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HYDROGEN BONDING. 42. CHARACTERIZATION OF REVERSED-PHASE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC C_{18} STATIONARY PHASES

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The linear free energy equation

$$\log k' = c + rR_2 + s\pi_2^H + a\Sigma a_2^H + b\Sigma\beta_2 + vV_x$$

was applied to the capacity factors for various series of solutes on C_{18} stationary phases with aqueous methanol and acetonitrile eluents. Here, k' are the capacity factors for a series of solutes with a given C_{18} phase and a given eluent, and R_2, π_2^H, $\Sigma\alpha_2^H$, $\Sigma\beta_2$ and V_x are parameters or descriptors of the solutes as follows: R_2 is an excess molar refraction, π_2^H is the solute polarizability/dipolarity, $\Sigma\alpha_2^H$ and $\Sigma\beta_2$ are the solute hydrogen-bond acidity and basicity and V_x is the solute volume. It is shown that although the regression coefficients *r, s, a, b* and *v* vary widely with the C_{18} column and mobile phase used, the ratios *r/v, s/v, a/v* and *b/v* are remarkably constant. Thus, for the retention of 25 series of solutes on six different C_{18} columns with 30–90% aqueous methanol as the eluent, all the 25 LFER equations can be combined into one general equation:

$$\log k' = c + v(0{\cdot}13\,R_2 - 0{\cdot}32\,\pi_2^H - 0{\cdot}22\,\Sigma\alpha_2^H - 0{\cdot}90\,\Sigma\beta_2^O + 1{\cdot}00\,V_x)$$

where only *c* and *v* vary from system to system. For 11 other phases for which data are available, the ratios *v/A* and *(v+c)/A* are constant, where *A* is the quantity of stationary phase per unit surface area. Similar results were found with C_{18} phases and aqueous acetonitrile as eluents. Although a first examination of equations based on the first equation above suggests that various C_{18} phases behave differently, for example the *v* coefficient, that is related to the observed hydrophobicity of a stationary phase relative to the mobile phase, varies considerably from phase to phase with the same eluent, a detailed analysis led to the conclusion that all the C_{18} phases examined have roughly the same hydrophobicity, when the *v* coefficients are corrected for the quantity of stationary phase per unit surface area. It is suggested that these corrected *v* coefficients, *v/A* or *(v+c)/A*, can be regarded as the 'intrinsic' phase hydrophobicity. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

The effect of solute structure and mobile phase composition on reversed-phase high-performance liquid chromatography (RP-HPLC) has been investigated fairly thoroughly. Several different methods have been used to study factors such as solute selectivity and the analysis of complex mixtures, including the use of interaction indices,[1] functional group contributions,[2] principal component analysis[3] and various solvation equations.[4–12] There have been several studies, also, on the characterization of RP-HPLC stationary phases, although many are restricted to measurement of the ratio of capacity factors, k', of two test solutes, as summarized by Poole and Poole.[13] Of the more extensive studies, Delaney *et al*.[14] characterized 10 stationary phases by chemometric methods, but with a limited selection of solutes. More recently, Schmitz *et al*.[15] examined 26 HPLC columns using nine different solutes, by various chemometric methods. They showed that the columns could be grouped into three sets; C_8 phases, C_{18} phases and polymer-coated phases. Righezza and Chrétien,[16] in a very comprehensive study, included normal phase systems as well as reversed-phase

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Table 1. Solutes tested by Chrétien *et al*.[17] and their descriptors

Solute	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^O$	V_x
Nitrobenzene	0·845	1·11	0·00	0·28	0·890
Naphthalene	1·340	0·92	0·00	0·20	1·085
Phenanthrene	2·055	1·29	0·00	0·26	1·454
Methyl benzoate	0·733	0·85	0·00	0·46	1·072
Biphenyl	1·360	0·99	0·00	0·22	1·324
Diethyl phthalate	0·729	1·40	0·00	0·88	1·710
Anthracene	2·290	1·34	0·00	0·26	1·454
p-Cresol	0·820	0·87	0·57	0·31	0·916
2-Phenylethanol	0·811	0·91	0·30	0·64	1·056
Benzophenone	1·447	1·50	0·00	0·50	1·481
Benzyl alcohol	0·803	0·87	0·33	0·56	0·916
3-Phenylpropanol	0·821	0·90	0·30	0·67	1·197
4-Phenylbutanol	0·811	0·90	0·33	0·70	1·338
6-Phenylhexanol	0·804	0·90	0·33	0·72	1·620

systems. For the latter, they also showed by hierarchical ascending classification and correspondence factor analysis that phases in RP-HPLC systems could be grouped into sets. In an earlier study, Chrétien *et al*.[17] determined logk' values on 14 ODS columns with the same mobile phase of 70% methanol–30% water. Application of correspondence factor analysis (CFA) suggested that five factors influenced solute selectivity, the main one being the phase hydrophobicity. We shall consider the results of Chrétien *et al*.[17] in more detail later.

Our approach to the characterization of HPLC phases (or, more correctly, systems) is different to the chemometric method, and involves the use of the linear free energy relationship (LFER) or solvation equation:[18]

$$\log SP = c + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2 + vV_x \qquad (1)$$

where *SP* is a property for a series of solutes in a fixed solvent system; in this work, *SP* will be k' for solutes in a

Table 2. Regression equations for Chrétien *et al*.'s data set

No.	Column	*c*	*r*	*s*	*a*	*b*	*v*	*R*	sd	*n*	*F*
A	RSIL C_{18} LL, 90×4 (Alltech)	−0·16	0·27	−0·47	−0·21	−0·50	0·79	0·991	0·048	14	83
B	RSIL C_{18} HL, 90×4 (Alltech)	−0·11	0·40	−0·77	−0·39	−0·96	1·29	0·997	0·046	14	242
C	Partisil ODS, 90×4 (Whatman)	−0·29	0·22	−0·37	−0·17	−0·38	0·63	0·989	0·041	14	73
D	Partisil ODS2, 90×4 (Whatman)	−0·13	0·44	−0·81	−0·40	−0·85	1·26	0·995	0·059	14	145
E	Partisil ODS3, 90×4 (Whatman)	−0·19	0·28	−0·60	−0·30	−0·78	1·09	0·997	0·034	14	287
F	Spherisorb ODS-2, 90×4 (Phase Separations)	−0·24	0·41	−0·76	−0·43	−0·97	1·25	0·996	0·050	14	213
G	μBondapak C_{18}, 90×4 (Waters)	−0·12	0·22	−0·45	−0·23	−0·67	0·89	0·995	0·038	14	150
H	Hypersil C_{18}, 90×4 (Shandon)	−0·21	0·36	−0·69	−0·32	−0·80	1·09	0·996	0·046	14	177
I	Spherosil XOA, 600 C_{18} 90×4 (Prolabo)	−0·04	0·44	−0·77	−0·43	−0·87	1·22	0·995	0·038	14	150
J	Nucleosil C_{18}, 90×4 (Macherey–Nagel)	0·00	0·35	−0·60	−0·31	−0·69	1·01	0·995	0·059	14	148
K	Nova Pak C_{18}, 100×5 (Waters)	−0·28	0·42	−0·89	−0·40	−1·05	1·45	0·998	0·043	14	327
L	Resolve C_{18} Radial Pak, 100×8 (Waters)	0·02	0·37	−0·59	−0·41	−0·71	0·93	0·995	0·048	14	154
M	μBondapak C_{18} Radial Pak, 100×8 (Waters)	0·04	0·23	−0·49	−0·25	−0·74	0·99	0·995	0·041	14	149
N	Zorbax ODS, 150×4·6 (Du Pont)	0·01	0·40	−0·83	−0·50	−1·06	1·40	0·997	0·052	14	225

Table 3. Details of the columns in Table 2

Column	Load (%)	End-capped	Particle size (μm)	Pore size (Å)	Surface area ($m^2\ g^{-1}$)	Surface coverage, *A* ($\mu mol\ m^{-2}$)	Particle shape
A							
B	16	Yes	5–10	80	550	1·66	Irregular
C	5	No	10	85	350	0·70	Irregular
D	16	No	10	85	350	2·60	Irregular
E	11	Yes	5–10	85	350	1·50	Irregular
F	12	Yes	5–10	80	220	2·94	Spherical
G	10	Yes	10	125	330	1·59	Irregular
H	10	Yes	5	100	200	2·62	Spherical
I							
J	13	No	5	100	350	2·03	Spherical
K	7	Yes	4	60	120	2·94	Spherical
L	10	No	5–10	90			Spherical
M	10	Yes	10	125	330	1·59	Irregular
N	15		5	75	330	2·55	Spherical

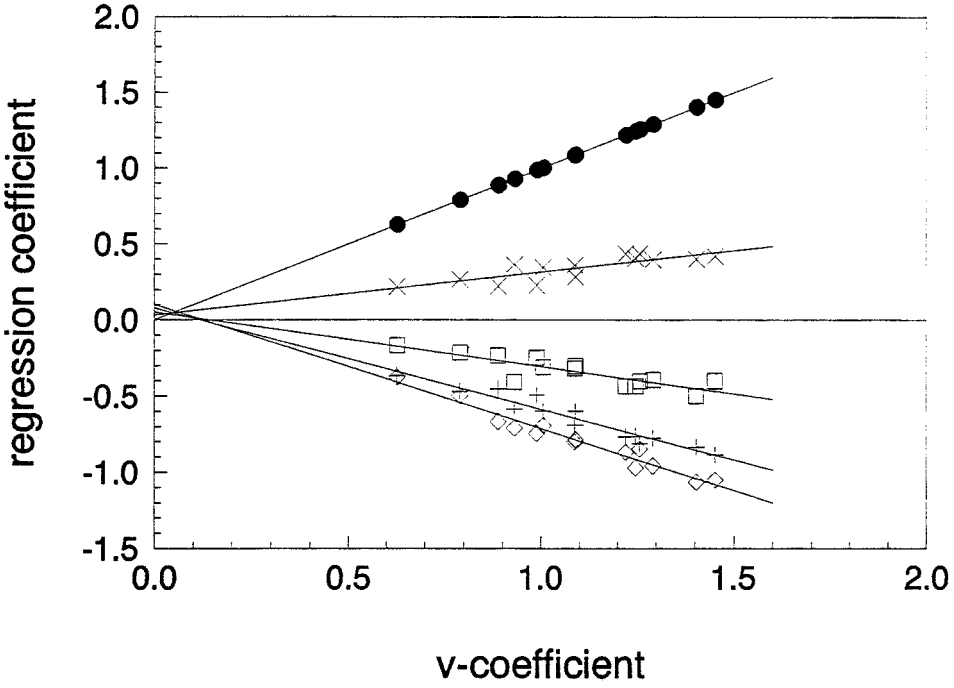

Figure 1. Plots of the regression coefficients vs the *v* coefficient for Chrétian *et al.*'s data set (Table 2). ×, *r* coefficient; ◇, *s* coefficient; +, *a* coefficient; ○, *b* coefficient; ●, *v* coefficient

given RP-HPLC stationary phase–mobile phase system. The explanatory variables in equation (1) are solute descriptors as follows:[18–20] R_2 is an excess molar refraction, π_2^H is the solute dipolarity/polarizability, $\sum\alpha_2^H$ and $\sum\beta_2$ are the solute overall or effective hydrogen-bond acidity and basicity and V_x is the McGowan characteristic volume.[7] For partitions between water and phases in which water is only sparingly soluble (e.g. hexane or chloroform), the basicity descriptor $\sum\beta_2^H$ is used, and for partitions between water and phases in which water is fairly soluble (e.g. octanol), the descriptor $\sum\beta_2^O$ is used.[12, 18–20] For RP-HPLC Processes, the $\sum\beta_2^O$ descriptor seems most appropriate,[12] and this is the basicity descriptor we shall use. The coefficients *c*, *r*, *s*, *a*, *b* and *v* in equation (1) are characteristic of the system, i.e. a particular RP-HPLC column with a particular mobile phase, so that if a number of columns are studied with the same mobile phase, the coefficients will characterize the various RP-HPLC columns. As input data we need sets of log*k*′ values for a reasonably wide range of solutes on various columns with a given mobile phase.

Table 4. Intrinsic hydrophobicity of columns A–N

Column	*v*	*v*+*c*	*A* (μmol m^{-2})	*v*/*A*	(*v*+*c*)/*A*
A	0·79	0·63			
B	1·29	1·18	1·66	0·78	0·71
C	0·63	0·33	0·70	0·90	0·47
D	1·26	1·13	2·60	0·48	0·43
E	1·09	0·90	1·50	0·73	0·60
F	1·25	1·01	2·94	0·43	0·34
G	0·89	0·77	1·59	0·56	0·48
H	1·09	0·88	2·62	0·42	0·34
I	1·22	1·18			
J	1·01	1·01	2·03	0·50	0·50
K	1·45	1·17	2·94	0·49	0·40
L	0·93	0·95			
M	0·99	1·02	1·59	0·62	0·64
N	1·40	1·41	2·55	0·55	0·55
				Av.: 0·59	0·50
				sd: 0·15	0·12

Our aim is not to probe the particular specificity of phases for one particular solute over another, or to deal with such matters as resolving power, but to set up a method for the general characterization of phases in terms of physicochemical quantities, in particular the coefficients in equation (1). We examine here only C_{18}-coated stationary phases, and leave functionally substituted phases until later.

RESULTS AND DISCUSSION

The data set of Chrétien *et al.*[17]

The first set of data we use is from the work of Chrétien *et al.*,[17] who studied the retention of a set of 47 congeneric

Table 5. Regression equations for Yamaguchi and co-workers' data set

Column	MeCN (%)	*c*	*r*	*s*	*a*	*b*	*v*	*n*	*r*	sd	*F*
LOC-ODS-E	60	−0·15	0·29	−0·67	−0·11	−1·17	1·04	67	0·994	0·042	1083
HIC-ODS-E	60	−0·09	0·27	−0·71	−0·35	−1·43	1·28	62	0·994	0·050	984
HIC-ODS-NE	60	−0·19	0·27	−0·66	−0·07	−1·20	1·17	66	0·994	0·045	928
LOC-ODS-E	70	−0·33	0·25	−0·62	−0·12	−1·05	0·94	70	0·995	0·039	1372
HIC-ODS-E	70	−0·22	0·33	−0·79	−0·17	−1·30	1·13	67	0·994	0·048	1063
HIC-ODS-NE	70	−0·32	0·25	−0·62	−0·15	−1·00	1·00	70	0·994	0·048	978

chalcones and 16 test compounds on 14 different C_{18} (ODS) columns with methanol–water (70:30) as the mobile phase. We had the necessary descriptors available for 14 of the test compounds, as given in Table 1. A very detailed explanation of the determination of the descriptors in equation (1) has been given in a review by Abraham and Chadha,[20] and so we do not deal with this aspect of our general method here. Application of equation (1) to the logk' values determined by Chrétien *et al*.[17] yielded the coefficients listed in Table 2. Also given are the standard deviation (sd), the correlation coefficient (*r*) and the *F*-statistic (*F*). The statistics are reasonably good, with *r* varying beween 0·989 and 0·997, and the overall sd of logk' varying between 0·034 and 0·059 units. Thus, for logk' values on column H,

$$\log k'(\mathrm{H}) = -0{\cdot}209 + 0{\cdot}362R_2 - 0{\cdot}690\pi_2^{\mathrm{H}} - 0{\cdot}317\sum\alpha_2^{\mathrm{H}} - 0{\cdot}799\sum\beta_2^{\mathrm{O}} + 1{\cdot}088\,V_x \quad (2)$$

From the coefficients in equation (2), we can deduce that the stationary phase interacts with solutes, preferentially to the mobile phase, through dispersion interactions (the *r* coefficient is positive), but that the stationary phase is less dipolar/polarizable (the *s* coefficient is negative), less hydrogen-bond basic (the *a* coefficient is negative) and less hydrogen-bond acidic (the *b* coefficient is negative) than the mobile phase. The important *v* coefficient (positive) shows that the stationary phase is more hydrophobic than the mobile phase. We use here the terminology of Tayar *et al*.:[21] an overall partition coefficient is a measure of lipophilicity, and the partition coefficient can be broken down into polar contributions [in our method, the sum of the first four terms in equation (1)] and a hydrophobic volume contribution, which is the vV_x term in equation (1).

Examination of Table 2 shows that the absolute values of the coefficients in equation (1) vary from HPLC column to column. For example, *b* varies from −0·375 (C) to −1·064 (N) and *v* from 0·627 (C) to 1·452 (K). As we have seen, these coefficients will reflect the difference in properties between the (constant) mobile phase and the solvated stationary phase that affect retention. Thus, for a given change in solute hydrogen-bond basicity logk' will be reduced in value much less with column C than with column N. However, the value of the coefficients must also reflect the amount if stationary phase on the column. If the amount of stationary phase increases, retention will increase, even though the difference in properties between the mobile phase and the stationary phase remains constant. We can see this effect on the coefficients in Table 2 by noting that the ratio of the coefficients remains fairly constant, even though the absolute value alters from equation to equation. Thus, in the HPLC columns C, K and N where the *b* and *v* coefficients show the largest absolute difference between the columns, the *b*/*v* ratio is −0·60 (C), −0·72 (K) and −0·76 (N).

Table 6. Ratio of coefficients for Yamaguchi and co-workers' phases

Column	MeCN (%)	*r*/*v*	*s*/*v*	*a*/*v*	*b*/*v*
LOC-ODS-E	60	0·28	−0·64	−0·11	−1·13
HIC-ODS-E	60	0·21	−0·55	−0·27	−1·12
HIC-ODS-NE	60	0·23	−0·56	−0·06	−1·03
LOC-ODS-E	70	0·27	−0·66	−0·13	−1·12
HIC-ODS-E	70	0·29	−0·70	−0·15	−1·15
HIC-ODS-NE	70	0·25	−0·62	−0·15	−1·00

In Figure 1 are plotted the coefficients vs the *v* coefficient for all 14 columns. Good straight lines are obtained that pass close to the origin, so that each coefficient can be considered proportional to *v*. Therefore, the sets of equations in Table 2 can be written as

$$\log k' = c + g(krR_2 + ks\pi_2^{\mathrm{H}} + ka\Sigma\alpha_2^{\mathrm{H}} + kb\Sigma\beta_2^{\mathrm{O}} + kvV_x) \quad (3)$$

where *c* and *g* depend on the column, but *kr*, *ks*, *ka*, *kb* and *kv* are constant across all the columns. If we set *kv*=1, then *kr*, *ks*, *ka* and *kb* are the slopes of the lines shown in Figure 1, and the constant *g* is identical with the *v* coefficient:

$$\log k' = c + v(krR_2 + ks\pi_2^{\mathrm{H}} + ka\Sigma\alpha_2^{\mathrm{H}} + kb\Sigma\beta_2^{\mathrm{O}} + 1{\cdot}00\,V_x) \quad (4)$$

If we insert the slopes that we calculate for the lines, we have

$$\log k' = c + v(0{\cdot}28\,R_2 - 0{\cdot}66\pi_2^{\mathrm{H}} - 0{\cdot}36\sum\alpha_2^{\mathrm{H}} - 0{\cdot}81\sum\beta_2^{\mathrm{O}} + 1{\cdot}00\,V_x) \quad (5)$$

Equation (5) is a general equation that correlates the logk' values for 14 solutes on 14 ODS phases in terms of two parameters, *c* and *v*, that vary from column to column. Of course, since the other coefficients in Table 2 are related to the *v* coefficient (see Figure 1), we could have chosen *c* and *b* (or *c* and *s*, etc.) as the two parameters. However, the *c* and *v* parameters are easier to interpret. We can regard the sum of *c* plus *v* as the logk' value of a solute with zero

Table 7. Regression equations for RP-HPLC C_{18} systems

Stationary phase	Mobile phase	Ref.[a]	*c*	*r*	*s*	*a*	*b*	*v*
Hypersil ODS	50% methanol	TOM	−0·67	0·17	−0·67	−0·19	−1·85	2·46
Hypersil ODS	75% methanol	TOM	−0·91	0·09	−0·46	−0·27	−1·26	1·59
Hypersil ODS (Shandon)	30% methanol	HAF	−0·55	0·24	−0·70	−0·13	−2·65	3·22
Hypersil ODS (Shandon)	45% methanol	HAF	−0·53	0·22	−0·61	−0·21	−2·35	2·53
Hypersil ODS (Shandon)	60% methanol	HAF	−0·72	0·16	−0·54	−0·26	−1·95	2·09
Hypersil ODS (Shandon)	75% methanol	HAF	−0·89	0·12	−0·46	−0·28	−1·60	1·63
Hypersil ODS (Shandon)	90% methanol	HAF	−1·12	0·11	−0·42	−0·30	−1·24	1·23
C_{18} (Perkin-Elmer)	75% methanol	GAE	−0·58	0·19	−0·46	−0·28	−0·98	1·15
Zorbax ODS	40% methanol	YPZ	−0·32	0·35	−0·86	−0·31	−2·32	2·96
Zorbax ODS	50% methanol	YPZ	−0·45	0·37	−0·83	−0·30	−2·16	2·68
Zorbax ODS	60% methanol	YPZ	−0·59	0·32	−0·73	−0·30	−1·91	2·32
Zorbax ODS	70% methanol	YPZ	−0·68	0·26	−0·63	−0·29	−1·68	1·96
Nucleosil 5-C_{18}	45% methanol	KHN	0·11	0·20	−0·56	−0·44	−1·76	2·02
Nucleosil 5-C_{18}	50% methanol	KHN	0·12	0·19	−0·51	−0·44	−1·62	1·78
Nucleosil 5-C_{18}	55% methanol	KHN	0·11	0·22	−0·48	−0·43	−1·48	1·55
Nucleosil 5-C_{18}	60% methanol	KHN	0·10	0·20	−0·42	−0·40	−1·31	1·34
Nucleosil 5-C_{18}	65% methanol	KHN	0·13	0·20	−0·34	−0·37	−1·13	1·10
Nucleosil 5-C_{18}	70% methanol	KHN	0·09	0·16	−0·32	−0·33	−0·96	0·95
Nucleosil 5-C_{18}	75% methanol	KHN	0·09	0·15	−0·28	−0·29	−0·77	0·76
Nucleosil 5-C_{18}	80% methanol	KHN	0·09	0·12	−0·23	−0·25	−0·65	0·62
Spherisorb ODS-2	40% methanol	SMI	−0·36	0·37	−0·83	−0·49	−2·07	2·70
Spherisorb ODS-2	50% methanol	SMI	−0·24	0·25	−0·69	−0·46	−1·84	2·14
Spherisorb ODS-2	60% methanol	SMI	−0·32	0·25	−0·65	−0·43	−1·53	1·77
Spherisorb ODS-2	70% methanol	SMI	−0·36	0·28	−0·58	−0·44	−1·23	1·35
Spherisorb ODS-2	80% methanol	SMI	−0·45	0·28	−0·55	−0·40	−0·90	1·03
YMC Pack ODS-A	30% acetonitrile	SY	−0·35	0·58	−0·73	−0·18	−2·34	2·24
Zorbax ODS	40% acetonitrile	YPZ	−0·11	0·19	−0·44	−0·56	−2·01	2·00
Zorbax ODS	50% acetonitrile	YPZ	−0·12	0·25	−0·45	−0·45	−1·62	1·57
Zorbax ODS	60% acetonitrile	YPZ	−0·13	0·21	−0·41	−0·41	−1·32	1·25
Spherisorb ODS-2	30% acetonitrile	SMI	−0·11	0·38	−0·63	−0·63	−2·10	2·27
Spherisorb ODS-2	40% acetonitrile	SMI	−0·08	0·29	−0·53	−0·54	−1·65	1·72
Spherisorb ODS-2	50% acetonitrile	SMI	−0·11	0·22	−0·44	−0·52	−1·34	1·33
Spherisorb ODS-2	60% acetonitrile	SMI	−0·21	0·18	−0·40	−0·46	−1·09	1·10
Spherisorb ODS-2	70% acetonitrile	SMI	−0·29	0·15	−0·37	−0·43	−0·87	0·89
Spherisorb ODS-2	80% acetonitrile	SMI	−0·41	0·12	−0·34	−0·37	−0·76	0·78
ERC-1000 (ODS)	50% acetonitrile	HH1	−0·20	0·02	−0·18	−0·58	−1·50	1·60
ERC-1000 (ODS)	60% acetonitrile	HH1	−0·26	−0·02	−0·17	−0·52	−1·34	1·37
ERC-1000 (ODS)	70% acetonitrile	HH1	−0·39	−0·01	−0·18	−0·50	−1·19	1·24
ERC-1000 (ODS)	80% acetonitrile	HH1	−0·52	−0·01	−0·19	−0·47	−1·02	1·10
ERC-1000 (ODS)	90% acetonitrile	HH1	−0·62	0·01	−0·22	−0·39	−0·80	0·92
Unisil C_{18}	20% acetonitrile	HH3	−0·26	0·24	−0·39	−0·29	−2·11	2·81
Unisil C_{18}	30% acetonitrile	HH3	−0·24	0·21	−0·30	−0·31	−1·53	2·15
Unisil C_{18}	40% acetonitrile	HH3	−0·32	0·28	−0·26	−0·26	−1·18	1·67
Unisil C_{18}	50% acetonitrile	HH3	−0·33	0·28	−0·24	−0·22	−0·90	1·27
Unisil C_{18}	60% acetonitrile	HH3	−0·37	0·28	−0·21	−0·18	−0·69	1·00
Unisil C_{18}	70% acetonitrile	HH3	−0·34	0·24	−0·19	−0·13	−0·53	0·78
Unisil C_{18}	80% acetonitrile	HH3	−0·35	0·21	−0·15	−0·10	−0·38	0·60
Unisil C_{18}	90% acetonitrile	HH3	−0·30	0·17	−0·13	−0·06	−0·28	0·41
Spherisorb ODS-2	30% tetrahydrofuran	SMI	0·19	−0·07	−0·33	−0·12	−2·38	1·95
Spherisorb ODS-2	40% tetrahydrofuran	SMI	0·14	−0·11	−0·26	−0·19	−1·75	1·37
Spherisorb ODS-2	50% tetrahydrofuran	SMI	0·03	−0·11	−0·21	−0·20	−1·30	0·96
Spherisorb ODS-2	60% tetrahydrofuran	SMI	−0·09	−0·09	−0·20	−0·26	−0·98	0·69

Table 7. Continued

Stationary phase	Mobile phase	Ref.	*n*	*R*	sd	*F*
Hypersil ODS	50% methanol	TOM	69	0·992	0·10	809
Hypersil ODS	75% methanol	TOM	69	0·987	0·09	466
Hypersil ODS (Shandon)	30% methanol	HAF	23	0·996	0·06	382
Hypersil ODS (Shandon)	45% methanol	HAF	23	0·996	0·06	519
Hypersil ODS (Shandon)	60% methanol	HAF	29	0·996	0·07	543
Hypersil ODS (Shandon)	75% methanol	HAF	29	0·994	0·06	407
Hypersil ODS (Shandon)	90% methanol	HAF	29	0·994	0·05	354
C_{18} (Perkin-Elmer)	75% methanol	GAE	59	0·986	0·06	369
Zorbax ODS	40% methanol	YPZ	23	0·996	0·06	378
Zorbax ODS	50% methanol	YPZ	23	0·995	0·06	371
Zorbax ODS	60% methanol	YPZ	23	0·994	0·06	286
Zorbax ODS	70% methanol	YPZ	23	0·992	0·07	202
Nucleosil 5-C_{18}	45% methanol	KHN	31	0·992	0·06	304
Nucleosil 5-C_{18}	50% methanol	KHN	34	0·994	0·05	502
Nucleosil 5-C_{18}	55% methanol	KHN	35	0·994	0·04	523
Nucleosil 5-C_{18}	60% methanol	KHN	35	0·994	0·04	455
Nucleosil 5-C_{18}	65% methanol	KHN	35	0·992	0·05	351
Nucleosil 5-C_{18}	70% methanol	KHN	35	0·992	0·04	343
Nucleosil 5-C_{18}	75% methanol	KHN	32	0·991	0·04	299
Nucleosil 5-C_{18}	80% methanol	KHN	33	0·989	0·04	235
Spherisorb ODS-2	40% methanol	SMI	112	0·995	0·07	2069
Spherisorb ODS-2	50% methanol	SMI	114	0·993	0·08	1551
Spherisorb ODS-2	60% methanol	SMI	126	0·992	0·07	1408
Spherisorb ODS-2	70% methanol	SMI	126	0·991	0·06	1337
Spherisorb ODS-2	80% methanol	SMI	126	0·987	0·06	919
YMC Pack ODS-A	30% acetonitrile	SY	26	0·988	0·08	169
Zorbax ODS	40% acetonitrile	YPZ	23	0·994	0·07	289
Zorbax ODS	50% acetonitrile	YPZ	23	0·994	0·05	294
Zorbax ODS	60% acetonitrile	YPZ	23	0·995	0·04	310
Spherisorb ODS-2	30% acetonitrile	SMI	103	0·993	0·08	1320
Spherisorb ODS-2	40% acetonitrile	SMI	112	0·991	0·08	1155
Spherisorb ODS-2	50% acetonitrile	SMI	127	0·990	0·07	1222
Spherisorb ODS-2	60% acetonitrile	SMI	127	0·990	0·06	1259
Spherisorb ODS-2	70% acetonitrile	SMI	127	0·988	0·05	993
Spherisorb ODS-2	80% acetonitrile	SMI	127	0·985	0·05	771
ERC-1000 (ODS)	50% acetonitrile	HH1	44	0·995	0·04	766
ERC-1000 (ODS)	60% acetonitrile	HH1	51	0·996	0·03	1278
ERC-1000 (ODS)	70% acetonitrile	HH1	57	0·997	0·04	1623
ERC-1000 (ODS)	80% acetonitrile	HH1	60	0·996	0·04	1294
ERC-1000 (ODS)	90% acetonitrile	HH1	62	0·992	0·05	717
Unisil C_{18}	20% acetonitrile	HH3	21	0·994	0·05	268
Unisil C_{18}	30% acetonitrile	HH3	34	0·994	0·04	475
Unisil C_{18}	40% acetonitrile	HH3	37	0·992	0·04	362
Unisil C_{18}	50% acetonitrile	HH3	37	0·989	0·04	279
Unisil C_{18}	60% acetonitrile	HH3	37	0·987	0·03	228
Unisil C_{18}	70% acetonitrile	HH3	37	0·982	0·03	167
Unisil C_{18}	80% acetonitrile	HH3	37	0·978	0·02	138
Unisil C_{18}	90% acetonitrile	HH3	37	0·976	0·02	126
Spherisorb ODS-2	30% tetrahydrofuran	SMI	30	0·996	0·06	604
Spherisorb ODS-2	40% tetrahydrofuran	SMI	30	0·995	0·05	481
Spherisorb ODS-2	50% tetrahydrofuran	SMI	30	0·994	0·04	425
Spherisorb ODS-2	60% tetrahydrofuran	SMI	30	0·993	0·04	343

[a] TOM: T. L. Hafkenscheid and E. Tomlinson, *Int. J. Pharm.* **17**, 1 (1983).
HAF: T. L. Hafkenshied, *J. Chromatogr. Sci.* **24**, 307 (1986); see Ref. 12.
GAE: F. Gago, J. Alvarez-Builla and J. Elguero, *J. Liq. Chromatogr.* **10**, 1031 (1987).
YPZ: F. Yuqi, Z. Pengling and H. Zhide, *Chromatographia* **25**, 382 (1988).
KHN: A. Kaibara, M. Hirose and T. Nakagawa, *Chromatographia* **29**, 551 (1990); data from the authors.
SMI: R. M. Smith and C. M. Burr, *J. Chromatogr.* **481**, 85 (1989); see Ref. 12.
SY: S. Yamauchi and H. Mori, *J. Chromatogr.* **515**, 305 (1990); data from the authors.
HH1: T. Hanai and J. Hubert, *J. Chromatogr.* **302**, 89 (1984); see Ref. 12.
HH3: T. Hanai and J. Hubert, *J. High Resolut. Chromatogr. Chromatogr. Commun.* **6**, 20 (1983); see Ref. 12.

values of R_2, π_2^H, $\sum\alpha_2^H$ and $\sum\beta_2^O$ and with a V_x value of 1·00, i.e. of about average size within the 14 solutes studied.

It is not possible, however, to predict *c* and *v*. The former will include a contribution from the phase ratio in the system under consideration, and the latter will depend on such factors as the actual amount of coating or the amount of coating per unit surface area. In Table 3 are given as many details as we could obtain from the suppliers of the 14 columns under study. There is no evident connection between *v* and factors such as pore size or surface area, but there is a strong connection with the surface loading of the stationary phase in the column, expressed as μmol m^{-2} (*A*), Table 4. We find that $v/A = 0{\cdot}59$ with an sd of 0·15, and that $(v+c)/A = 0{\cdot}50$ with an sd of 0·12 only (see Table 4). In general, it would not be correct to use the quantity $v+c$ because the phase ratio, included in the *c* coefficient, will vary with the packing density of the column, with the stationary phase and with the mobile phase. However, for C_{18} phases, which might have similar packing densities, and the same mobile phase, the phase ratio contribution to the *c* coefficient can be taken as roughly constant. In any case, we can take the almost constant v/A or $(v+c)/A$ ratios as a measure of the intrinsic hydrophobicity of the stationary phase. By this we mean the observed hydrophobicity, as deduced from the *v* coefficient, corrected for the surface loading of the stationary phase in the column. Therefore, although the various columns have *v* coefficients that range from 0·63 to 1·45 (with 70% methanol mobile phase), the intrinsic hydrophobicity remains roughly constant. We suggest that this is a chemically reasonable result—a parameter such as the 'real' or 'intrinsic' hydrophobicity of a C_{18} phase should not alter greatly from column to column.

It should be noted, however, that the 14 C_{18} columns are not exactly the same; thus the v/A ratio varies from 0·42 to 0·90 with an sd of 0·15 units. Our suggestion that all 14 C_{18} phases have about the same intrinsic hydrophobicity is thus not in conflict with the conclusion of Chrétien *et al*.,[17] who showed by correspondence factor analysis that there were differences in solute selectivity between the 14 phases.

The data set of Yamaguchi and co-workers[22, 23]

Yamaguchi *et al*.[22] studied the retention behaviour of alkanes, alcohols, alkylbenzenes, halogenated benzenes and polyaromatic hydrocarbons on four columns. These were of equal size and packed with the same support (ODS). The packings were high loading (16 wt%) with and without end-capping (HIC-E and HIC-NE), and low loading (8·9 wt%) with and without end-capping (LOC-E and LOC-NE). The mobile phases were various acetonitrile–water mixtures, Yamaguchi *et al*.[22] concluded that although the capacity

Table 8. Ratios of coefficients for RP-HPLC C_{18}–methanol systems

Stationary phase	Mobile phase	Ref.[a]	*r*/*v*	*s*/*v*	*a*/*v*	*b*/*v*
Hypersil ODS	50% methanol	TOM	0·07	−0·27	−0·08	−0·75
Hypersil ODS	75% methanol	TOM	0·06	−0·29	−0·17	−0·79
Hypersil ODS (Shandon)	30% methanol	HAF	0·08	−0·22	−0·04	−0·82
Hypersil ODS (Shandon)	45% methanol	HAF	0·09	−0·24	−0·08	−0·93
Hypersil ODS (Shandon)	60% methanol	HAF	0·07	−0·26	−0·13	−0·93
Hypersil ODS (Shandon)	75% methanol	HAF	0·07	−0·28	−0·17	−0·98
Hypersil ODS (Shandon)	90% methanol	HAF	0·09	−0·34	−0·24	−1·01
C_{18} (Perkin-Elmer)	75% methanol	GAE	0·16	−0·40	−0·24	−0·85
Zorbax ODS	40% methanol	YPZ	0·12	−0·29	−0·10	−0·78
Zorbax ODS	50% methanol	YPZ	0·14	−0·31	−0·11	−0·81
Zorbax ODS	60% methanol	YPZ	0·14	−0·31	−0·13	−0·82
Zorbax ODS	70% methanol	YPZ	0·13	−0·32	−0·15	−0·86
Nucleosil 5-C_{18}	45% methanol	KHN	0·10	−0·28	−0·22	−0·87
Nucleosil 5-C_{18}	50% methanol	KHN	0·11	−0·29	−0·25	−0·91
Nucleosil 5-C_{18}	55% methanol	KHN	0·14	−0·31	−0·28	−0·95
Nucleosil 5-C_{18}	60% methanol	KHN	0·15	−0·32	−0·30	−0·98
Nucleosil 5-C_{18}	65% methanol	KHN	0·18	−0·31	−0·34	−1·03
Nucleosil 5-C_{18}	70% methanol	KHN	0·17	−0·34	−0·34	−1·01
Nucleosil 5-C_{18}	75% methanol	KHN	0·20	−0·37	−0·39	−1·02
Nucleosil 5-C_{18}	80% methanol	KHN	0·19	−0·38	−0·39	−1·04
Spherisorb ODS-2	40% methanol	SMI	0·14	−0·31	−0·18	−0·77
Spherisorb ODS-2	50% methanol	SMI	0·12	−0·32	−0·22	−0·86
Spherisorb ODS-2	60% methanol	SMI	0·14	−0·37	−0·24	−0·86
Spherisorb ODS-2	70% methanol	SMI	0·21	−0·43	−0·33	−0·91
Spherisorb ODS-2	80% methanol	SMI	0·27	−0·53	−0·39	−0·88
		Av.:	0·13	−0·32	−0·22	−0·90
		sd:	0·05	0·07	0·10	0·09

[a] See footnote to Table 7.

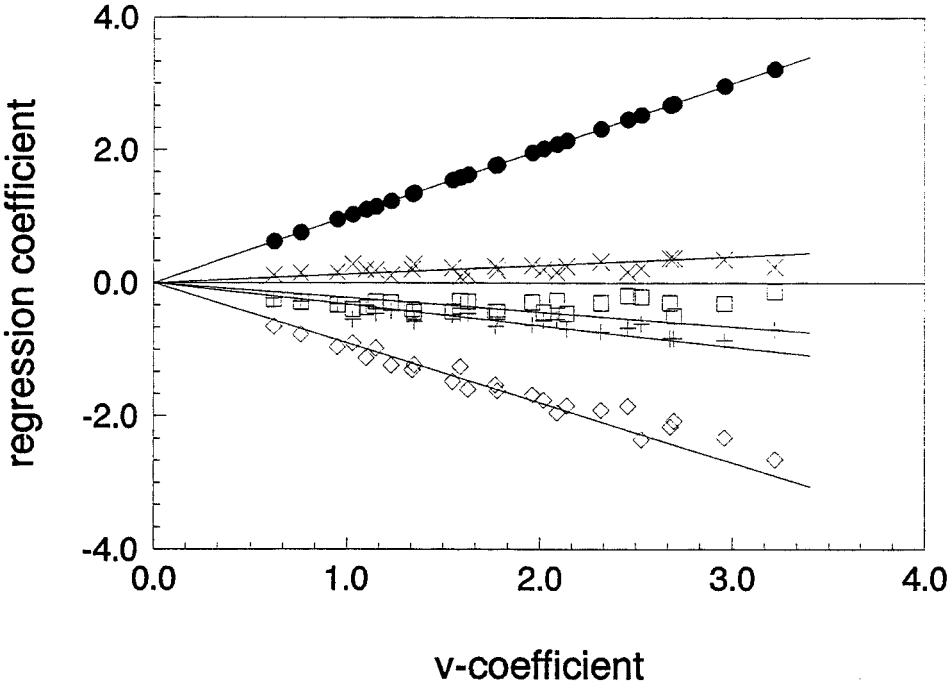

Figure 2. Plots of the regression coefficients vs the *v* coefficient for the other C_{18}–aqueous methanol sets (Table 8). Symbols as in Figure 1

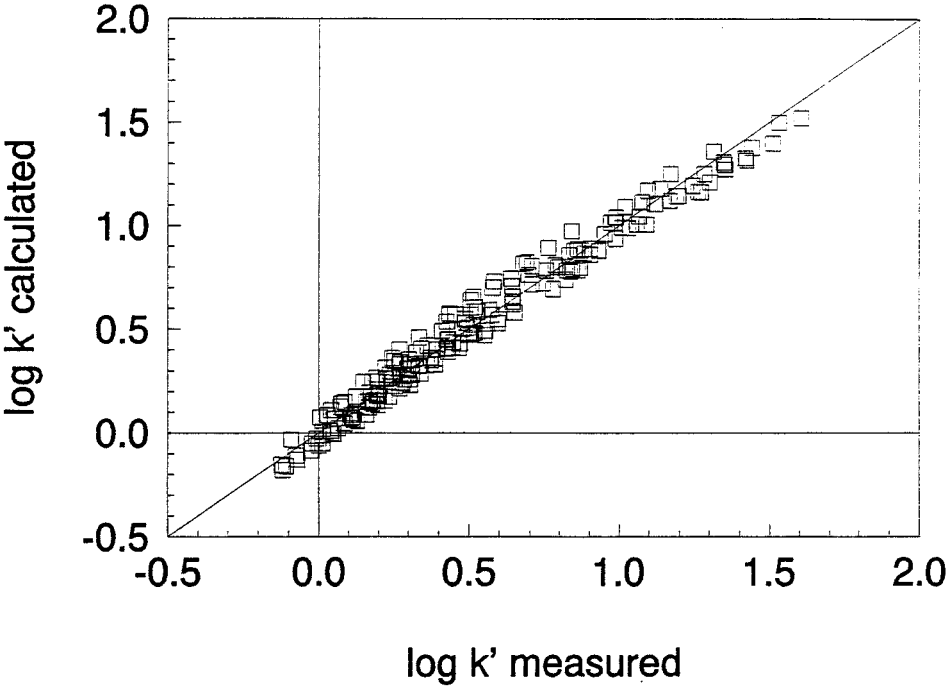

Figure 3. Plot of calculated vs observed log*k′* for Chrétian *et al.*'s data. Calculated values from equation (6)

Table 9. Ratios of coefficients for RP-HPLC C_{18}–MeCN and THF systems

Stationary phase	Mobile phase	Ref.[a]	*r*/*v*	*s*/*v*	*a*/*v*	*b*/*v*
YMC Pack ODS-A	30% acetonitrile	SY	0·26	−0·33	−0·08	−1·05
Zorbax ODS	40% acetonitrile	YPZ	0·09	−0·22	−0·28	−1·01
Zorbax ODS	50% acetonitrile	YPZ	0·16	−0·29	−0·29	−1·03
Zorbax ODS	60% acetonitrile	YPZ	0·17	−0·33	−0·33	−1·06
Spherisorb ODS-2	30% acetonitrile	SMI	0·17	−0·28	−0·28	−0·93
Spherisorb ODS-2	40% acetonitrile	SMI	0·17	−0·31	−0·31	−0·96
Spherisorb ODS-2	50% acetonitrile	SMI	0·17	−0·33	−0·39	−1·01
Spherisorb ODS-2	60% acetonitrile	SMI	0·16	−0·36	−0·42	−0·99
Spherisorb ODS-2	70% acetonitrile	SMI	0·17	−0·41	−0·48	−0·98
Spherisorb ODS-2	80% acetonitrile	SMI	0·15	−0·43	−0·47	−0·97
ERC-1000 (ODS)	50% acetonitrile	HH1	0·01	−0·11	−0·36	−0·94
ERC-1000 (ODS)	60% acetonitrile	HH1	−0·01	−0·13	−0·38	−0·98
ERC-1000 (ODS)	70% acetonitrile	HH1	−0·01	−0·14	−0·40	−0·96
ERC-1000 (ODS)	80% acetonitrile	HH1	−0·01	−0·17	−0·42	−0·93
ERC-1000 (ODS)	90% acetonitrile	HH1	0·01	−0·24	−0·43	−0·87
Unisil C_{18}	20% acetonitrile	HH3	0·08	−0·14	−0·10	−0·75
Unisil C_{18}	30% acetonitrile	HH3	0·10	−0·14	−0·14	−0·71
Unisil C_{18}	40% acetonitrile	HH3	0·17	−0·16	−0·16	−0·71
Unisil C_{18}	50% acetonitrile	HH3	0·22	−0·19	−0·17	−0·71
Unisil C_{18}	60% acetonitrile	HH3	0·28	−0·21	−0·18	−0·69
Unicil C_{18}	70% acetonitrile	HH3	0·30	−0·25	−0·16	−0·68
Unisil C_{18}	80% acetonitrile	HH3	0·35	−0·26	−0·17	−0·63
Unisil C_{18}	90% acetonitrile	HH3	0·42	−0·31	−0·16	−0·67
LOC-ODS-E	60% acetonitrile		0·28	−0·64	−0·11	−1·13
HIC-ODS-E	60% acetonitrile		0·21	−0·55	−0·27	−1·12
HIC-ODS-NE	60% acetonitrile		0·23	−0·56	−0·06	−1·03
LOC-ODS-E	70% acetonitrile		0·27	−0·66	−0·13	−1·12
HIC-ODS-E	70% acetonitrile		0·29	−0·70	−0·15	−1·15
HIC-ODS-NE	70% acetonitrile		0·25	−0·62	−0·15	−1·00
		Av.:	0·18	−0·33	−0·26	−0·92
		sd:	0·11	0·18	0·13	0·16
Spherisorb ODS-2	30% tetrahydrofuran	SMI	−0·04	−0·17	−0·06	−1·22
Spherisorb ODS-2	40% tetrahydrofuran	SMI	−0·08	−0·19	−0·14	−1·28
Spherisorb ODS-2	50% tetrahydrofuran	SMI	−0·11	−0·21	−0·21	−1·35
Spherisorb ODS-2	60% tetrahydrofuran	SMI	−0·13	−0·29	−0·37	−1·43
		Av.:	−0·09	−0·22	−0·19	−1·32
		sd:	0·04	0·05	0·13	0·09

[a] See footnote to Table 7.

factors on the two LOC columns were lower than those on the two HIC columns, the retention behaviour on the various columns was similar.

Analysis of Yamaguchi *et al*.'s data set[22] via equation (1) is difficult, as the only compounds that are hydrogen-bond acids are the alcohols. We therefore combined the data with those of Yamaguchi and Hanai[23] on phenols to give a large and varied set of solutes, although for only three of the phases previously studied. The derived regression equations are summarized in Table 5. We do not give the solute descriptors, because these have been set out previously.[12, 18] The equations are all statistically fairly good, with values of *r* of 0·994, sd between 0·039 and 0·048 and *F* between 928 and 1372. We cannot construct plots as shown in Figure 1, but we can show that the ratios of the coefficients are reasonably constant between 60 and 70% acetonitrile (Table 6). This provides some confirmation of our analysis of the Chrétien *et al*.s data set, and of the suggestion of Yamaguchi and co-workers that the retention behaviour on the columns with and without end-capping is similar.

General analysis

In order to see if our analysis, as summarized by Figure 1, is in any way general, we obtained regression equations for various RP-HPLC systems with C_{18} phases, and list these in Table 7. We have not used equations with less than about 20 data points, even though some such equations have been published. The variation of the coefficients with system is even larger than that for the restricted set of systems in Table 2, with the *v* coefficient varying between 0·62 and

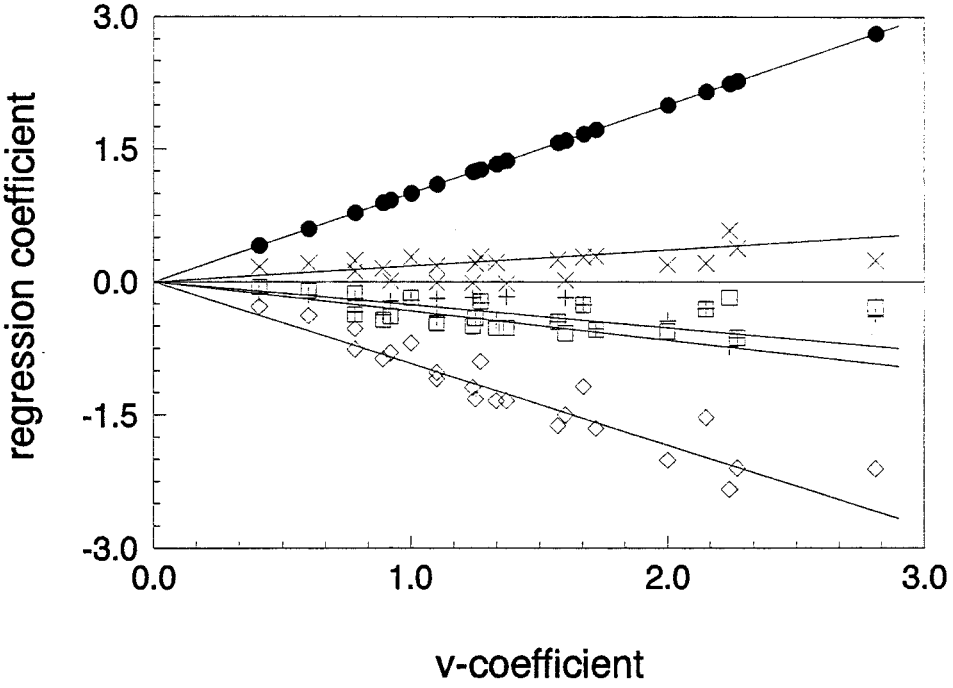

Figure 4. Plots of the regression coefficients vs the *v* coefficient for C_{18}–aqueous acetonitrile sets (Table 9). Symbols as in Figure 1

3·22 for methanol mobile phases and between 0·41 and 2·81 for acetonitrile mobile phases.

In spite of such large variations in the coefficients themselves, the ratio of coefficients is remarkably constant. In Table 8 are collected the ratios for all the equations in Table 7 with methanol mobile phases, together with the average (av.) and the standard deviation (sd). For 25 systems, with different C_{18} phases and elements with different methanol concentrations, the ratios are constant with sd values of *ca* 0·08 units; this is illustrated by the plot of *b* coefficients vs *v* coefficients shown in Figure 2. Now the coefficients themselves vary considerably, and so do the sd values for the coefficients in the equations. If we average the sd values for the *b* and *v* coefficients in the various equations, for example, we can calculate by the propagation of errors the corresponding sd value for *b*/*v* expected as a result of random error in the coefficients. This turns out to be *ca* 0·05 for *b*/*v* and nearer 0·03 for the other ratios. In addition, there will be systematic errors as a result of widely different data sets used in the various equations. Hence the observed sd values of betweeen 0·05 and 0·10 are about as expected. We can say that the ratios *r*/*v*, *s*/*v*, *a*/*v* and *b*/*v* seem to be characteristic of C_{18} phases over a fairly wide range of aqueous methanol mixtures. This considerably extends the analysis via equations (3)–(5), and we can write for log*k*′ values for the 25 systems, with eluents with different methanol concentrations,

$$\log k' = c + v(0{\cdot}13\,R_2 - 0{\cdot}32\,\pi_2^{\mathrm{H}} - 0{\cdot}22\,\Sigma\alpha_2^{\mathrm{H}} - 0{\cdot}90\,\Sigma\beta_2^{\mathrm{O}} + 1{\cdot}00\,V_x) \quad (6)$$

where *c* and *v* now depend on the particular C_{18} phase and particular methanol-containing eluent.

We did not include Chrétien *et al.*'s data sets that we used above in the general analysis to obtain equation (6), because we restricted the general analysis to data sets with at least 20 points. Thus, although equation (5) is different to equation (6), the differences can probably be attributed to the small number of solutes in Chrétien *et al.*'s data sets for which we have descriptors, rather than to differences in the C_{18} column properties. This can be tested by fitting Chrétien *et al.*'s data to equation (6), obtaining the *c* and *v* parameters, and then calculating the log*k*′ values for all the solutes in all Chrétien *et al.*'s phases. A plot of the calculated and observed log*k*′ values is shown in Figure 3. The good fit indicates that equation (6) can also be applied to Chrétien *et al.*'s data, and that it is probably of general validity for C_{18} phases with aqueous methanol eluents.

In Table 7 are given details of regression equations with aqueous acetonitrile eluents. The coefficient ratios are given in Table 9, and a plot of the coefficients vs the *v* coefficients is shown in Figure 4. The ratios for acetonitrile eluents are similar to those for methanol eluents, but we prefer to keep the two sets of ratios separate. Once again, it seems clear

that all the C_{18} phases fall into the same pattern as regards the ratio of coefficients, and we can construct a similar equation to equation (6) for acetonitrile eluents:

$$\log k' = c + v(0{\cdot}18\,R_2 - 0{\cdot}33\,\pi_2^H - 0{\cdot}26\,\Sigma\alpha_2^H - 0{\cdot}92\,\Sigma\beta_2^O + 1{\cdot}00\,V_x) \quad (7)$$

We can use our analysis, as represented by equations (6) and (7), to resolve the different approaches of Cheong and Carr[24] and Rosés and Bosch.[25] The former workers used an LFER approach similar to the one that we use, and concluded that more than one solvent parameter was needed to account for all the processes or interactions that influence RP-HPLC retention. Certainly, solvent properties such as dipolarity/polarizability, hydrogen-bond acidity and hydrophobicity are important influences on retention, as we can see from the numerous regression equations we have listed. However also, and crucially, we have shown that these properties, as judged from the regression coefficients, are all linearly related over a solvent composition range from 30 to 90% methanol and from 30 to 90% acetonitrile. Hence the finding of Rosés and Bosch[25] that a single solvent parameter is sufficient to predict retention over a fairly wide range of solvent composition is not in conflict with the conclusion of Cheong and Carr,[24] and can be explained simply through equations (6) and (7).

The few systems in which aqueous tetrahydrofuran is the eluent seem to give rise to larger b/v ratios and to smaller a/v ratios than for the other systems with aqueous methanol and aqueous acetonitrile as eluents (see Table 9), but more such systems need to be examined.

Our analysis shows that a wide variety of C_{18} phases behave similarly as regards their relative dipolarity/polarizability, hydrogen-bond acidity and hydrogen-bond basicity to hydrophobicity. In retrospect, this might have been expected, and certainly indicates that the general chemical nature of the phases is similar. Other workers, e.g. Schmitz *et al.*[15] and Righezza and Chrétien,[16] have shown that there are differences amongst C_{18} phases. These differences, although significant in terms of separation of particular pairs of compound, are in general not very large. Thus, for 11 C_{18} phases, with the same 55% methanol eluent. Schmitz *et al.*[15] found that the capacity ratios of aniline to phenol were on average 0·88 with an sd of 0·23; transformed into logk' values, the average was $-0{\cdot}07$ with an sd of 0·11 log units. This is of the same order as the sd values of the ratios we have found, the latter also being in logarithmic form. Hence our analysis, as we stated in the Introduction, does not deal with the ranking of phases as regards particular separations, but with setting out a method for the overall classification of phases. As we shall show in a subsequent publication, a wider variety of phases than just C_{18} phases does lead to significant differences in coefficient ratios, so that the ratios can be used to classify phases in a chemically meaningful way.

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