ELSEVIER

Journal of Chromatography A, 945 (2002) 83–96

JOURNAL OF CHROMATOGRAPHY A

www.elsevier.com/locate/chroma

Retention of ionizable compounds on high-performance liquid chromatography
XI. Global linear solvation energy relationships for neutral and ionizable compounds

Sonia Espinosa, Elisabeth Bosch, Martí Rosés*

Departament de Química Analítica, Universitat de Barcelona Diagonal 647, E-08028 Barcelona, Spain

Received 23 July 2001; received in revised form 12 October 2001; accepted 6 November 2001

Abstract

A global linear solvation energy relationship (LSER) that simultaneously models retention in reversed-phase liquid chromatography as a function of solute LSER descriptors and mobile phase pH and composition has been derived from both the local LSER model and the linear solvent strength theory. At most only 13 mobile phase parameters and seven solute parameters are required to establish the global LSER model for neutral and ionizable solutes. This model implies only one mobile phase and two solute parameters more than the model previously set for neutral solutes. The additional mobile phase and solute parameters account for the ionization of the solute. The model has been successfully tested for 30 solutes of different type (acids, bases and non ionizable compounds) at 10 different pH values in three different acetonitrile–water mobile phases.

Keywords: Linear solvation energy relationships; Retention models; Linear solvent strength theory; Ionizable compounds

1. Introduction

The retention of a solute in reversed-phase liquid chromatography (RPLC) is a very complex process which depends on many factors. On one hand, on the phase system, i.e., stationary phase characteristics [1,2], type of organic modifier and mobile phase composition [3–6]. On the other hand, on the solute molecular properties of the compounds to be separated [3]. Moreover, the temperature is also another factor to be considered [7–9].

Many models have been developed to predict the retention of a solute in RPLC, but there are so many physical and chemical properties of the system to consider that there is not a unique and general model established.

2. Theory

2.1. Linear solvation energy relationship (LSER) models for neutral solutes

The linear solvent strength theory (LSST) model

*Corresponding author. Tel.: +34-93-4021-796; fax: +34-93-4021-233.

E-mail address: marti@apolo.qui.ub.es (M. Rosés).

0021-9673/02/$ – see front matter
PII: S0021-9673(01)01486-8

relates the retention changes of a neutral compound with the composition of the mobile phase following a linear exponential model [10–15] only over a limited range of organic solvent:

$$\log k = \log k_w - m_k \phi \quad (1)$$

where k is the solute retention factor at a specific mobile phase composition, ϕ, expressed as a volume fraction of organic modifier in the mobile phase. k_w is the solute retention factor extrapolated to mobile phase equivalent to pure water, and m_k is a solute-dependent solvent strength parameter specific to the organic modifier on the stationary phase under consideration. Eq. (1) is never exact over the entire range of mobile phase compositions and the values of k_w and m_k obtained vary substantially with the type of mobile phase modifier. This model is the basis of the most popular programs, such as DryLab or ChromSword, for optimization of high-performance liquid chromatography (HPLC) separations [16].

The LSER model has been widely used to predict the retention of neutral organic compounds under reversed-phase liquid chromatographic conditions. The model relates the retention at a single mobile phase composition as a function of the solute molecular properties:

$$\log k = c + eE + sS + aA + bB + vV \quad (2)$$

where k is the solute retention factor. The solute descriptors are the excess molar refraction E (in $cm^3/10$), the dipolarity/polarizability S, the solute's effective hydrogen-bond acidity A and hydrogen-bond basicity B, and McGowan's characteristic volume V (in $cm^3\ mol^{-1}/100$).

The coefficients in Eq. (2) are calculated from the retention of a series of compounds with known descriptors by multiple linear regression and are characteristic of the difference in solvation properties of both phases forming the chromatographic system. The e constant determines the difference in capacity of the solvated stationary and mobile phases to interact with solute n- and π-electrons; the s constant, to the difference in capacity of the solvated stationary and mobile phases to take part in dipole–dipole and dipole–induced dipole interactions; the a and b constants are measures of the differences in hydrogen-bond basicity and acidity, respectively, of the stationary and the mobile phases; and the v constant is a measure of the relative ease of forming a cavity for the solute in the solvated stationary and mobile phases.

In order to predict retention for multiple neutral solutes at multiple mobile phase compositions, and eventually to make selectivity and optimization much more efficient, Wang et al. [10] modelled by the LSER theory the $\log k_w$ and m_k linear free energy parameters from Eq. (1):

$$\log k_w = c_w + e_w E + s_w S + a_w A + b_w B + v_w V \quad (3)$$

$$m_k = c_m + e_m E + s_m S + a_m A + b_m B + v_m V \quad (4)$$

and replacing Eqs. (3) and (4) in Eq. (1), a global linear solvation energy relationship model (global LSER) was derived:

$$\log k = (c_w - c_m\phi) + (e_w - e_m\phi)E + (s_w - s_m\phi)S + (a_w - a_m\phi)A + (b_w - b_m\phi)B + (v_w - v_m\phi)V \quad (5)$$

The same model is obtained considering the coefficients of Eq. (2) as linear relationships of ϕ. At most, only 12 coefficients are required to establish the global LSER, but many more coefficients would be required if the same data were fitted using one LSER model for each mobile phase composition [10].

2.2. LSER models for ionizable compounds

All the models explained above can be only applied to the retention of neutral compounds and some modifications should be considered in order to apply them to ionizable compounds. In fact, the retention of an ionizable compound in RPLC is different from the retention of a neutral one. At a fixed mobile phase composition, the retention of a neutral compound remains constant at any mobile phase pH. But an ionizable compound presents an equilibrium between its acidic (HA) and its basic (A) forms related by the dissociation constant where the concentration of each form depends on factors that affect the extent of the dissociation (composition, ionic strength and pH of the mobile phase). The ionic form of the compound exhibits a shorter retention

time than the one of the neutral form, and the observed retention factor (k) is an average of the retention factors of the acid (k_{HA}) and basic forms (k_A) [14,15,17–22], according to the mole fraction of each species (HA or A) in the mobile phase solution:

$$k = (k_{HA} + k_A 10^{pH-pK})/(1 + 10^{pH-pK}) \quad (6)$$

The mobile phase pH can be measured in any of the rigorous ${}^{s}_{s}$pH or ${}^{s}_{w}$pH scales [23–25] and the pK value will be given in the same scale. We shall use here the notation for pH and pK definition recommended by the IUPAC [23–26]. A left hand superscript indicates the solvent where the pH is measured or pK determined. A left hand subscript indicates the solvent (mobile phase s, or water w, usually) where the hydrogen ion activity coefficient is referred to unity at infinite dilution. We also use the approximation that all ionic activity coefficients are unity. Since the ionic strength of the HPLC buffers used is small, the error introduced with this assumption is much smaller that the errors implied in the LSST and LSER models.

The great changes in the retention of an ionizable compound do not allow to estimate accurately its retention using the original LSER model, where only the descriptors of the neutral form of the solute are considered. Some modifications to Eq. (2) have been done with the purpose of using the same model to predict the retention of ionized or partially ionized compounds in RPLC, too. In a previous work [17] two different descriptors, D and P, were added independently to Eq. (2) to account for the ionization of the solutes. The D descriptor is the degree of ionization of the solute at the pH of the mobile phase and the P descriptor considers the effective acid dissociation constant for the mobile phase composition (${}^{s}_{s}$pK).

Both new models were applied to the retention of a group of neutral and phenolic compounds on a polymeric column with methanol–water (50:50, v/v) at ${}^{s}_{s}$pH values of 4, 7, 9, 11 and 12 as mobile phase, in order to compare them. The new models performed much better than Eq. (2). However, the P solute descriptor performed better than the D descriptor, because with this last descriptor, the accuracy of the predicted retention was getting worse as the mobile phase pH was increasing (for acidic neutral compounds). However, this model did not allow to be generalised to different types of solutes (acids and bases) [27].

In the search of an appropriate solute descriptor for the ionization, a further model based in the degree of ionization of a solute was developed, too [27]. In the previous model with the D descriptor, the retention of the ionized form of a solute was assumed to be insignificant compared to the neutral form, and it was neglected. But in this instance, the retention factors of the neutral (k_0) and ionized forms (k_1) of a compound were considered and both of them were related through an f parameter defined as:

$$\log f = \log k_1 - \log k_0 \quad (7)$$

Eq. (6) can then be rewritten in its logarithmic form as:

$$\log k = \log k_0 + \log[1 - D(1 - f)] \quad (8)$$

where D is the degree of ionization of the solute:

$$D = 10^{pH-pK}/(1 + 10^{pH-pK}) \quad (9)$$

In Eq. (9), pK is the dissociation constant of the solute at the mobile phase composition and pH is the mobile phase pH value, which again can be given in the ${}^{s}_{s}$pH or ${}^{s}_{w}$pH scales.

Since the $\log k_0$ value is linearly related to the solute descriptors of the neutral compound, and considering Eqs. (2) and (8), the final correlation equation is:

$$\log k = c + eE + sS + aA + bB + vV + d \log [1 - D(1 - f)] \quad (10)$$

where d should be equal to 1. The results obtained with the model with the P solute descriptor were compared to the results obtained with Eq. (10) using the same set of neutral and phenolic compounds in the mobile phases described previously [27]. The P solute descriptor can be easily calculated from the pK value of the phenol at the mobile phase composition, but generalisation of the correlation equation to different mobile phase pH values and to basic compounds is not possible. However, prediction of retention from the $\log [1-D(1-f)]$ solute descriptor requires accurate mobile phase pH measurements and solute pK estimation, but the same correlation

equation can be used to estimate retention of acids or bases at any mobile phase pH.

Eq. (10) is derived from Eq. (2) when the descriptor that accounts for the ionization is considered. Since Eq. (5) predicts retention for multiple neutral solutes at multiple mobile phase compositions, considering Eqs. (1) and (2), a similar equation to Eq. (5) can be modelled including the descriptor for ionization, and will predict the retention for multiple ionizable or neutral solutes at multiple mobile phase compositions:

$$\log k = (c_w - c_m\phi) + (e_w - e_m\phi)E + (s_w - s_m\phi)S + (a_w - a_m\phi)A + (b_w - b_m\phi)B + (v_w - v_m\phi)V + \log\left[1 - D(1 - f)\right] \quad (11)$$

where the coefficient d has been taken equal to 1, as predicted by the theory.

In this work, Eqs. (10) and (11) are tested for a wide group of ionizable and neutral solutes chromatographed at different mobile phases to check the goodness-of-fit and the accuracy in the retention prediction. The D parameter requires knowledge of the ${}^{s}_{w}pK$ value of the solute at the ϕ mobile phase composition. In a previous work [13] we have set up linear relationships between ${}^{s}_{w}pK$ and ϕ according to the model:

$${}^{s}_{w}pK = {}^{w}_{w}pK - m_{pK}\phi \quad (12)$$

where ${}^{w}_{w}pK$ should be the pK value of the solute in water. However, the relationship is linear in a limited range of ϕ and therefore ${}^{w}_{w}pK$ should be considered only a fitting parameter more or less close to the true pK value in water. This approach is similar to the one followed with the log k_w value of Eq. (1).

3. Experimental

3.1. Apparatus

pH measurements were taken with a Ross combination electrode Orion 8102 (glass electrode and a reference electrode with a 3.0 M KCl solution in water as a salt bridge) in a Crison micropH 2002 potentiometer with a precision of ±0.1 mV (±0.002 pH units). The retention data were measured on a 15 cm×4.6 mm I.D. Polymer Labs PLRP-S 100 Å column (15–20 μm) in an Isco (Lincoln, NE, USA) Model 2350 dual-pump system with a 20-μl loop valve. A Shimadzu (Kyoto, Japan) Model SPD-10Avp UV–Vis detector was used set at 254 nm for the acids and the bases, 282 nm for the phenols and 200 nm for the potassium bromide (0.01%), which was used as the hold-up time marker. All data were taken by triplicate at 25 °C with the potentiometric cell and the column thermostated with water jackets. Flow was 1 ml min^{-1} for 40% and 60% acetonitrile and 3 ml min^{-1} for 20% acetonitrile mobile phases.

3.2. Chemicals

Acetonitrile was HPLC grade from Merck and water purified by the Milli-Q plus system from Millipore. Other chemicals were reagent grade or better and obtained from Fluka, Aldrich, Merck or Carlo Erba.

3.3. Procedure

The mobile phases were prepared by mixing the aqueous buffers described in Table 1 with acetonitrile, at 20%, 40% and 60% of organic solvent by volume. The buffers were the same used in previous works [13,23]. In order to measure the mobile phase pH, the electrode system was calibrated using the usual aqueous standard reference buffers of potassium hydrogenphthalate (${}^{w}_{w}pH = 4.00$) and potassium dihydrogenphosphate/disodium hydrogenphosphate (${}^{w}_{w}pH = 7.02$). Then the pH of the aqueous HPLC buffer was measured after mixing it with the organic modifier, obtaining the ${}^{s}_{w}pH$ value. ${}^{s}_{s}pH$ can be calculated subtracting the δ value from the ${}^{s}_{w}pH$ value [23]. Both ${}^{s}_{w}pH$ and ${}^{s}_{s}pH$ scales have been recommended by the IUPAC [26], but for the sake of simplicity, the ${}^{s}_{w}pH$ scale will be used in this work. The mobile phase pH values are presented in Table 1.

4. Results and discussion

4.1. Variation of the retention with mobile phase pH

The retention factors of several ionizable and non-ionizable compounds were measured on a polymeric column at the mobile phase pH values described in

Table 1
Mobile phase pH values ($^{s}_{w}$pH) of the studied aqueous buffers with different acetonitrile contents

Aqueous buffer	ϕ (Acetonitrile)		
	0.20	0.40	0.60
0.01 *M* H_3PO_4	2.07	2.20	2.24
$6.40\cdot10^{-3}$ *M* H_3Cit–$3.60\cdot10^{-3}$ *M* KH_2Cit	3.24	3.53	3.77
$9.35\cdot10^{-3}$ *M* KH_2Cit–$6.52\cdot10^{-3}$ *M* KNaHCit	4.31	4.70	5.13
$3.46\cdot10^{-3}$ *M* HAc–$6.54\cdot10^{-3}$ *M* NaAc	5.38	5.99	6.35
$5.81\cdot10^{-3}$ *M* KNaHCit–$4.19\cdot10^{-3}$ *M* Na_3Cit	6.49	6.89	7.11
$5.22\cdot10^{-3}$ *M* KH_2PO_4–$4.78\cdot10^{-3}$ *M* Na_2HPO_4	7.43	7.80	8.02
$9.44\cdot10^{-4}$ *M* KH_2PO_4–$9.06\cdot10^{-3}$ *M* Na_2HPO_4	8.41	8.62	8.99
$7.84\cdot10^{-3}$ *M* Bu-NH_3^+–$2.16\cdot10^{-3}$ *M* Bu-NH_2	9.78	9.52	9.36
$1.64\cdot10^{-3}$ *M* Bu-NH_3^+–$8.36\cdot10^{-3}$ *M* Bu-NH_2	10.84	10.73	10.42
0.01 *M* Na_3PO_4	12.38	12.70	13.19

Table 1. Each mobile phase was a mixture of the aqueous buffer, described in the table, and acetonitrile, at three different percentages (20, 40 and 60%, v/v). Then, the retention factors of the ionizable compounds were fitted to Eq. (6), using the $^{s}_{w}$pH scale. The fit provided the $^{s}_{w}$p*K* values of the solute and the retention factors of the acid and basic forms of the solute (k_{HA} and k_A, respectively) at each acetonitrile composition of the mobile phase.

Following Eq. (7) and the values obtained from the fits of Eq. (6), the *f* parameter was calculated. The $^{s}_{w}$p*K*, k_{HA}, k_A and log *f* values for the studied compounds are summarised in Table 2 for the different mobile phases studied. The results in Table 2 shows that the log *f* value remains quite constant in each mobile phase composition, so an average value will be used in all further correlations involving the log $[1-D(1-f)]$ solute descriptor. Moreover, the average log *f* values between the different mobile phase compositions are quite similar (-1.6, -1.2 and -1.4 for 20, 40 and 60% acetonitrile, respectively). The mean value of these three log *f* values is -1.4 ± 0.2 and the model has been also tested with this global average log *f* value. This constancy of the log *f* values simplifies enormously the model, since the retention of the ionic form is easily calculated from that of the neutral form of the solute at any mobile phase composition.

4.2. Application of the solvation parameter model for neutral and ionic compounds

In order to apply Eq. (10) to a group of solutes, their solute descriptors are needed. Table 3 shows the solute descriptor for all the solutes studied in this work. The log $[1-D(1-f)]$ solute descriptor was calculated at each mobile phase pH using Eq. (9) with the $^{s}_{w}$pH values of Table 2 and the average log *f* value at each mobile phase composition (see Table 2). The coefficients in Eq. (10) were calculated by the method of multiple linear regression. Eq. (10) is obtained from Eq. (8) and since the log k_0 values are linearly related to the solute descriptors for the neutral compound, Eq. (8) predicts the *d* coefficient to be 1.00. In this work, the *d* coefficient was calculated in all the multiple regressions in order to check the validity of the model.

Table 4 shows the coefficients of the solvation parameter model for each mobile phase pH in the three different acetonitrile–water mobile phases studied, after elimination of some outliers (any compound with an standard residual $>|3|$ was removed). In all the described systems, the *d* coefficient value is reasonably constant and close to the theoretical value of 1.00 which supports the reliability of the model. Moreover, the coefficients and statistics are quite good and very similar at the different mobile phase pH when working with same acetonitrile composition, and an average value for each coefficient is also given. The model was also applied to the whole retention data at all the mobile phase pH values, and a global equation was obtained for each acetonitrile composition (see Table 4 and equation designed by ''All pH''), with similar statistics to the single mobile phase pH equations. The standard deviation of each coefficient for these correlations is also given below the corresponding coefficient. These standard deviations show that all

Table 2
Description of the retention of several solutes with mobile phase pH using Eqs. (6) and (7) at different acetonitrile contents

Compound	ϕ (Acetonitrile)											
	0.20				0.40				0.60			
	${}^{s}_{w}pK$	k_{HA}	k_A	Log f	${}^{s}_{w}pK$	k_{HA}	k_A	Log f	${}^{s}_{w}pK$	k_{HA}	k_A	Log f
Naphthoic acid	4.41	65.02	0.33	−2.29	5.10	4.26	0.15	−1.45	5.80	1.14	0.01	−2.31
2-Nitrobenzoic acid	2.92	7.12	0.25	−1.45	3.60	1.21	0.12	−0.99	4.34	0.43	0.00	–
3-Nitrobenzoic acid	3.91	11.15	0.42	−1.43	4.40	1.50	0.14	−1.03	5.00	0.51	0.01	−1.96
4-Nitrobenzoic acid	3.79	13.28	0.47	−1.45	4.31	1.61	0.15	−1.03	4.93	0.53	0.01	−1.98
Benzoic acid	4.74	7.20	0.22	−1.52	5.30	1.19	0.12	−1.01	5.79	0.51	0.00	–
Resorcinol	10.48	1.18	0.02	−1.85	10.99	0.47	0.08	−0.78	11.46	0.22	−0.04	–
Phenol	10.77	6.08	0.20	−1.48	11.55	1.52	0.09	−1.23	11.92	0.63	0.00	–
2,4-Dichlorophenol	8.15	87.33	2.23	−1.59	8.88	6.66	0.45	−1.17	9.68	1.67	0.01	−2.18
2,4-Dinitrophenol	4.04	44.62	1.35	−1.52	4.37	4.57	0.28	−1.22	4.79	1.24	0.07	−1.27
β-Naphthol	10.24	73.58	3.37	−1.34	11.18	5.89	0.13	−1.65	11.62	1.54	0.02	−1.97
2-Nitrophenol	7.37	50.13	1.17	−1.63	7.92	6.49	0.24	−1.42	8.74	1.97	0.05	−1.59
3,5-Dichlorophenol	8.68	130.83	2.60	−1.70	9.33	8.36	0.33	−1.40	9.82	1.94	0.02	−1.94
3-Bromophenol	9.60	43.17	0.98	−1.64	10.32	4.52	0.27	−1.23	10.79	1.29	0.03	−1.59
4-Chlorophenol	10.08	26.75	0.78	−1.53	10.76	3.32	0.20	−1.22	11.20	1.02	0.02	−1.66
m-Cresol	11.03	13.38	0.05	−2.43	11.59	2.34	0.07	−1.55	12.19	0.82	−0.01	–
3-Aminophenol (phenol)	10.84	1.08	0.07	−1.21	11.43	0.47	0.09	−0.73	12.35	0.24	−0.03	–
3-Aminophenol (amino)	4.28	0.30	1.08	−0.56	3.68	0.11	0.47	−0.63	3.40	0.04	0.24	−0.80
2,4,6-Trimethylpyridine	7.03	0.31	10.28	−1.52	6.58	0.18	1.74	−0.98	6.11	0.13	0.83	−0.79
4-Chloroaniline	3.55	0.45	35.34	−1.90	3.11	0.19	5.01	−1.42	2.93	0.46	1.66	−0.56
Aniline	4.35	0.31	7.11	−1.37	3.96	0.17	2.02	−1.08	3.57	0.11	0.96	−0.93
N-Ethylaniline	4.95	1.72	87.70	−1.71	4.57	0.29	12.00	−1.61	3.87	0.06	3.33	−1.74
N,*N*-Dimethylbenzylamine	8.51	0.50	23.98	−1.68	8.15	0.28	3.99	−1.16	7.68	0.09	1.49	−1.23
p-Toluidine	4.83	0.40	14.92	−1.57	4.58	0.23	2.99	−1.12	4.08	0.11	1.22	−1.04
Pyridine	4.91	0.19	1.51	−0.90	4.61	0.16	0.65	−0.62	4.03	0.11	0.45	−0.63
2,6-Dimethylaniline	3.57	0.93	38.37	−1.61	3.22	0.21	6.06	−1.46	2.78	0.08	2.01	−1.38
Benzene		72.85				11.38				3.37		
Acetophenone		27.65				4.38				1.58		
Benzaldehyde		25.17				4.41				1.63		
Nitrobenzene		68.4				8.85				2.56		
Methylphenylether		77.75				11.49				3.22		
Benzonitrile		34.87				5.42				1.76		
Log f (average)				−1.56				−1.17				−1.45
Log f (SD)				0.37				0.29				0.54

coefficients are significant at the 95% significance level. The main advantage of the global correlation equation is that it can be used to estimate retention of acids or bases at any mobile phase ${}^{s}_{w}$pH for each mobile phase composition.

Table 5 shows the coefficients of Eq. (10) obtained when using the global average log f value of −1.4 at all the mobile phase compositions. Statistics similar to the ones of Table 4 are obtained, and this confirms that an average log f value can be taken for all mobile phase compositions.

4.3. Variation of LSER coefficients with mobile phase composition

The coefficients summarised in Tables 4 and 5 show the importance of the solute descriptors that influence the chromatographic retention. Positive coefficients imply an increase in log k, i.e., partition into the stationary phase is favoured. And negative coefficients imply a decrease in log k, i.e., partition into the mobile phase is favoured. The values of the coefficients obtained in this work agree with the

Table 3
Solute descriptors for the ionizable and non-ionizable compounds studied in this work

Compound	*E*	*S*	*A*	*B*	*V*
Naphthoic acid	1.460	1.30	0.60	0.45	1.301
2-Nitrobenzoic acid	0.990	1.10	0.00	0.70	1.106
3-Nitrobenzoic acid	0.990	1.08	0.76	0.52	1.106
4-Nitrobenzoic acid	0.990	1.07	0.62	0.54	1.106
Benzoic acid	0.730	0.90	0.59	0.40	0.932
Resorcinol	0.980	1.00	1.10	0.58	0.834
Phenol	0.805	0.89	0.60	0.30	0.775
2,4-Dichlorophenol	0.960	0.84	0.53	0.19	1.020
2,4-Dinitrophenol	1.200	1.50	0.10	0.55	1.124
β-Naphthol	1.520	1.08	0.61	0.40	1.144
2-Nitrophenol	1.015	1.05	0.05	0.37	0.949
3,5-Dichlorophenol	1.020	1.00	0.91	0.00	1.020
3-Bromophenol	1.060	1.15	0.70	0.16	0.950
4-Chlorophenol	0.915	1.08	0.67	0.20	0.898
m-Cresol	0.822	0.88	0.57	0.34	0.916
3-Aminophenol	1.130	1.15	0.65	0.78	0.875
2,4,6-Trimethylpyridine	0.634	0.69	0.00	0.60	1.098
4-Chloroaniline	1.060	1.13	0.30	0.35	0.939
Aniline	0.955	0.96	0.26	0.50	0.816
N-Ethylaniline	0.945	0.85	0.17	0.51	1.098
N,*N*-Dimethylbenzylamine	0.668	0.80	0.00	0.69	1.239
p-Toluidine	0.923	0.95	0.23	0.52	0.957
Pyridine	0.631	0.84	0.00	0.47	0.675
2,6-Dimethylaniline	0.972	0.98	0.10	0.49	1.098
Benzene	0.610	0.52	0.00	0.14	0.716
Acetophenone	0.818	1.01	0.00	0.48	1.014
Benzaldehyde	0.820	1.00	0.00	0.39	0.873
Nitrobenzene	0.871	1.11	0.00	0.28	0.891
Methylphenylether	0.708	0.75	0.00	0.29	0.916
Benzonitrile	0.742	1.11	0.00	0.33	0.871

results obtained by many authors when working in RPLC using linear solvation energy relationships with isocratic elution [1,3,5,7,28–37] or gradient elution [38]. All of them conclude that, in general, the solute size (V) and hydrogen bond basicity (B) are the most important solute descriptors governing retention in RPLC, whereas the solute excess molar refraction (E), the dipolarity/polarizability (S) and the hydrogen bond acidity (A) have a small influence on retention.

The v coefficient is large and positive in all cases, i.e., increasing the solute size leads to increased retention. In fact, the acetonitrile–water mobile phase is a highly cohesive medium, due mainly to the cohesive density of water. The water molecules form hydrogen bonding network structures and to create a cavity inside this mobile phase requires considerable free energy, much greater than the free energy of cavity formation in the stationary phase. The different cohesivity between the two phases favours the cavity formation in the stationary phase, which implies a positive v coefficient value. The larger the water content in the mobile phase, the greater its cohesive energy density. Therefore, the v coefficient becomes increasingly positive as the water content increases in the mobile phase. This effect is showed in Tables 4 and 5.

The b coefficients are all large and negative (see Tables 4 and 5) which indicates that the mobile phase is a much stronger hydrogen bond acid than the stationary phase. The Kamlet and Taft [39–41] hydrogen-bond acidity parameters show that water ($\alpha = 1.17$) is a much stronger hydrogen bond acid than acetonitrile ($\alpha = 0.19$), and the more water

Table 4
Fits of the solvation parameter model (Eq. (10)) for the different mobile phase compositions, using the log f average value described in Table 2 for each mobile phase composition

ϕ (Acetonitrile)	System constants								Statistics			
	${}^{s}_{w}$pH	c	e	s	a	b	v	d	r	S.E.	F	n
0.20	2.07	0.70	0.72	−0.20	−0.90	−2.73	1.65	1.05	0.994	0.116	287	29
	3.24	0.62	0.96	−0.28	−0.88	−2.53	1.50	0.97	0.987	0.154	141	30
	4.31	0.13	0.60	−0.45	−0.90	−2.44	2.54	1.20	0.983	0.161	109	29
	5.38	−0.12	0.33	−0.25	−0.78	−2.55	2.84	1.25	0.985	0.166	123	30
	6.49	0.23	0.46	−0.12	−0.79	−2.65	2.24	1.07	0.981	0.192	96	30
	7.43	0.15	0.41	−0.12	−0.78	−2.67	2.37	1.11	0.975	0.222	74	30
	8.41	0.25	0.49	−0.17	−0.81	−2.72	2.27	1.07	0.971	0.230	63	30
	9.78	0.15	0.28	−0.10	−0.70	−2.58	2.41	0.96	0.963	0.230	48	30
	10.84	−0.48	0.70	−0.05	−0.63	−2.89	2.80	1.21	0.984	0.173	113	29
	12.38	0.10	0.33	0.10	−0.48	−2.35	2.13	1.22	0.976	0.243	78	30
	Mean	0.17	0.53	−0.16	−0.77	−2.61	2.28	1.11				
	SD	0.34	0.22	0.15	0.13	0.16	0.43	0.10				
	All pH	0.19	0.63	−0.23	−0.82	−2.68	2.25	1.05	0.980	0.173	1163	294
	SD	0.08	0.09	0.08	0.04	0.07	0.09	0.02				
0.40	2.20	0.58	0.62	−0.22	−0.71	−1.64	0.50	0.96	0.985	0.126	123	30
	3.53	0.46	0.65	−0.36	−0.77	−1.80	0.84	0.92	0.977	0.130	81	30
	4.70	0.01	0.29	−0.41	−0.76	−1.56	1.66	1.35	0.975	0.138	74	30
	5.99	−0.15	0.20	−0.26	−0.68	−1.60	1.73	1.21	0.975	0.157	75	30
	6.89	0.07	0.32	−0.23	−0.66	−1.66	1.36	1.06	0.969	0.176	59	30
	7.80	0.17	0.34	−0.24	−0.65	−1.69	1.25	1.07	0.968	0.183	56	30
	8.62	0.19	0.33	−0.26	−0.67	−1.63	1.22	1.05	0.965	0.186	52	30
	9.52	0.24	0.40	−0.33	−0.66	−1.80	1.26	1.02	0.966	0.181	54	30
	10.73	0.06	0.22	−0.16	−0.54	−1.75	1.42	1.24	0.970	0.188	61	30
	12.70	0.14	0.13	−0.04	−0.14	−0.95	0.89	1.25	0.963	0.219	48	30
	Mean	0.18	0.35	−0.25	−0.62	−1.61	1.21	1.11				
	SD	0.21	0.17	0.10	0.18	0.24	0.38	0.14				
	All pH	0.24	0.39	−0.31	−0.68	−1.65	1.18	1.08	0.968	0.160	725	298
	SD	0.08	0.08	0.08	0.03	0.06	0.09	0.02				
0.60	2.24	0.37	0.44	−0.22	−0.73	−1.65	0.40	0.73	0.984	0.114	118	30
	3.77	0.22	0.60	−0.41	−0.68	−1.38	0.47	0.61	0.955	0.135	40	30
	5.13	0.01	0.25	−0.52	−0.69	−1.21	1.11	1.06	0.957	0.150	41	30
	6.35	−0.44	0.16	−0.17	−0.82	−1.13	1.35	1.37	0.960	0.220	43	29
	7.11	−0.23	0.22	−0.09	−0.63	−1.23	0.95	1.03	0.977	0.154	81	30
	8.02	−0.39	0.30	0.07	−0.74	−1.17	0.90	1.26	0.977	0.188	76	29
	8.99	−0.15	0.22	0.01	−0.74	−1.16	0.78	1.21	0.976	0.177	69	28
	9.36	−0.13	0.30	0.00	−0.76	−1.27	0.76	1.23	0.977	0.176	73	28
	10.42	0.02	0.58	−0.53	−0.65	−1.45	0.92	1.47	0.980	0.145	73	25
	13.19	−0.44	0.03	0.16	−0.52	−1.46	1.21	1.21	0.986	0.167	121	28
	Mean	−0.12	0.31	−0.17	−0.69	−1.31	0.88	1.12				
	SD	0.27	0.18	0.25	0.08	0.17	0.30	0.27				
	All pH	−0.04	0.41	−0.31	−0.74	−1.18	0.80	1.03	0.974	0.139	830	275
	SD	0.07	0.07	0.07	0.03	0.05	0.08	0.02				

r = Overall correlation coefficient; S.E. = standard error in the estimate; F = F-statistic; n = number of solutes.

Table 5
Fits of the solvation parameter model (Eq. (10)) for the different mobile phase compositions, using the global average log f value of −1.4 for all the mobile phase compositions

ϕ (Acetonitrile)	System constants								Statistics			
	${}^{s}_{w}$pH	c	e	s	a	b	v	d	r	S.E.	F	n
0.20	2.07	0.69	0.74	−0.18	−0.91	−2.75	1.63	1.16	0.994	0.115	292	29
	3.24	0.64	1.01	−0.27	−0.88	−2.52	1.42	1.05	0.986	0.157	137	30
	4.31	0.13	0.53	−0.24	−0.87	−2.45	2.39	1.30	0.989	0.133	163	29
	5.38	−0.12	0.35	−0.23	−0.78	−2.57	2.81	1.35	0.985	0.167	121	30
	6.49	0.22	0.43	−0.13	−0.79	−2.64	2.29	1.20	0.982	0.187	102	30
	7.43	0.13	0.39	−0.13	−0.78	−2.67	2.43	1.25	0.975	0.221	74	30
	8.41	0.27	0.51	−0.20	−0.82	−2.74	2.28	1.19	0.970	0.233	61	30
	9.78	0.16	0.28	−0.10	−0.68	−2.63	2.43	1.08	0.963	0.229	49	30
	10.84	−0.03	0.45	−0.02	−0.57	−2.84	2.48	1.36	0.972	0.229	66	30
	12.38	0.16	0.35	0.07	−0.46	−2.31	2.06	1.36	0.976	0.245	77	30
	Mean	0.22	0.50	−0.14	−0.75	−2.61	2.22	1.23				
	SD	0.26	0.22	0.11	0.15	0.16	0.41	0.11				
	All pH	0.19	0.63	−0.22	−0.81	−2.68	2.23	1.17	0.981	0.17	1187	293
	SD	0.08	0.09	0.08	0.04	0.06	0.09	0.02				
0.40	2.20	0.59	0.59	−0.24	−0.71	−1.63	0.54	0.82	0.985	0.13	124	30
	3.53	0.43	0.59	−0.37	−0.77	−1.81	0.94	0.80	0.978	0.13	83	30
	4.70	0.05	0.29	−0.46	−0.76	−1.58	1.68	1.17	0.974	0.14	71	30
	5.99	−0.11	0.23	−0.26	−0.69	−1.61	1.67	1.03	0.972	0.17	66	30
	6.89	0.09	0.35	−0.22	−0.66	−1.67	1.30	0.89	0.968	0.18	57	30
	7.80	0.19	0.36	−0.24	−0.65	−1.70	1.21	0.89	0.967	0.18	56	30
	8.62	0.18	0.32	−0.24	−0.66	−1.61	1.22	0.89	0.965	0.19	52	30
	9.52	0.21	0.39	−0.30	−0.66	−1.75	1.25	0.86	0.967	0.18	54	30
	10.73	0.06	0.23	−0.18	−0.57	−1.69	1.39	1.03	0.969	0.19	59	30
	12.70	0.09	0.08	0.00	−0.18	−0.99	0.98	1.05	0.962	0.22	47	30
	Mean	0.18	0.34	−0.25	−0.63	−1.61	1.22	0.94				
	SD	0.20	0.16	0.12	0.17	0.23	0.34	0.12				
	All pH	0.25	0.40	−0.30	−0.68	−1.63	1.15	0.91	0.967	0.16	708	299
	SD	0.08	0.08	0.08	0.03	0.06	0.09	0.02				
0.60	2.24	0.37	0.45	−0.22	−0.73	−1.65	0.38	0.75	0.984	0.11	118	30
	3.77	0.23	0.61	−0.41	−0.68	−1.37	0.45	0.64	0.955	0.14	40	30
	5.13	−0.01	0.24	−0.51	−0.69	−1.20	1.13	1.10	0.958	0.15	43	30
	6.35	−0.45	0.16	−0.17	−0.81	−1.13	1.37	1.41	0.960	0.22	43	29
	7.11	−0.24	0.21	−0.09	−0.63	−1.23	0.97	1.07	0.977	0.15	82	30
	8.02	−0.39	0.30	0.07	−0.74	−1.17	0.90	1.31	0.977	0.19	77	29
	8.99	−0.15	0.22	0.01	−0.74	−1.16	0.78	1.26	0.976	0.18	69	28
	9.36	−0.13	0.31	−0.01	−0.76	−1.28	0.75	1.28	0.976	0.18	72	28
	10.42	0.03	0.57	−0.55	−0.64	−1.47	0.93	1.52	0.979	0.15	71	25
	13.19	−0.42	0.05	0.15	−0.51	−1.45	1.18	1.27	0.986	0.16	124	28
	Mean	−0.11	0.31	−0.17	−0.69	−1.31	0.88	1.16				
	SD	0.28	0.18	0.24	0.09	0.17	0.31	0.28				
	All pH	−0.02	0.41	−0.31	−0.74	−1.19	0.79	1.07	0.973	0.14	812	276
	SD	0.07	0.07	0.07	0.03	0.05	0.08	0.02				

r = Overall correlation coefficient; S.E. = standard error in the estimate; F = F-statistic; n = number of solutes.

content in the mobile phase, the more important the hydrogen bond acidity character of the mobile phase. Therefore, solutes with greater hydrogen bond acceptor ability (large *B* descriptor value) are less retained.

The variation of the LSER coefficients with the mobile phase composition (ϕ) is given in Fig. 1. The variation can be approximated to a straight line and in this instance the correlations for each mobile phase composition can be combined to obtain the global linear solvation energy relationship defined by Eq. (11).

4.4. Application of the global solvation parameter model to neutral and ionizable compounds

The global solvation parameter model (Eq. (11)) is derived considering both LSST and LSER models. The LSST model describes a linear relationship between the solute retention and the volume fraction of organic solvent, but this behaviour is only observed over a limited range of mobile phase composition. To check if the studied mobile phase range (from 20 to 60%, v/v, of acetonitrile) is inside this linear range, Eq. (1) was applied to the retention factor of the uncharged forms of the studied solutes at the mobile phase compositions studied. As Table 6 shows, good fits and statistics are obtained.

The log k_w and m_k parameters of Table 6 have been correlated with the solute descriptors and the following relationships have been obtained:

$$\log k_w = 0.27 + 0.88E - 0.29S - 0.94A - 3.46B + 2.93V$$
$$\mathrm{SD} = 0.20,\ r = 0.963,\ F = 62 \quad (13)$$

$$m_k = 0.19 + 0.63E + 0.23S - 0.41A - 3.63B + 3.93V$$
$$\mathrm{SD} = 0.19,\ r = 0.973,\ F = 86 \quad (14)$$

which confirm the applicability of the global solvation parameter model (Eq. (11)).

The linearity of the variation of ${}^{s}_{w}pK$ values with solvent composition has been also tested and the results are also given in Table 6. Linear variations are observed for all studied solutes.

Therefore, the global solvation parameter model has been applied to the retention data, and the following equation has been obtained:

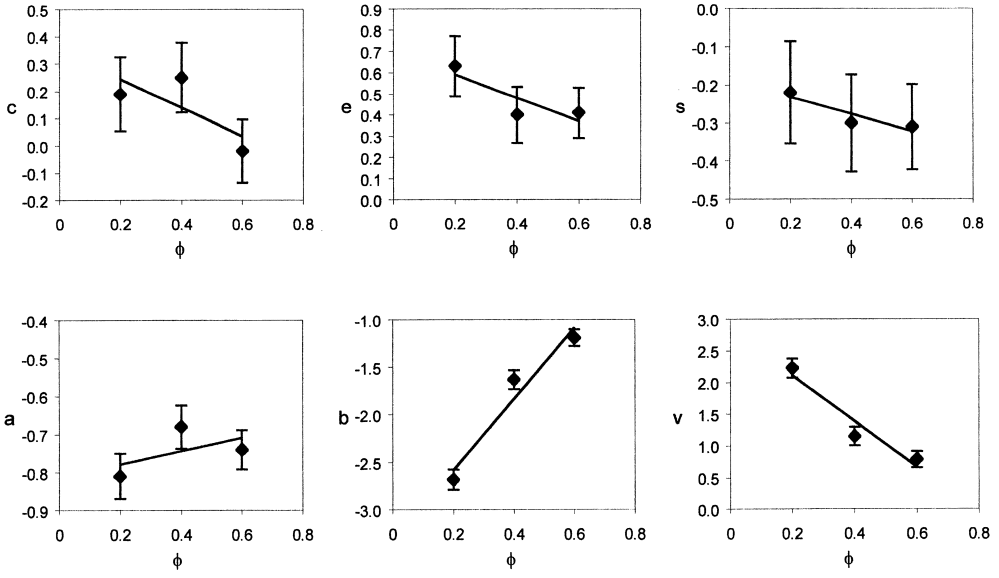

Fig. 1. Plots of LSER regression coefficients (described in Table 5) vs. mobile phase composition (ϕ) considering a log f value of -1.4 for all mobile phase composition. The error bars are the 90% confidence intervals of the data points and the solid lines are the best regression lines that fit the data.

Table 6
Correlations of log k_0 and ${}^{s}_{w}pK$ values of the studied solutes with the mobile phase composition (ϕ) according to Eqs. (1) and (12)

Substance	Log $k = \log k_w - m_k \phi$ (Eq.(1))					${}^{s}_{w}pK = {}^{w}_{w}pK - m_{pK}\phi$ (Eq. (12))				
	Log k_w	m_k	r	SD	F	${}^{w}_{w}pK$	m_{pK}	r	SD	F
Naphthoic acid	2.59	4.39	0.980	0.25	25	3.71	−3.47	1.000	0.01	6440
2-Nitrobenzoic acid	1.41	3.05	0.988	0.13	43	2.20	−3.55	0.999	0.03	945
3-Nitrobenzoic acid	1.65	3.35	0.985	0.16	33	3.34	−2.72	0.998	0.05	211
4-Nitrobenzoic acid	1.75	3.50	0.984	0.18	32	3.20	−2.85	0.998	0.05	271
Benzoic acid	1.37	2.88	0.980	0.17	24	4.22	−2.62	1.000	0.01	3675
Resorcinol	0.42	1.82	0.998	0.03	236	10.03	−2.45	0.990	0.10	50
Phenol	1.24	2.47	0.992	0.09	66	10.23	−2.87	0.994	0.09	90
2,4-Dichlorophenol	2.71	4.29	0.985	0.21	33	7.37	−3.82	0.999	0.04	867
2,4-Dinitrophenol	2.36	3.89	0.988	0.17	41	3.65	−1.87	0.996	0.04	139
β-Naphthol	2.62	4.20	0.985	0.21	32	9.64	−3.45	0.974	0.23	18
2-Nitrophenol	2.34	3.52	0.989	0.15	44	6.64	−3.42	0.993	0.12	67
3,5-Dichlorophenol	2.94	4.57	0.984	0.23	32	8.14	−2.85	0.996	0.07	120
3-Bromophenol	2.32	3.81	0.986	0.18	36	9.09	−2.97	0.973	0.20	18
4-Chlorophenol	2.07	3.55	0.987	0.16	39	9.59	−2.80	0.975	0.18	19
m-Cresol	1.68	3.03	0.990	0.12	48	10.44	−2.90	1.000	0.02	2523
3-Aminophenol (phenol)						10.02	−3.80	0.992	0.14	60
3-Aminophenol (amino)	0.34	1.61	0.998	0.03	238	4.64	2.15	0.980	0.12	25
2,4,6-Trimethylpyridine	1.48	2.74	0.973	0.18	18	7.49	2.30	1.000	0.01	6348
4-Chloroaniline	2.15	3.32	0.987	0.15	39	3.82	1.55	0.972	0.11	17
Aniline	1.25	2.18	0.989	0.09	45	4.74	1.95	1.000	0.00	4.82E+28
N-Ethylaniline	2.60	3.55	0.992	0.13	65	5.54	2.70	0.986	0.13	34
N,*N*-Dimethylbenzylamine	1.92	3.01	0.984	0.15	30	8.93	2.08	1.000	0.01	2296
p-Toluidine	1.67	2.72	0.987	0.13	37	5.25	1.88	0.982	0.10	27
Pyridine	0.41	1.32	0.975	0.08	19	5.40	2.20	0.984	0.11	30
2,6-Dimethylaniline	2.17	3.20	0.989	0.13	48	3.98	1.98	0.998	0.04	231
Benzene	2.48	3.34	0.993	0.11	69					
Acetophenone	2.00	3.11	0.986	0.15	37					
Benzaldehyde	1.94	2.97	0.988	0.13	40					
Nitrobenzene	2.49	3.57	0.990	0.14	50					
Methylphenylether	2.54	3.46	0.993	0.11	75					
Benzonitrile	2.14	3.24	0.990	0.13	50					

$$\log k = (0.43 - 0.56\phi) + (0.95 - 1.08\phi)E + (-0.24 - 0.18\phi)S + (-0.90 + 0.34\phi)A + (-3.40 + 3.84\phi)B + (2.59 - 3.15\phi)V + \log[1 - D(1 - f)] \quad n = 870,$$
$$\mathrm{SD} = 0.18,\ r = 0.961,\ F = 948 \qquad (15)$$

The values of the coefficients of this equation are in good agreement with those of Tables 4 and 5. *e* and *v* are positive and *s*, *a* and *b*, negative. The largest absolute values are for *b* and *v* coefficients. The larger the absolute value of the coefficient, the larger its variation with the mobile phase composition. The log *k* (calculated) vs. the log *k* (experimental) plot for this model is presented in Fig. 2.

The global solvation parameter model for neutral and ionizable compounds requires thirteen mobile–stationary phase parameters, only one parameter more (log *f*, which here has been taken as −1.4) than the 12 parameters of the global solvation model established for neutral solutes (c_w, c_m, e_w, e_m, s_w, s_m, a_w, a_m, b_w, b_m, v_w, v_m) [10]. It also requires seven solute parameters, the five parameters of the model for neutral solutes (*E*, *S*, *A*, *B*, and *V*) and the two parameters needed to account for the ionization of the solute (the ${}^{w}_{w}pK$ and m_{pK} of Eq. (12)). These two parameters are needed to estimate the degree of ionization of the solute at the mobile phase, ${}^{s}_{w}pK$, and from this and the log *f* value, the log $[1-D(1-f)]$ descriptor.

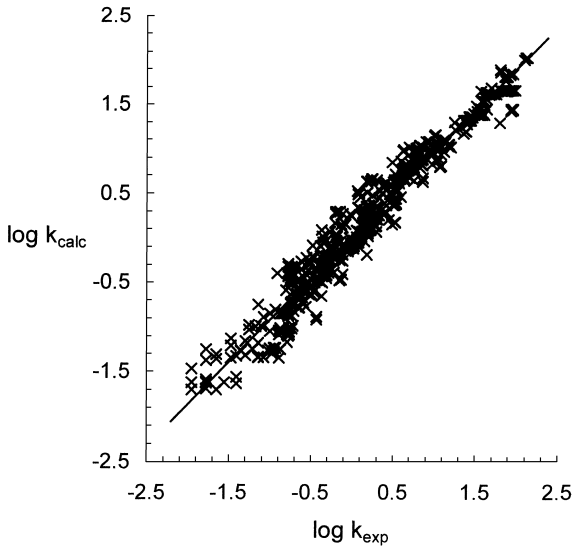

Fig. 2. Plot of the log k (calculated) from Eq. (16) vs. the experimental log k values for all the studied compounds at several mobile phase pH values and compositions.

4.5. Comparison of the global solvation parameter model with other solvation models

The global LSER model for neutral and ionizable solutes should be compared with a model that we developed earlier for neutral solutes [42] and we have recently extended to ionizable solutes [13].

The retention of non-ionizable solutes was successfully related to mobile phase (P^N_m) and solute (p) polarity parameters through an equation of the type:

$$\log k = (\log k)_0 + p(P^N_m - P^N_s) \quad (16)$$

where $(\log k)_0$ and P^N_s are system constants related to the phase ratio and polarity of the stationary phase, respectively.

Extension of this model to ionizable solutes (in a similar form than extension of the global LSER equation) leads to the following equation:

$$\log k = (\log k)_0 + p(P^N_m - P^N_s) + \log [1 - D(1 - f)] \quad (17)$$

The mobile phase parameter P^N_m is related to mobile phase composition (ϕ) by a hyperbolic equation [42]. However, for a limited range of ϕ, this equation can be approximated to a linear equation such as:

$$P^N_m = r_w - r_m \phi \quad (18)$$

Combination of Eqs. (17) and (18) and rearrangement of terms leads to the equation:

$$\log k = (\log k)_0 - pP^N_s + (r_w - r_m \phi)p + \log [1 - D(1 - f)] \quad (19)$$

Eqs. (11) and (19) differ only in two points. One difference is that the intercept of Eq. (11) ($c_w - c_m \phi$) is mobile phase dependent, but solute independent, whereas the intercept of Eq. (19) [$(\log k)_0 - pP^N_s$] is solute dependent, but mobile phase independent.

The main difference is that Eq. (11) requires five solute–solvent interaction terms which require five solute descriptors and 10 mobile phase parameters. Eq. (19) uses one unique solute–solvent interaction term that requires one unique solute descriptor (p) and two mobile phase parameters (r_w and r_m) (three mobile phase parameters in the general hyperbolic equation [42]).

The final equation obtained with this model [13] was:

$$\log k = -1.22 + p(P^N_m + 0.02) + \log [1 - D(1 - f)] \quad (20)$$

and the plot log k (calculated) vs. log k (experimental) is presented in Fig. 3. The correlation obtained is:

$$\log k_{calc} = 0.001 + 0.988 \log k_{exp}$$
$$n = 737, \text{SD} = 0.18, r = 0.972, F = 15\,393 \quad (21)$$

which should be compared with the correlation of Fig. 2:

$$\log k_{calc} = 0.019 + 0.942 \log k_{exp}$$
$$n = 870, \text{SD} = 0.17, r = 0.977, F = 18\,500 \quad (22)$$

The statistics of both correlations are very similar, although inspection of Figs. 2 and 3 reveals that deviations in Fig. 3 are more concentrated in the low log k values. The number of points in Fig. 3 is smaller than in Fig. 2 because neutral compounds were not studied in the previous work [13]. Therefore we must conclude that both models predict

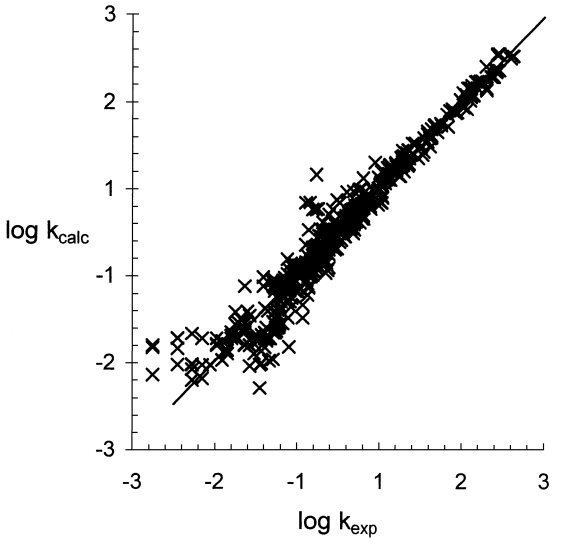

Fig. 3. Plot of the log k (calculated) from Eq. (21) vs. the experimental log k values for all the studied compounds at several mobile phase pH values.

retention with a similar accuracy. Eq. (17) is simpler than Eq. (11) because it requires less solute and mobile–stationary phases parameters, so it can be more easy to implement in HPLC retention prediction programs [16]. However, the global linear solvation energy relationship model characterises better the fundamental solute–solvent interactions in the HPLC system and therefore, it will provide more chemical information.

Acknowledgements

We acknowledge financial support from the DGICYT of the Spanish Government (projects PB97-0878 and PB98-1257) and from the Catalan Government (grant 1999SGR00047). S.E. was supported by a grant from the Catalan Government (1998FI 00639).

References

[1] L.C. Tan, P.W. Carr, M.H. Abraham, J. Chromatogr. A 752 (1996) 1.
[2] Á. Sándi, L. Szepesy, J. Chromatogr. A 818 (1998) 19.
[3] M.H. Abraham, M. Rosés, J. Phys. Org. Chem. 7 (1994) 672.
[4] K. Valkó, L.R. Snyder, J.L. Glajch, J. Chromatogr. A 656 (1993) 501.
[5] L.C. Tan, P.W. Carr, J. Chromatogr. A 799 (1998) 1.
[6] Á. Sándi, M. Nagy, L. Szepesy, J. Chromatogr. A 893 (2000) 215.
[7] P.W. Carr, R.M. Doherty, M.J. Kamlet, R.W. Taft, W. Melander, C. Horvath, Anal. Chem. 58 (1986) 2674.
[8] J. Li, P.W. Carr, Anal. Chem. 69 (1997) 2202.
[9] D. Bolliet, C.F. Poole, Analyst 123 (1998) 295.
[10] A. Wang, L.C. Tan, P.W. Carr, J. Chromatogr. A 848 (1999) 21.
[11] L.R. Snyder, J.W. Dolan, J.R. Gant, J. Chromatogr. 165 (1979) 3.
[12] M.A. Quarry, R.L. Grob, L.R. Snyder, Anal. Chem. 58 (1986) 907.
[13] S. Espinosa, E. Bosch, M. Rosés, J. Chromatogr. A submitted for publication.
[14] R.M. Lopes Marques, P.J. Schoenmakers, J. Chromatogr. 592 (1992) 157.
[15] P.J. Schoenmakers, R. Tijssen, J. Chromatogr. A 656 (1993) 577.
[16] T. Baczek, R. Kaliszan, H.A. Claessens, M.A. van Straten, LC–GC Eur. 14 (2001) 304.
[17] D. Bolliet, C.F. Poole, M. Rosés, Anal. Chim. Acta 368 (1998) 129.
[18] J.P. Foley, W.E. May, Anal. Chem. 59 (1987) 102.
[19] J.P. Foley, W.E. May, Anal. Chem. 59 (1987) 110.
[20] C. Horváth, W. Melander, I. Molnár, Anal. Chem. 49 (1977) 142.
[21] P.J. Schoenmakers, S. van Molle, C.M.G. Hayes, L.G.M. Uunk, Anal. Chim. Acta 250 (1991) 1.
[22] J.A. Lewis, D.C. Lommen, W.D. Raddatz, J.W. Dolan, L.R. Snyder, I. Molnar, J. Chromatogr. 592 (1992) 183.
[23] S. Espinosa, E. Bosch, M. Rosés, Anal. Chem. 72 (2000) 5193.
[24] I. Canals, J.A. Portal, E. Bosch, M. Rosés, Anal. Chem. 72 (2000) 1802.
[25] I. Canals, F.Z. Oumada, M. Rosés, E. Bosch, J. Chromatogr. A 911 (2001) 191.
[26] IUPAC Compendium of Analytical Nomenclature. Definitive Rules 1997, 3rd ed., Blackwell, Oxford, 1998.
[27] M. Rosés, D. Bolliet, C.F. Poole, J. Chromatogr. A 829 (1998) 29.
[28] P.C. Sadek, P.W. Carr, R.M. Doherty, M.J. Kamlet, R.W. Taft, M.H. Abraham, Anal. Chem. 57 (1985) 2971.
[29] J.J. DeStefano, J.A. Lewis, L.R. Snyder, LC–GC Int. Mag. Liq. Gas Chromatogr. 10 (1992) 130.
[30] M.J. Kamlet, R.M. Doherty, P.W. Carr, D. Mackay, M.H. Abraham, R.W. Taft, Environ. Sci. Technol. 22 (1988) 503.
[31] R.W. Taft, M.H. Abraham, G.R. Famini, R.M. Doherty, J.M. Abboud, M.J. Kamlet, J. Pharm. Sci. 74 (1985) 807.
[32] M.J. Kamlet, R.M. Doherty, M.H. Abraham, Y. Marcus, R.W. Taft, J. Phys. Chem. 92 (1988) 5244.
[33] M.J. Kamlet, D.J. Abraham, R.M. Doherty, R.W. Taft, M.H. Abraham, J. Pharm. Sci. 75 (1986) 350.

[34] M.J. Kamlet, R.M. Doherty, V. Fiserova-Bergerova, P.W. Carr, M.H. Abraham, R.W. Taft, J. Pharm. Sci. 76 (1987) 14.
[35] J.A. Riddick, W.B. Bunger, T.K. Sakano, Organic Solvents, 4th ed., Wiley-Interscience, New York, 1986.
[36] M.H. Abraham, G.S. Whiting, R.M. Doherty, W.J. Shuely, J. Chromatogr. 587 (1991) 213.
[37] D.E. Leahy, J. Pharm. Sci. 75 (1986) 629.
[38] J. Li, B. Cai, J. Chromatogr. A 905 (2001) 35.
[39] C. Reichardt, Chem. Rev. 94 (1994) 2319.
[40] M.H. Abraham, P.L. Grellier, J.M. Abboud, R.M. Doherty, R.W. Taft, Can. J. Chem. 66 (1988) 2673.
[41] C.M. Du, K. Valkó, C. Bevan, D. Reynolds, M.H. Abraham, J. Chromatogr. Sci. 38 (2000) 503.
[42] E. Bosch, P. Bou, M. Rosés, Anal. Chim. Acta 299 (1994) 219.