different positions, e.g., four isomers of butanols, 4–7. A disadvantage of this approach is that much time is required for the P measurement, but this may be diminished by using additivity rules for estimation of P[25,30].

The parameter C_w may be roughly correlated with log k' for a wide variety of compounds, but the correlation will depend on whether they are in the gas, liquid or solid state[16]. The other difficulty is that some compounds are completely soluble in
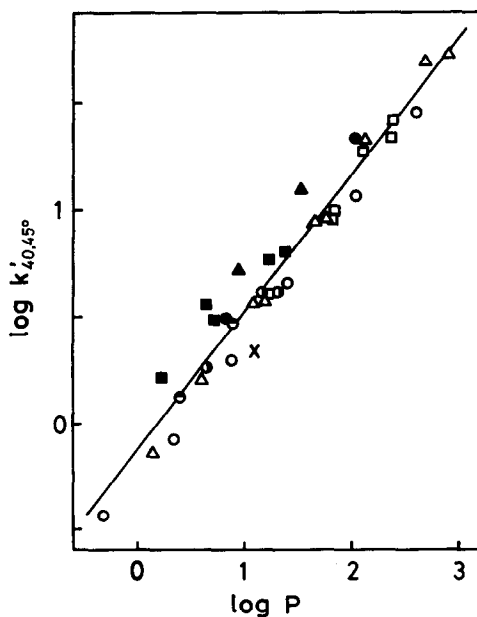

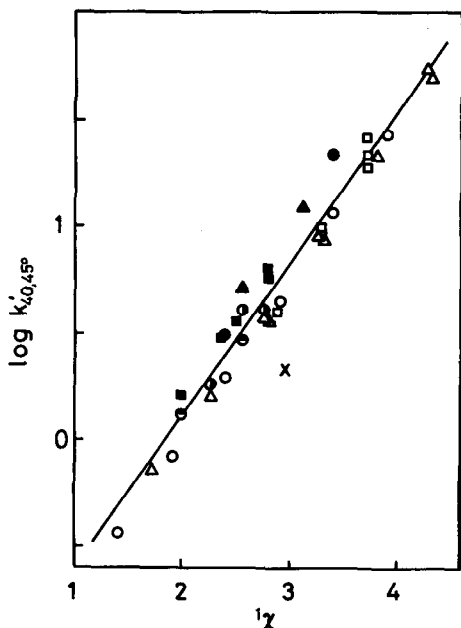Fig. 2. Log $k'_{40,45°}$ values plotted against log P for alcohols and ethers. Symbols as in Fig. 1.

Fig. 3. Log $k'_{40,45°}$ values plotted against $^1\chi$ for alcohols and ethers. Symbols as in Fig. 1.

water, e.g., 1–3. All alcohols investigated in this work are liquids at 25°C. The correlation of log k' with log C_w is reasonably good as shown in Table II. However, the log k' values for branched alcohols are larger than those for linear alkanols-1 when compared at the same C_w value.

As Table II shows, $^1\chi$ and $^1\chi^v$ are better correlated with log k' than the zero- and second-order connectivity indices. For compounds with heteroatoms, generally, $^1\chi^v$ is a better correlational parameter than $^1\chi$[21]. However, for alcohols and ethers, $^1\chi$ is better correlated than $^1\chi^v$, as shown in Table II. This may be ascribed to the similarity of alcohols and ethers. For alkanes and carboxylic acids[11], $^1\chi^v$ is better correlated, though only slightly, than $^1\chi$. A merit of this approach is that $^1\chi$ is easily calculable from the chemical structure, though the basis for a correction of cyclization is not very clear. It is the best correlated of the parameters investigated herein (Table II). The order of log k' for compounds 36 and 37 is correctly predicted by $^1\chi$, in contrast with S and log P (Table I). However, this approach cannot distinguish geometric isomers (23–29 and 39 and 40) and incorrectly predicts the order of log k' for 2- and 3-alkanols (Table I).

Effects of methanol content and temperature

We investigated the effect the methanol volume percentage, $\varphi_{methanol}$, on log k' at 45°C. In methanol–water solvents, the following equation is used in a limited range of $\varphi_{methanol}$[3,6,8,9,20]:

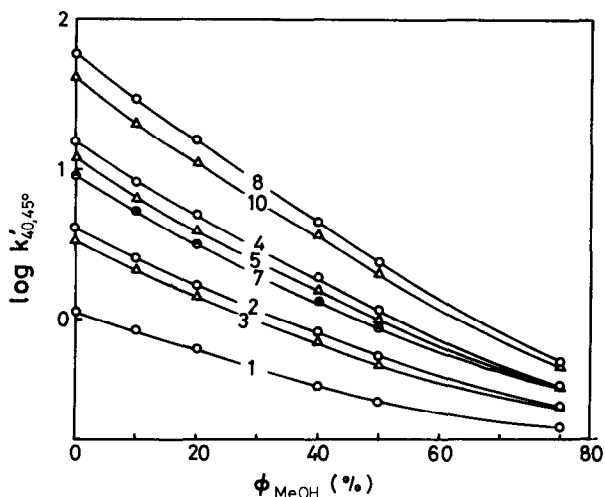$$\log k' = \alpha\, \varphi_{methanol} + \log k_0'^* \qquad (2)$$

Fig. 4. Log $k'_{45°}$ values plotted against the volume percentage of methanol in water for eight alcohols. The numerals indicate the alcohols in Table I.

Here log k'_0* is obtained by linear extrapolation to 0% methanol according to eqn. 2. The log $k'_{0,45°}$ values (water as eluent) were determined for sixteen hydrophilic alcohols and ethers shown in Table III.

In Fig. 4, the log $k'_{45°}$ values for some compounds are shown as a function of $\varphi_{methanol}$. The linearity does not hold over the whole composition range, 0–80% meth-

TABLE III

COMPARISON OF OBSERVED LOG $k'_{0,45°}$ VALUES WITH log $k'_{0,45°}$ VALUES OBTAINED BY LINEAR EXTRAPOLATION OF LOG $k'_{45°}$ TO 0% METHANOL

r = Correlation coefficient for the linear relationship between log k' and $\varphi_{methanol}$.

Compound	log k'_0	log k'_0*	n	r
1	0.058	0.050	4*	0.9998
2	0.611	0.563	4*	0.9996
3	0.523	0.488	4*	0.9995
4	1.189	1.126	4*	0.9999
5	1.079	0.999	4*	0.9997
6	1.120	1.091	4*	0.9998
7	0.957	0.899	4*	0.9993
8	1.765	1.740	4*	0.9999
9	1.671	1.611	4*	0.9993
10	1.613	1.553	4*	0.9999
11	1.671	1.609	2**	1.0000
12	1.654	1.631	3***	0.9999
13	1.499	1.361	2**	1.0000
30	1.395	1.304	2**	1.0000
36	1.139	0.903	2**	1.0000
38	1.594	1.334	2**	1.0000

* 50, 40, 20 and 10% methanol.
** 50 and 40% methanol.
*** 50, 40 and 20% methanol.

anol, but is good in the range 10–50% methanol, as judged from the correlation coefficients in Table III. As this table shows, for all compounds, log k'_0 value is larger than log $k'_0{}^*$. Thus we cannot obtain the correct log k'_0 value by linear extrapolation to 0% methanol.

For linear alkanols, analogously to alkylbenzenes[10], alkanes and fatty acids[11], log k' shows a linear relationship with the number, m, of carbon atoms:

$$\log k' = Am + B \tag{3}$$

The A value, viz. the increment in log k' per methylene, decreased with increasing methanol content and temperature. Our A values as a function of $\varphi_{methanol}$ are slightly higher than those obtained by others[11], but are close to those of Karger et al.[20]. An increase in temperature in the range of 25–45°C resulted in a slight decrease in log k'.

Implications of the present results

There have been numerous studies on the estimation of P from HPLC k' data, since the flask-shake method for the measurement of P is time-consuming[3–9]. What log k' value determined under various conditions is best correlated with the log P value? As demonstrated in Fig. 2, a rough linearity between log k' and log P holds for alcohols and ethers:

$$\log P = \alpha \log k' + \beta \tag{4}$$

In Table IV are shown parameters for the correlation of log P with log k' obtained under different temperatures and $\varphi_{methanol}$ values. The log k' value at 25°C is better correlated than that at 45°C. This may be related to the temperature (25°C) at which P was determined. With respect to $\varphi_{methanol}$, log k'_0 extrapolated to 0% methanol is best for all methanol contents investigated. The same conclusion was reached for various aromatic compounds[6,9]. The measurement of P for solutes with high P values is generally difficult, because of slow partition of the solute between water and octanol. For such compounds, the HPLC method will be useful.

The log k'_{40} data for six alcohols (4, 8, 11, 14, 15 and 22) were reported under conditions different from ours, a μBondapak C_{18} column and ambient temperature[20]. These data are better correlated with S than with log P and $^1\chi$ (Table V). This result is different from that of Table II, and arises from the exclusion (Table V) or inclusion (Table II) of log k' data on branched cyclohexanols (23–29). In general, the correlation with various molecular parameters will depend on a variety of compounds, columns and other experimental conditions. As Tables II and IV show, log k' data determined experimentally are better correlated than various molecular parameters. Therefore, log k' can be predicted more accurately from the value obtained under other conditions than from various molecular parameters.

The present log k' data for alcohols can be used for prediction of log k' values for other compounds obtained under different experimental conditions. In general, a log k' value for an alcohol ROH can be expressed in terms of its components:

$$\log k'(\text{ROH}) = \log k'(\text{R}) + \log k'(\text{OH}) \tag{5}$$

TABLE IV

CORRELATION OF LOG P WITH LOG k' UNDER DIFFERENT CONDITIONS FOR ALCO-
HOLS (A) AND ETHERS (E)

r = Correlation coefficient; $\log P = \alpha \log k'_x + \beta$.

x	Compound (n)	α	β	r	S.D.
50,45°	A(30)*	1.684	0.646	0.9929	0.113
40,45°	A(27)*	1.448	0.363	0.9923	0.105
20,45°	A(18)*	1.193	−0.059	0.9912	0.090
10,45°	A(10)	1.048	−0.219	0.9852	0.095
0,45°	A(14)*	0.943	−0.358	0.9787	1.061
0,45°**	A(27)*	0.943	−0.297	0.9934	0.097
50,25°	A(26)*	1.593	0.568	0.9942	0.099
50,30°	A(27)*	1.650	0.560	0.9943	0.102
80,45°	A(16)	3.583	2.239	0.9911	0.132
50,45°	E(10)	1.688	0.235	0.9903	0.126
40,45°	E(9)	1.556	−0.059	0.9755	0.128
0,45°**	E(9)	1.036	−0.653	0.9758	0.127
50,45°	A + E(40)*	1.670	0.552	0.9731	0.214
40,45°	A + E(36)*	1.462	0.266	0.9713	0.188
0,45°	A + E(16)*	0.909	−0.375	0.9239	0.191
0,45°**	A + E(36)*	0.963	−0.382	0.9849	0.137

    * Benzyl alcohol is included.
   ** Data extrapolated to 0% methanol.

Eqn. 3 is an example of this type of equation. Similarly, for an α-amino acid, $RCH(NH_2)COOH$, we can write:

$$\log k'[RCH(NH_2)COOH] = \log k'(R) + \log k'[CH(NH_2)COOH] \qquad (6)$$

When alcohols and amino acids are eluted under the same conditions, X, eqn. 7 is expected to hold for each pair from eqns. 5 and 6:

$$\log k'_X[RCH(NH_2)COOH] = \log k'_X(ROH) + \text{constant} \qquad (7)$$

TABLE V

CORRELATION OF LITERATURE LOG k' VALUES* WITH OTHER PARAMETERS FOR SIX
ALCOHOLS**

Log $k' = \alpha x + \beta$.

x	r	S.D.
$\log k'_{40,45°}$	0.9990	0.013
$\log k'_{50,45°}$	0.9985	0.016
$\log k'_{0,45°}$***	0.9994	0.010
$\log P$	0.9805	0.057
S	0.9947	0.030
$^1\chi$	0.9908	0.039

    * From ref. 20.
   ** Alcohols 4, 8, 11, 14, 15 and 22.
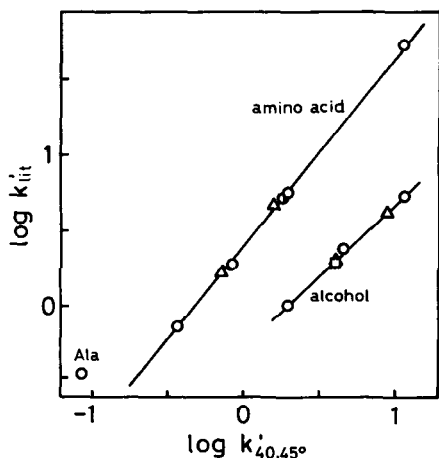 *** Data extrapolated to 0% methanol.

Fig. 5. Log k' values for seven pairs of alcohols[20] and α-amino acids[33] plotted against log $k'_{40,45^\circ}$. Alcohol, amino acid pairs in order of increasing hydrophobicity: 1, α-aminobutyric acid; 3, valine; 2, norvaline; 5, isoleucine; 6, leucine; 4, norleucine; 14, α-aminooctanoic acid.

When alcohols are eluted under two conditions, X and Y, eqn. 8 holds

$$\log k'_X(ROH) = a \log k'_Y(ROH) + constant \tag{8}$$

Some examples are included in Table II).

When amino acids are eluted under condition X and alcohols under condition Y, eqn. 9 is expected for alcohol and amino acid pairs from eqns. 7 and 8:

$$\log k'_X [RCH(NH_2)COOH] = a \log k'_Y(ROH) + b \tag{9}$$

TABLE VI

CORRELATIONAL PARAMETERS FOR EQN. 9 AND PREDICTION OF LOG k' FOR PHENYL-ALANINE

Condition	n	a	b	r	S.D.	log k' (Phe)
80,45°	7	3.13	2.061	0.9995	0.020	—*
50,45°	7	1.45	0.639	0.9996	0.017	0.78
40,45°	7	1.25	0.396	0.9997	0.017	0.81
20,45°	7	0.99	0.055	0.9997	0.017	0.87
10,45°	6**	0.90	−0.084	0.9992	0.016	—*
0,45°	6**	0.80	−0.195	0.9993	0.015	0.91
0*,45°	7	0.82	−0.179	0.9997	0.015	0.89
50,25°	7	1.41	0.548	0.9988	0.032	0.80
50,30°	7	1.46	0.551	0.9996	0.018	0.80

* We could not estimate this value, since log k' for benzyl alcohol was not determined under this condition.

** Hexanol-1 is not included, since log k' for this alcohol could not be determined under this condition.

Fig. 5 shows that this equation holds for seven pairs of alcohols and amino acids, except for the pair of alanine and methanol. Alanine[33] and methanol (data not shown in Table I) deviate from the linear relationship between log k' and m for linear amino acids[33] and alcohols, respectively. The log k' data for the amino acids were taken from the literature (5-μm LiChrosorb RP-18, eluent 0.5 M perchloric acid, pH 0.2, 70°C and flow-rate 2.0 ml/min)[33]. By using this linear relationship and the log k' value for benzyl alcohol, we can predict the log k' value for phenylalanine under the above conditions, though this value was not determined experimentally[33]. As Table VI shows, the estimated log k' (Phe) values are dependent slightly on the conditions used to determine the log k' (benzyl alcohol) value. The average log k' (Phe) value is 0.84.

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