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Global linear solvation energy relationships for retention prediction in reversed-phase liquid chromatography

Aosheng Wang[a], Lay Choo Tan[b], Peter W. Carr[a,*]

[a]*Department of Chemistry, Smith and Kolthoff Hall, University of Minnesota, 207 Pleasant Street S.E., Minneapolis, MN 55455, USA*
[b]*Novartis Pharmaceuticals Corporation, 59 Route 10, East Hanover, NJ 07936, USA*

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Abstract

A *global* linear solvation energy relationship (LSER) that simultaneously models retention in reversed-phase liquid chromatography as a function of both solute LSER descriptors and mobile phase composition has been derived from both the local LSER model and the linear solvent strength theory (LSST). At most only twelve coefficients are required to establish the *global* LSER model. Many more coefficients would be required if the same data set were modeled using the *local* LSER model. The global LSER was tested with the retention data obtained in acetonitrile–water, tetrahydrofuran–water, and methanol–water mobile phases each at four or five mobile phase compositions for a large number of highly variegated solutes. Although fewer regression coefficients are used in a global LSER fit than in a series of local LSER fits for the same data, the results show that the goodness-of-fit of the global LSER is as good as that obtained in the local LSERs. The results also show that the residuals of the LSST fits are smaller than those of both the local LSER fits and the global LSER fit and that the residuals of a global LSER fit result mainly from the local LSER model and are not due to the LSST model.

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

1. Introduction

Retention prediction and selectivity optimization are very important in rapid method development in reversed-phase liquid chromatography (RPLC) [1]. However, retention in RPLC is a very complicated process [2–6] and depends on many physical and chemical properties of the system such as temperature [7–9], solute molecular properties [10], stationary phase characteristics [11], and mobile phase composition [10,12,13]. Although a universal and robust retention model for RPLC has not yet been developed, many practical retention models [14], such as linear solvent strength theory (LSST) and linear solvation energy relationships (LSER), have been developed and widely used. In RPLC, LSST models retention of a single solute as a function of mobile phase composition, while LSER models retention at a single mobile phase composition as a function of solute molecular properties. It is therefore reasonable and highly advantageous to combine the two to formulate a more general model to predict retention for multiple solutes at multiple mobile

*Corresponding author. Tel.: +1-612-624-0253; fax: +1-612-626-7541.

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phase compositions and eventually to make selectivity optimization more efficient.

1.1. Linear solvent strength theory

It has been shown [15–17] that, in binary aqueous–organic mobile phases on a RPLC column, the retention of a single solute can for practical purposes be modeled as a quasi-linear function of the mobile phase composition over a limited yet useful range of mobile phase compositions:

$$\log k' = \log k'_w - S\phi \quad (1)$$

where k' is the solute retention factor at a specific mobile phase composition, ϕ is the mobile phase composition expressed as the volume fraction of the organic modifier in the eluent, and $\log k'_w$ and S are solute parameters to be determined from the experimental data for a specific combination of solute, organic modifier, stationary phase and temperature. k'_w is the solute retention factor *extrapolated* to mobile phase equivalent to pure water, and S is a solute-dependent solvent strength parameter specific to the organic modifier on the stationary phase under consideration.

The approximate nature of Eq. (1) must be understood. Jandera and co-workers have pointed out that simple solubility parameter theory requires a quadratic relationship [18,19]. The work of Dorsey and co-workers [20–22] and others [23–25] substantiate the fact that Eq. (1) is never exact over the entire range of mobile phase compositions. Furthermore, the value of k'_w obtained by extrapolation according to Eq. (1) varies substantially with the type of mobile phase modifier [12,15,26] which it should not if the equation were valid over the entire range in ϕ.

Putting aside the approximate nature of Eq. (1), let us consider the fundamental meaning of the two model parameters: $\log k'_w$ and S. First, k'_w is the hypothetical retention factor that the solute would have in a purely aqueous eluent, and logarithmic retention ($\log k'$) can be related to the logarithmic equilibrium constant ($\log K$) for the retention process as follows:

$$\log k' = \log \Phi + \log K \quad (2)$$

where Φ is the ratio of the volume of the stationary phase to the volume of the mobile phase within the column assuming a pure partition process. Therefore, $\log k'_w$ is related as follows to the free energy of solute transfer from water to the stationary phase

$$\Delta G^\circ_w = -2.3RT \log \frac{k'_w}{\Phi} \quad (3)$$

Second, if we set ϕ equal to unity, from Eq. (1) we see that

$$S = \log k'_w - \log k'_{org} \quad (4)$$

where $\log k'_{org}$ denotes the logarithmic retention factor in a purely organic eluent. From Eqs. (1), (3) and (4) and assuming that the stationary phase is not modified by sorption of mobile phase, S can be related as follows to the free energy of solute transfer from water to pure organic mobile phase:

$$\Delta G^\circ_S = -2.3RTS \quad (5)$$

These thermodynamic representations of $\log k'_w$ and S are used below.

Once these two model parameters, $\log k'_w$ and S, are determined from retention data for a single solute at a minimum of two mobile phase compositions, then in principle, the LSST equation can be used to predict the retention of the same solute at any other mobile phase composition within the calibration range. This is the basis for the highly developed DryLab optimization method of Snyder and co-workers [1,27–29].

However, the calibration of the LSST model based on one solute is not transferable to a second solute because even on the same stationary phase with the same mobile phase different solutes require different model parameters ($\log k'_w$ and S). Therefore, a separate LSST equation for each solute of interest has to be calibrated at two mobile phase compositions, and the number of retention measurements increases as the number of solutes of interest increases.

1.2. Linear solvation energy relationship

During last two decades Kamlet, Taft, and their co-workers have developed the basic concept of linear solvation energy relationships (LSERs) [30–

35]. They have shown that, in thousands of chemically distinct systems involving some property which is linearly related to either a free energy of reaction, a free energy of transfer, or an activation energy, one can correlate such properties with various fundamental molecular properties of the solvents or solutes involved. Chromatographic retention and in particular logarithmic retention factors (log k') are linear free energy parameters and as such one can linearly correlate these data with the molecular properties of the solutes using the LSER model [36–43]. This group and others have shown [11,12,44–55] that retention in RPLC can be modeled using the LSER approach:

$$\log k' = \log k'_0 + vV_2 + s\pi_2^* + a\sum\alpha_2^H + b\sum\beta_2^H + rR_2 \quad (6)$$

where the subscript 2 denotes solute molecular descriptors including molar volume (V_2), dipolarity/polarizability (π_2^*), overall hydrogen-bond acidity ($\Sigma\alpha_2^H$), overall hydrogen-bond basicity ($\Sigma\beta_2^H$), and excess molar refraction (R_2). Each solute property is multiplied by a coefficient that represents the difference in complementary ''solvent'' property between the stationary and mobile phases. These coefficients (*v, s, a, b* and *r*) as well as the log k'_0constant are model parameters to be calibrated from the experimental data for different solutes at a given mobile phase composition. Once the six model parameters are determined from the retention data for at least six different solutes, but preferably 3 or 4 solutes per parameter, at a given mobile phase composition, then in principle this LSER model can be used to predict the retention of any solute whose LSER descriptors are known at the same mobile phase composition [13,55].

However, the calibration of the LSER model at one mobile phase composition can not be transferred to a second mobile phase composition even on the same column because at a different mobile phase composition a different set of model coefficients (log k'_0, *v, s, a, b* and *r*) are needed to fit the LSER model [12]. Therefore, a separate LSER equation at each mobile phase composition has to be established using at least six solutes, and the number of retention measurements required increases as the number of mobile phase compositions increases.

1.3. Derivation of the global LSER model

It would be much more efficient if we could extend a set of LSST equations (see Eq. (1)) calibrated for a collection of solutes to additional solutes without having to empirically determine the new LSST model for each new solute. We believe that this extended calibration might be possible if all the required LSER descriptors are available and we could combine both the LSER model and the LSST model into a single model which we here term a *global* LSER model.

Since log k'_w and S are, in principle, linear free energy parameters for a specific process, we should be able to model both log k'_w and S by LSER theory. Consider now how the two coefficients of the LSST model can be modeled by two LSERs:

$$\log k'_w = \log k'_{0,w} + v_wV_2 + s_w\pi_2^* + a_w\sum\alpha_2^H + b_w\sum\beta_2^H + r_wR_2 \quad (7)$$

$$S = \log k'_{0,S} + v_SV_2 + s_S\pi_2^* + a_S\sum\alpha_2^H + b_S\sum\beta_2^H + r_SR_2 \quad (8)$$

Replacing the two coefficients in the LSST model with the two LSER models (Eqs. (7) and (8)), we get an equivalent LSER model at a single mobile phase composition:

$$\begin{aligned}\log k' &= \log k'_w - S\phi \\ &= \left(\log k'_{0,w} + v_wV_2 + s_w\pi_2^* + a_w\sum\alpha_2^H + b_w\sum\beta_2^H + r_wR_2\right) - \left(\log k'_{0,S} + v_SV_2 + s_S\pi_2^* + a_S\sum\alpha_2^H + b_S\sum\beta_2^H + r_SR_2\right)\phi \end{aligned} \quad (9)$$

Collecting terms appropriately, Eq. (9) can be rewritten as:

$$\begin{aligned}\log k' = &(\log k'_{0w} - \log k'_{0,S}\phi) + (v_w - v_S\phi)V_2 \\ &+ (s_w - s_S\phi)\pi_2^* + (a_w - a_S\phi)\sum\alpha_2^H \\ &+ (b_w - b_S\phi)\sum\beta_2^H + (r_w - r_S\phi)R_2 \end{aligned} \quad (10)$$

or it can be reorganized as:

$$\log k' = \log k'_{0w} - \log k'_{0,S}\phi + v_w V_2 - v_S\phi V_2 + s_w\pi_2^* - s_S\phi\pi_2^* + a_w\sum\alpha_2^H - a_S\phi\sum\alpha_2^H + b_w\sum\beta_2^H - b_S\phi\sum\beta_2^H + r_w R_2 - r_S\phi R_2 \quad (11)$$

Comparing Eq. (10) with Eq. (6), we can see that the coefficients in Eq. (6) when applied at multiple mobile phase compositions can be linearly related to the mobile phase compositions. Thus, in order for the LSST and LSER to simultaneously hold each LSER coefficient must be a linear function of ϕ:

$$\log k'_0 = \log k'_{0,w} - \log k'_{0,S}\phi \quad (12)$$

$$v = v_w - v_S\phi \quad (13)$$

$$s = s_w - s_S\phi \quad (14)$$

$$a = a_w - a_S\phi \quad (15)$$

$$b = b_w - b_S\phi \quad (16)$$

$$r = r_w - r_S\phi \quad (17)$$

We can arrive at the above linear relationships between the LSER coefficients ($\log k'_0$, v, s, a, b and r) and ϕ from an entirely different perspective. Let us start with Eq. (6) and ask the question: if Eq. (6) is valid for a collection of solutes at specific value of ϕ, how can Eq. (1) be valid for a specific solute at multiple mobile phase compositions? Mathematically, this will only be possible in two ways: each LSER coefficient is a linear function of ϕ or the individual LSER coefficients are nonlinear functions of ϕ but collectively for any given solute the nonlinearities cancel out. We reject this second hypothesis because it requires that the nonlinear dependence of each coefficient to vary from solute to solute. Consider a non-polar solute such as benzene. It has virtually no HB acidity or basicity, in general s coefficients are small, and scarcely vary with ϕ (see below). Thus in order for $\log k'$ for benzene to vary linearly with ϕ then v would have to be linear with ϕ. Now consider a good hydrogen bond accepting solute such as benzamide. Here the $b\Sigma\beta_2^H$ term contributes almost as much to $\log k'$ as does the vV_2 term. In order for $\log k'$ to be linear with ϕ the nonlinear part of v for benzamide would have to cancel the combined nonlinear parts of s, a, b, or r for this species. This explanation of the nonlinear dependence of each coefficient is needlessly too complex and is extremely unlikely in general. We are thus led to the same conclusion, that is, for Eqs. (1) and (6) to be true simultaneously it follows that the LSER coefficients must be linear functions of ϕ.

The general result then is that, for any specific mobile phase modifier (acetonitrile, methanol, or THF) and any specific RPLC column, we can express retention as a simultaneous function of mobile phase composition (ϕ) and solute LSER descriptors with a maximum of 12 coefficients using the global LSER given in Eq. (11). This is obviously a tremendous experimental simplification since commonly we require six coefficients for every value of ϕ examined. The chief purpose of the present work is to determine if there is any diminution in the goodness-of-fit in using a single *global* LSER for each type of modifier in RPLC instead of doing the LSER fitting at each value of ϕ tested.

There are some similarities between the global LSER model and the Abraham–Roses–Poole equations published recently [56]. The Abraham–Roses–Poole equations were derived from fitting the local LSERs to the experimental data collected on different types of C_{18} columns with methanol–water or acetonitrile–water mobile phases. The equations require that the ratios of LSER coefficients (s/v, a/v, b/v, and r/v) be constant. Consequently, all LSER equations for methanol mobile phases can be combined into a single general equation

$$\log k' = c + v\left(V_2 - 0.32\pi_2^* - 0.22\sum\alpha_2^H - 0.90\sum\beta_2^H + 0.13R_2\right) \quad (18)$$

and all LSER equations for acetonitrile mobile phases can be combined into another general equation

$$\log k' = c + v\left(V_2 - 0.33\pi_2^* - 0.26\sum\alpha_2^H - 0.92\sum\beta_2^H + 0.18R_2\right) \quad (19)$$

where only c and v depend on the particular system.

Note that the values of c and v in Eqs. (18) and (19) should vary with mobile phase composition and hence must be determined by measurements on at least two solutes at every mobile phase composition of interest. Thus, the use of Eqs. (18) and (19) requires more experimentation than the use of the global LSER, that is the combined LSER–LSST, approach disclosed here. Work is in progress to test a combination of the LSER–LSST approach and Abraham–Roses–Poole approach.

If we rearrange Eq. (13) to express ϕ as a linear function of the v coefficient and substitute the function in Eqs. (14) to (17), we find that the global LSER model also requires that the s, a, b, and r coefficients be linear functions of the v coefficient:

$$s = s_0 - s_1 v \tag{20}$$

$$a = a_0 - a_1 v \tag{21}$$

$$b = b_0 - b_1 v \tag{22}$$

$$r = r_0 - r_1 v \tag{23}$$

where s_0, s_1, a_0, a_1, b_0, b_1, r_0 and r_1 are constants. These linear relationships are consistent with the Abraham–Roses–Poole equations. However, the Abraham–Roses–Poole equations predict zero intercepts in all linear relationships between the s, a, b, and r coefficients and the v coefficient which can not be confirmed by the global LSER model.

The Abraham–Roses–Poole equations appear to be more general than the global LSER model since one Abraham–Roses–Poole equation can cover more than one type of C_{18} column. However, the global LSER model differs from Abraham–Roses–Poole equations in at least three important ways. First, while the Abraham–Roses–Poole equations were derived from fitting the local LSERs to the experimental data, the global LSER is derived from the local LSER model and the LSST model. We note that LSST is the basis for some of the most important optimizing schemes in LC [1,27–29]. Second, the Abraham–Roses–Poole equations *do not* predict the linear relationship between the LSER coefficients and mobile phase composition. In contrast, the linear relationships between the LSER coefficients and mobile phase composition are imposed by the LSST component in the global LSER. These linear relationships eliminate the need to determine the LSER coefficients at every mobile phase composition of interest which must be done one way or another for the Abraham–Roses–Poole equations even if only c and v need to be determined as a function of mobile phase composition. Finally, the global LSER is used to model retention on one column only, not on multiple columns as with Abraham–Roses–Poole equations. We believe that, by focusing on one column and the range of mobile phase composition for which the LSST model is valid, the global LSER should provide better precision in retention prediction and should be more useful in practice as a basis for method development.

2. Experimental

The retention data used in this paper were taken from Ref. [57] which gives detailed descriptions of the experimental conditions employed. The retention data were collected at four volume/volume ratios (20%, 30%, 40% and 50%) for acetonitrile and tetrahydrofuran mobile phases and at five volume/volume ratios (10%, 20%, 30%, 40% and 50%) for methanol mobile phase. All measurements were made with a Hewlett-Packard 1090 liquid chromatograph, and temperature was controlled at 25.0±0.1°C. HPLC-grade solvents were used for the mobile phases, and all test solutes were obtained commercially. Zorbax-C_8 (Du Pont; particle size, 5 μm; pore size, 100Å) was used as the stationary phase. Columns of different dimensions (5 cm×2.1 mm I.D., 5 cm×4.6 mm I.D., 7.5 cm×4.6 mm I.D. and 15 cm×4.6 mm I.D.) were packed from the same lot of packing material in order to accommodate the very wide range in k' values encountered with the highly variegated set of solutes and mobile phase compositions.

The test solutes were judiciously chosen to span a wide range in solute properties in terms of size, dipolarity/polarizability and hydrogen bond donor/acceptor characteristics, which includes both aliphatic and aromatic alchohols, aldehydes, amides, esters, ethers, ketones, nitriles, nitro and halogenated compounds (Table 1). Fifty seven solutes were used in acetonitrile–water mobile phases, fifty seven solutes were used in tetrahydrofuran–water mobile phases,

Table 1
LSER descriptor values for the test solutes

	Solute	$V_x/100$[a]	π_2^*	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$	R_2	MeOH[b]	ACN[b]	THF[b]
1	Diethyl ether	0.7309	0.25	0	0.45	0.041	·	·	·
2	Acetonitrile	0.4042	0.9	0.07	0.32	0.237	·		·
3	2-Propanol	0.59	0.36	0.33	0.56	0.212	·	·	·
4	Methanol	0.3082	0.44	0.43	0.47	0.278			·
5	1-Butanol	0.7309	0.42	0.37	0.48	0.224	·	·	·
6	Cyclohexanol	0.9041	0.54	0.32	0.57	0.46	·	·	·
7	Acetone	0.547	0.7	0.04	0.49	0.179	·	·	·
8	2-Butanone	0.6879	0.7	0	0.51	0.166	·	·	·
9	Cyclopentanone	0.7202	0.86	0	0.52	0.373	·	·	·
10	2-Hexanone	0.9697	0.68	0	0.51	0.136	·	·	·
11	*n*-Propyl formate	0.7466	0.63	0	0.38	0.132		·	·
12	*n*-Butyl acetate	1.0284	0.6	0	0.45	0.071	·	·	·
13	Ethyl propionate	0.8875	0.58	0	0.45	0.087	·	·	·
14	Ethyl butyrate	1.0284	0.58	0	0.45	0.068	·	·	·
15	*n*-Propionitrile	0.5451	0.9	0.02	0.36	0.162	·	·	·
16	*n*-Nitropropane	0.7055	0.95	0	0.31	0.242	·	·	·
17	*n*-Valeronitrile	0.8269	0.9	0	0.36	0.177	·	·	·
18	Butyraldehyde	0.6879	0.65	0	0.45	0.187	·	·	
19	2,2,2-Trifluoroethanol	0.5022	0.6	0.57	0.25	0.015	·	·	·
20	Methylene chloride	0.4943	0.57	0.1	0.05	0.387	·	·	·
21	Chloroform	0.6167	0.49	0.15	0.02	0.425	·	·	·
22	Dibromomethane	0.5995	0.67	0.1	0.1	0.714	·	·	·
23	*N*,*N*-Dimethylformamide	0.6468	1.31	0	0.74	0.367	·	·	·
24	*N*,*N*-Diethylformamide	0.9286	1.25	0	0.76	0.305	·	·	·
25	Dimethyl sulfoxide	0.6126	1.74	0	0.89	0.522	·	·	
26	*N*,*N*-Dimethylacetamide	0.7877	1.33	0	0.78	0.363	·	·	
27	*N*,*N-Diethylacetamide*	1.0695	1.3	0	0.78	0.296	·	·	
28	Dioxane	0.681	0.75	0	0.64	0.329	·	·	·
29	Benzene	0.7164	0.52	0	0.14	0.61	·	·	·
30	Toluene	0.8573	0.52	0	0.14	0.601		·	·
31	Benzaldehyde	0.873	1	0	0.39	0.82	·	·	·
32	Acetophenone	1.0139	1.01	0	0.48	0.818	·	·	·
33	Propiophenone	1.1548	0.95	0	0.51	0.804		·	·
34	Benzonitrile	0.8711	1.11	0	0.33	0.742	·	·	·
35	*m*-Toluenitrile	1.012	1.1	0	0.34	0.74		·	·
36	Nitrobenzene	0.8906	1.11	0	0.28	0.871	·	·	·
37	*m*-Nitrotoluene	1.0315	1.1	0	0.25	0.874		·	·
38	Anisole	0.916	0.75	0	0.29	0.708	·	·	·
39	Methyl benzoate	1.0726	0.85	0	0.46	0.733	·	·	·
40	Ethyl benzoate	1.2135	0.85	0	0.46	0.689		·	·
41	Phenol	0.7751	0.89	0.6	0.3	0.805	·	·	·
42	*m*-Cresol	0.916	0.88	0.57	0.34	0.822	·	·	·
43	Benzylalcohol	0.916	0.87	0.33	0.56	0.803	·	·	·
44	2-Phenylethanol	1.0569	0.91	0.3	0.64	0.811	·	·	·
45	3-Phenylpropanol	1.1978	0.9	0.3	0.67	0.821		·	·
46	*N*-Benzylformamide	1.1137	1.8	0.4	0.63	0.99	·	·	·
47	Methyl phenyl sulfoxide	1.0795	1.58	0	0.92	1.104	·		·
48	Fluorobenzene	0.7341	0.57	0	0.1	0.477		·	·
49	Chlorobenzene	0.8388	0.65	0	0.07	0.718		·	·
50	Bromobenzene	0.8914	0.73	0	0.09	0.882			·
51	Benzophenone	1.4808	1.5	0	0.5	1.447		·	·
52	Benzyl cyanide	1.012	1.15	0	0.45	0.751		·	·

Table 1. Continued

	Solute	$V_x/100$[a]	π_2^*	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$	R_2	MeOH[b]	ACN[b]	THF[b]
53	Benzyl bromide	1.0323	0.98	0	0.2	1.014		·	·
54	*p*-Nitrobenzyl bromide	1.2065	1.5	0	0.4	1.27		·	·
55	*p*-Nitrobenzyl chloride	1.1539	1.34	0	0.4	1.08		·	·
56	*o*-Nitrotoluene	1.0315	1.11	0	0.27	0.866		·	·
57	*p*-Nitrotoluene	1.0315	1.11	0	0.28	0.87		·	·
58	*p*-Cresol	0.916	0.87	0.57	0.31	0.82		·	·
59	*o*-Cresol	0.916	0.86	0.52	0.3	0.84		·	·
60	*p*-Ethylphenol	1.0569	0.9	0.55	0.36	0.8		·	·
61	*p*-Chlorophenol	0.8975	1.08	0.67	0.2	0.915		·	·

[a] Values of V_x were taken from Refs. [58,59], while values of π_2^*, $\Sigma\alpha_2^H$, $\Sigma\beta_2^H$, and R_2 were obtained from Ref. [60].

[b] A blank in these columns indicates that the retention time for the solute is either too short or too long to measure, so that the solute is not included.

and thirty nine solutes were used in the methanol–water mobile phases. The same set of solutes could not be used in each type of mobile phases due to the extremely small or large retention times of some solutes over the wide range of mobile phases used. However, the same set of solutes was used for each specific type of mobile phase at all compositions. As in Tan's work [57] the solute molecular volume (V_2) values were calculated using McGowan's method [58,59], and solute dipolarity/polarizability (π_2^*), hydrogen bond donor/acceptor ($\Sigma\alpha_2^H$, $\Sigma\beta_2^H$) and excess molar refraction (R_2) were obtained from Abraham [60]. With the wide range of mobile phase compositions of three different organic modifiers and the large number of very different test solutes, we feel that this retention data should allow a statistically meaningful test of the global LSER model in RPLC.

3. Results and discussion

The function of multiple linear regression and the related statistical functions in Excel of Microsoft Office 97 were used throughout the study. For each type of mobile phases, the log k' values at each mobile phase composition are used to fit the local LSER model and the log k' values at all mobile phase compositions are concatenated to fit the global LSER model. The regression coefficients and the related statistics for the global LSER fits and for the local LSER fits are given in Tables 2 and 3, respectively. The experimental log k' vs. the calculated log k' values are plotted in Fig. 1. The averaged standardized residuals vs. solutes are plotted in Fig. 2 for testing the distributions of residuals. To help identify the possible outliers, the residual for each solute at each composition is standardized by dividing it by its estimated standard deviation. To reduce the clutter in the figure, the standardized residuals for each solute at all compositions of a fixed type of organic modifier were averaged.

Overall, the global LSER fits for all three types of mobile phases are excellent with all the data points falling close to the regression lines (Fig. 1). The averaged standardized residuals for different solutes

Table 2
Regression coefficients and related statistics for the global LSER fits

	MeOH	ACN	THF
$\log k'_{0,w}$	−0.86±0.07	−0.22±0.08	−0.03±0.11
$\log k'_{0,S}$	−0.45±0.21	0.13±0.21	0.65±0.30
m_w	4.09±0.10	3.45±0.11	3.00±0.16
m_S	3.68±0.29	3.80±0.29	3.33±0.43
s_w	−0.39±0.07	−0.30±0.08	−0.48±0.12
s_S	0.39±0.20	−0.11±0.21	−0.50±0.33
a_w	−0.35±0.08	−0.51±0.08	0.11±0.12
a_S	−0.12±0.25	−0.20±0.21	0.29±0.32
b_w	−1.86±0.10	−3.23±0.11	−3.68±0.16
b_S	−0.59±0.30	−2.73±0.31	−3.93±0.43
r_w	0.16±0.07	0.17±0.09	0.77±0.13
r_S	−0.06±0.21	0.48±0.24	1.63±0.35
n[a]	195	228	228
SD[a]	0.08	0.07	0.10
ρ[a]	0.9931	0.9947	0.9870

[a] n, SD and ρ are the number of data points, estimated standard deviation, and correlation coefficient, respectively.

Table 3
Regression coefficients and related statistics for the local LSER fits

Mobile phase	log k'_0	v	s	a	b	r	n[a]	SD[a]	ρ[a]
50% MeOH	−0.72±0.05	2.27±0.07	−0.53±0.05	−0.27±0.07	−1.51±0.08	0.16±0.06	39	0.07	0.9915
40% MeOH	−0.66±0.06	2.63±0.08	−0.55±0.05	−0.27±0.07	−1.65±0.08	0.17±0.06	39	0.07	0.9924
30% MeOH	−0.64±0.06	2.99±0.09	−0.56±0.06	−0.34±0.08	−1.78±0.09	0.21±0.06	39	0.08	0.9926
20% MeOH	−0.67±0.07	3.26±0.10	−0.55±0.07	−0.42±0.08	−1.72±0.10	0.23±0.07	39	0.09	0.9915
10% MeOH	−0.94±0.08	3.80±0.10	−0.34±0.07	−0.25±0.09	−1.77±0.11	0.10±0.08	39	0.10	0.9915
50% ACN	−0.30±0.04	1.56±0.05	−0.24±0.04	−0.41±0.04	−1.80±0.05	−0.04±0.04	57	0.05	0.9932
40% ACN	−0.25±0.04	1.90±0.06	−0.26±0.04	−0.43±0.04	−2.16±0.06	−0.02±0.05	57	0.06	0.9937
30% ACN	−0.27±0.05	2.36±0.07	−0.23±0.05	−0.46±0.05	−2.54±0.07	−0.02±0.05	57	0.07	0.9947
20% ACN	−0.25±0.05	2.68±0.07	−0.29±0.05	−0.47±0.05	−2.59±0.07	0.11±0.06	57	0.07	0.9955
50% THF	−0.37±0.05	1.35±0.07	−0.25±0.05	−0.06±0.05	−1.70±0.07	−0.00±0.06	57	0.07	0.9830
40% THF	−0.28±0.06	1.66±0.09	−0.27±0.07	−0.00±0.07	−2.12±0.09	0.07±0.07	57	0.10	0.9812
30% THF	−0.20±0.07	1.97±0.09	−0.30±0.07	0.08±0.07	−2.52±0.09	0.23±0.08	57	0.10	0.9866
20% THF	−0.18±0.09	2.35±0.13	−0.41±0.10	0.01±0.10	−2.88±0.13	0.49±0.10	57	0.14	0.9843

[a] n, SD and ρ are the number of data points, estimated standard deviation and correlation coefficient, respectively.

are virtually randomly distributed (Fig. 2). Considering the large numbers of solutes, their chemical diversity, and the wide ranges in mobile phase compositions covered by the data, the quality of the global LSER model fits are quite satisfactory and effective. Simple inspection of the SD (estimated standard deviation) and ρ (correlation coefficient) given in Tables 2 and 3 indicates that the global fits are really quite good despite the considerable reduction in the number of fitting coefficients as compared to the local LSER fits. We note that only 12 fitting coefficients are needed for each global LSER fit but that 24, 30 and 24 coefficients are needed for the local LSER fits for the four acetonitrile, five methanol, and four THF compositions, respectively. Obviously more coefficients will be needed for the local LSER fits if more compositions were used.

Since the global LSER model extends both the local LSER model and the local LSST model, a comparison of the differences between these models should help us better understand them and possibly improve the models in the future.

3.1. Goodness-of-fit of the global LSER as compared to the local LSER

Since fewer regression coefficients are used in a global LSER fit than that in a series of local LSER fits, we expect that the goodness-of-fit of the global LSER fit should be worse than that of the local LSER fits. To test *if* the goodness-of-fit of the global LSER is significantly worse than that of the local LSERs, we did one-tailed F-tests on the residual mean square from a global LSER fit and the residual mean square pooled from the multiple local LSER fits (Table 4).

Despite the two-fold (or larger) decrease in the number of fitting coefficients used, the F-tests show that the goodness-of-fit of the global LSER is not statistically greater than that of the local LSERs. These results confirm that the local LSER model for a single mobile phase composition can be effectively extended to the global LSER model for multiple mobile phase compositions within the range of mobile phase compositions considered here. Hence, after only a total of twelve regression coefficients are empirically determined for each type of mobile phase, the global LSER model can be used to predict the retention of any solute whose LSER descriptors are known at any other mobile phase composition within the range of mobile phase compositions for which the LSST model is valid. In contrast, the local LSER model require a different set of six regression coefficients at every mobile phase composition (see Table 3). When retention prediction at more than two mobile phase compositions is attempted, the global

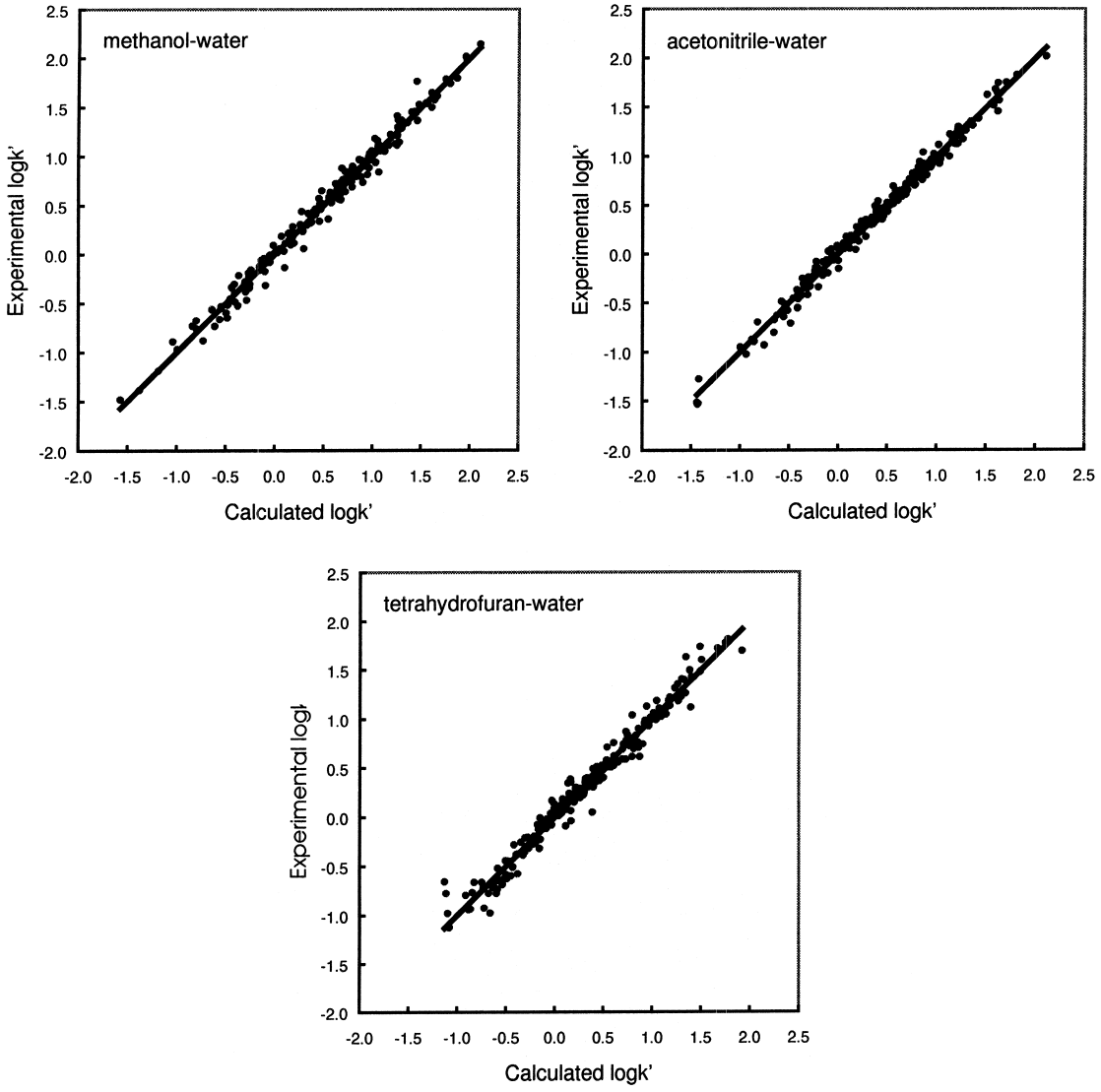

Fig. 1. Plots of experimental log k' values vs. calculated log k' values.

LSER approach will be more efficient than the local LSER model applied at the same number of mobile phase compositions.

3.2. Goodness-of-fit of the global LSER–LSST as compared to the local LSST

Since far fewer regression coefficients are used in a global LSER fit than that in a series of local LSST fits for the same data, we expect that the goodness-of-fit of the global LSER shall also be worse than that of the local LSSTs. To test *if* the goodness-of-fit of the global LSER is significantly worse than that of the local LSSTs, we did one-tailed *F*-tests also on the residual mean square from a global LSER fit and the residual mean square pooled from the multiple local LSST fits for the same data (Table 5).

The results indicate that the global LSER fits are

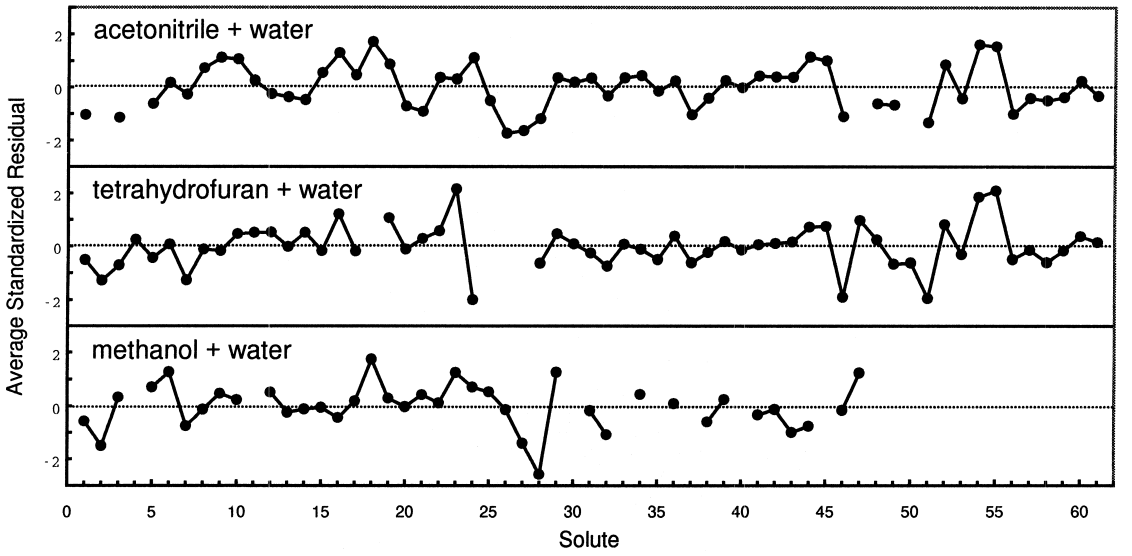

Fig. 2. Plots of averaged standardized residuals vs. solutes. To help identifying the possible outlier, the residual for each solute at each composition is standardized by dividing the residual by its estimated standard deviation. To reduce the clutter in the figure, the standardized residuals for each solute at all compositions of a fixed type of organic modifier were averaged. The averaged standardized residuals for different solutes are virtually randomly distributed with balanced numbers of both positive and negative deviations.

Table 4
F-tests on the residual mean squares from global LSER fits and the residual mean squares pooled from local LSER fits

Mobile phase	Residual source	s^{2a}	df[a]	*F*-ratio	F_c ($\alpha=0.1$)
MeOH	Global LSER	0.0072	183		
	Pooled local LSER	0.0069	165	1.05	1.22
ACN	Global LSER	0.0046	216		
	Pooled local LSER	0.0041	204	1.13	1.19
THF	Global LSER	0.0110	216		
	Pooled local LSER	0.0112	204	1.02	1.19

[a] s^2 and df are the residual mean squares and the degree of freedom for the *F*-test, respectively.

Table 5
F-tests on the residual mean squares from global LSER fits and the residual mean squares pooled from local LSST fits

Mobile phase	Residual source	s^{2a}	df[a]	*F*-ratio	F_c ($\alpha=0.1$)
MeOH	Global LSER	0.0072	183		
	Pooled LSST	0.0024	117	2.99	1.24
ACN	Global LSER	0.0046	216		
	Pooled LSST	0.0019	114	2.45	1.24
THF	Global LSER	0.0110	216		
	Pooled LSST	0.0020	114	5.49	1.24

[a] s^2 and df are the residual mean squares and the degree of freedom for the *F*-test, respectively.

significantly poorer than the local LSST fits. Since the standard errors of the pooled LSST fits are significantly better than that of the local LSER fits for the same data (Table 6), we conclude that the residuals of a global LSER fit must result primarily from the local LSERs. Clearly, the LSER method has not achieved the level of exhaustive fitting. Therefore, we are convinced that, for the global LSER approach to achieve the same precision that is possible with LSST, significant improvements in the LSER model and/or solute's descriptor values are necessary.

3.3. Comparison of the coefficients of the global LSER to that of the local LSER

The global LSER model given in Eq. (10) predicts that the LSER coefficients are linear functions of mobile phase composition. Therefore, if the global LSER model is valid over the composition range considered, an equation of the global LSER model should reduce to an equation of the local LSER model for a specific mobile phase composition (Eq. (6)). The coefficients of the reduced global LSER equation should be equal, within the appropriate confidence intervals, to the coefficients of the local LSER equation calculated from the same data for the same mobile phase composition.

To check the validity of this concept, the *v, s, a, b,* and *r* coefficients obtained from the local LSER fits and from the reduced global LSER fits are plotted together as functions of mobile phase composition (Fig. 3). Note that the data points in this figure are taken from the local LSER fits for different mobile phase compositions, the error bars are the 90% confidence intervals for the data points, and the solid lines are taken from the reduced global LSER fits. We see that, at nearly all mobile phase compositions, the coefficients of the reduced global LSER fits fall within 90% confidence intervals for the coefficients of the local LSER fits, which further increases our confidence in the overall validity of the global LSER approach.

To test *if* the local LSER coefficients vary linearly with mobile phase composition as required by the global LSER model, we did one-tailed *F*-tests on regressions of the local LSER coefficients on the mobile phase composition (Table 7). The results show that the linear relationship between the *v* and *b* coefficients and the mobile phase composition are significant for all three types of organic modifiers. However, the linear relationships between a few of the other coefficients and mobile phase composition are not statistically significant due to the relatively small contribution of the LSER descriptors associated with these coefficients to the retention.

Interestingly, the solid lines in Fig. 3 that are taken from the reduced global LSER fits are actually identical to the regression lines of the local LSER coefficients vs. mobile phase composition. This is so because the vector of mobile phase compositions used in a global LSER fit is the concatenation of the mobile phase composition for each solute at each mobile phase composition. This concatenation makes the vector orthogonal to all other vectors of LSER descriptor values used in the fit, which makes the values of the *v, s, a, b,* and *r* coefficients obtained from the reduced global LSER fit fall exactly on the regression lines of the local LSER coefficients. The same identity of regression coefficients of a global

Table 6
F-tests on the residual mean squares pooled from local LSER fits and the residual mean squares pooled from local LSST fits

Mobile phase	Residual source	s^{2a}	df[a]	*F*-ratio	F_c ($\alpha = 0.1$)
MeOH	Pooled LSER	0.0069	165		
	Pooled LSST	0.0024	117	2.81	1.25
ACN	Pooled LSER	0.0041	204		
	Pooled LSST	0.0019	114	2.19	1.24
THF	Pooled LSER	0.0112	204		
	Pooled LSST	0.0020	114	5.60	1.24

[a] s^2 and df are the residual mean squares and the degree of freedom for the *F*-test, respectively.

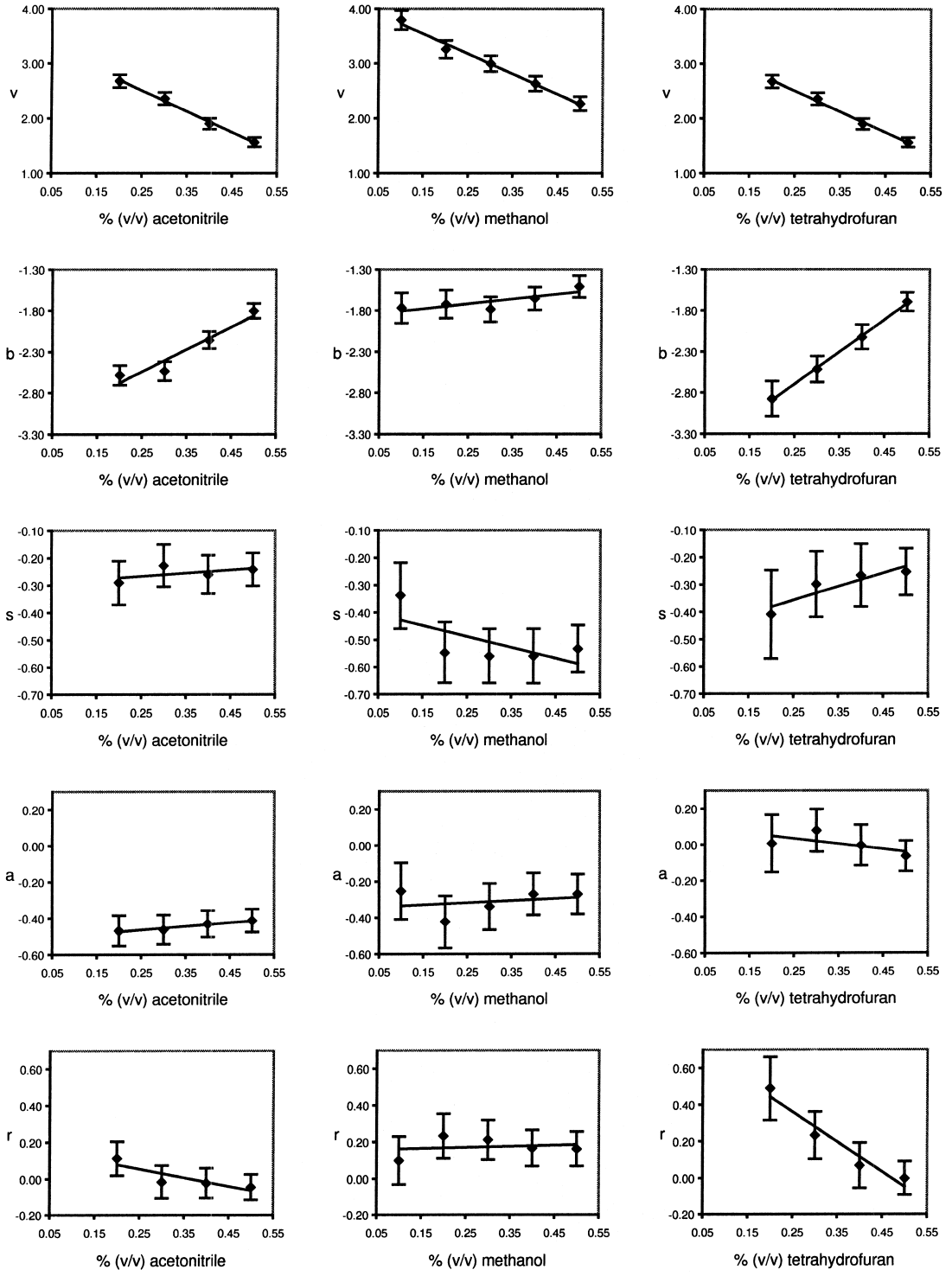

Fig. 3. Plots of LSER regression coefficients vs. mobile phase composition. Data points are taken from the local LSER fits and error bars are 90% confidence intervals for the data points; solid lines are constructed from the global LSER fits.

Table 7
F-test for linear regressions of local LSER coefficients on mobile phase compositions

Mobile phase	LSER coefficients	Source	s^{2a}	df[a]	*F*-ratio	F_c ($\alpha=0.1$)
MeOH	*v*	Regression	1.3518	1		
		Residual	0.0159	3	255.09	5.54
	b	Regression	0.0346	1		
		Residual	0.0157	3	6.59	5.54
	s	Regression	0.0154	1		
		Residual	0.0199	3	2.3	5.54
	a	Regression	0.0014	1		
		Residual	0.0186	3	0.22	5.54
	r	Regression	0.0003	1		
		Residual	0.0104	3	0.10	5.54
ACN	*v*	Regression	0.7216	1		
		Residual	0.0036	2	401.62	8.53
	b	Regression	0.0346	1		
		Residual	0.0296	2	25.24	8.53
	s	Regression	0.0006	1		
		Residual	0.0016	2	0.83	8.53
	a	Regression	0.0019	1		
		Residual	0.0001	2	33.14	8.53
	r	Regression	0.0114	1		
		Residual	0.0037	2	6.10	8.53
THF	*v*	Regression	0.5531	1		
		Residual	0.0017	2	664.34	8.53
	b	Regression	0.7741	1		
		Residual	0.0012	2	1316.36	8.53
	s	Regression	0.0124	1		
		Residual	0.0025	2	9.91	8.53
	a	Regression	0.0043	1		
		Residual	0.0060	2	1.44	8.53
	r	Regression	0.1336	1		
		Residual	0.0087	2	30.58	8.53

[a] s^2 and df are the mean squares and the degree of freedom for the *F*-test, respectively.

linear fit and a series of local linear fits for the same data also occurs in the LSER regression coefficients for log k'_w and *S* (see Tables 8 and 9 discussed in the next section). A separate study of this statistical identity will be forthcoming.

3.4. LSER equations for log k'_w and S

Log k'_w and *S* are the fitting coefficients of a LSST equation (Eq. (1)). In deriving the global LSER model, we asserted that both log k'_w and *S* are linear free energy variables and thus subject to the LSER formalism. Since the global LSER model is a simultaneous function of both mobile phase composition and solute LSER molecular descriptors, we can get the LSER equations for log k'_w and *S* from the global LSER equations as follows.

If we set ϕ in a global LSER fit to zero (pure water) and reduce the global LSER equation to a LSER equation for pure water, the reduced global

Table 8
LSER coefficients for the log k'_w values from global LSER fits and from LSST fits

Mobile phase	log $k'_{0,w}$	v_w	s_w	a_w	b_w	r_w
MeOH[a]	−0.86±0.07	4.09±0.10	−0.39±0.06	−0.35±0.08	−1.86±0.10	0.16±0.07
MeOH[b]	−0.86±0.08	4.09±0.11	−0.39±0.08	−0.35±0.10	−1.86±0.11	0.16±0.08
ACN[a]	−0.23±0.08	3.45±0.11	−0.30±0.08	−0.51±0.08	−3.23±0.11	0.17±0.09
ACN[b]	−0.22±0.07	3.45±0.10	−0.30±0.07	−0.51±0.07	−3.23±0.10	0.17±0.08
THF[a]	−0.03±0.11	3.00±0.16	−0.48±0.12	0.11±0.12	−3.68±0.16	0.77±0.13
THF[b]	−0.03±0.13	3.00±0.19	−0.48±0.15	0.11±0.14	−3.68±0.19	0.77±0.16

[a] LSER coefficients for the log k'_w values from the reduced global LSER equations for pure water ($\phi=0$).
[b] LSER coefficients for the log k'_w values from LSST fits.

LSER equation should be equivalent to the LSER fit for the log k'_w values obtained from the LSST fit for the solutes in the same data (Table 8). Similarly, if we subtract the reduced global LSER equation for pure water ($\phi=0$) from the reduced global LSER equation for pure organic modifier ($\phi=1$), the result should be equivalent to a LSER fit for the S values obtained from the same LSST fits as for log k'_w (Table 9).

The large differences in the LSER coefficients for log k'_w between the different types of organic modifiers indicate that the LSST equation can not be valid for the entire range in mobile phase composition. If LSST were exactly true log k'_w would be the same for all types of modifiers. Hence, the global LSER model, as a logical extension to the LSST model, can not be valid over the entire range in mobile phase composition either. The LSST equation is, at best, quasi-linear.

There are also apparent linear relationships between log k'_w and S values for all three organic modifiers (Fig. 4). Since the retention data used here includes a large number of chemically variegated set of solutes, these apparent linear relationships must be due to the propagation of random measurement error in the least-squares determination of log k'_w and S values and does not reflect chemical reality, as explained in detail in Tan and Carr's work [61].

4. Conclusions

A global LSER model can be derived by combining the local LSER model and the LSST model. Within the range of mobile phase compositions for which the LSST model is valid, the global LSER model can be used to simultaneously model retention as a function of both solute LSER descriptors and mobile phase composition. At most only 12 coefficients are required to establish the global LSER.

Table 9
LSER coefficients for the S values from global LSER fits and from LSST fits

Mobile phase	log $k'_{0,S}$	v_S	s_S	a_S	b_S	r_S
MeOH[a]	−0.45±0.21	3.68±0.29	0.39±0.20	−0.12±0.25	−0.59±0.30	−0.06±0.21
MeOH[b]	−0.45±0.14	3.68±0.19	0.39±0.13	−0.12±0.17	−0.59±0.20	−0.06±0.14
ACN[a]	0.13±0.21	3.80±0.29	−0.11±0.21	−0.20±0.21	−2.73±0.31	0.48±0.24
ACN[b]	0.13±0.14	3.80±0.20	−0.11±0.14	−0.20±0.15	−2.73±0.21	0.48±0.16
THF[a]	0.65±0.30	3.33±0.43	−0.50±0.33	0.29±0.32	−3.93±0.43	1.63±0.35
THF[b]	0.65±0.28	3.33±0.31	−0.50±0.31	0.29±0.31	−3.93±0.41	1.63±0.33

[a] LSER coefficients for the S values obtained by subtracting the reduced global LSER equations for pure water ($\phi=0$) from the reduced global LSER equations for pure organic modifiers ($\phi=1$).
[b] LSER coefficients for the S values from LSST fits.

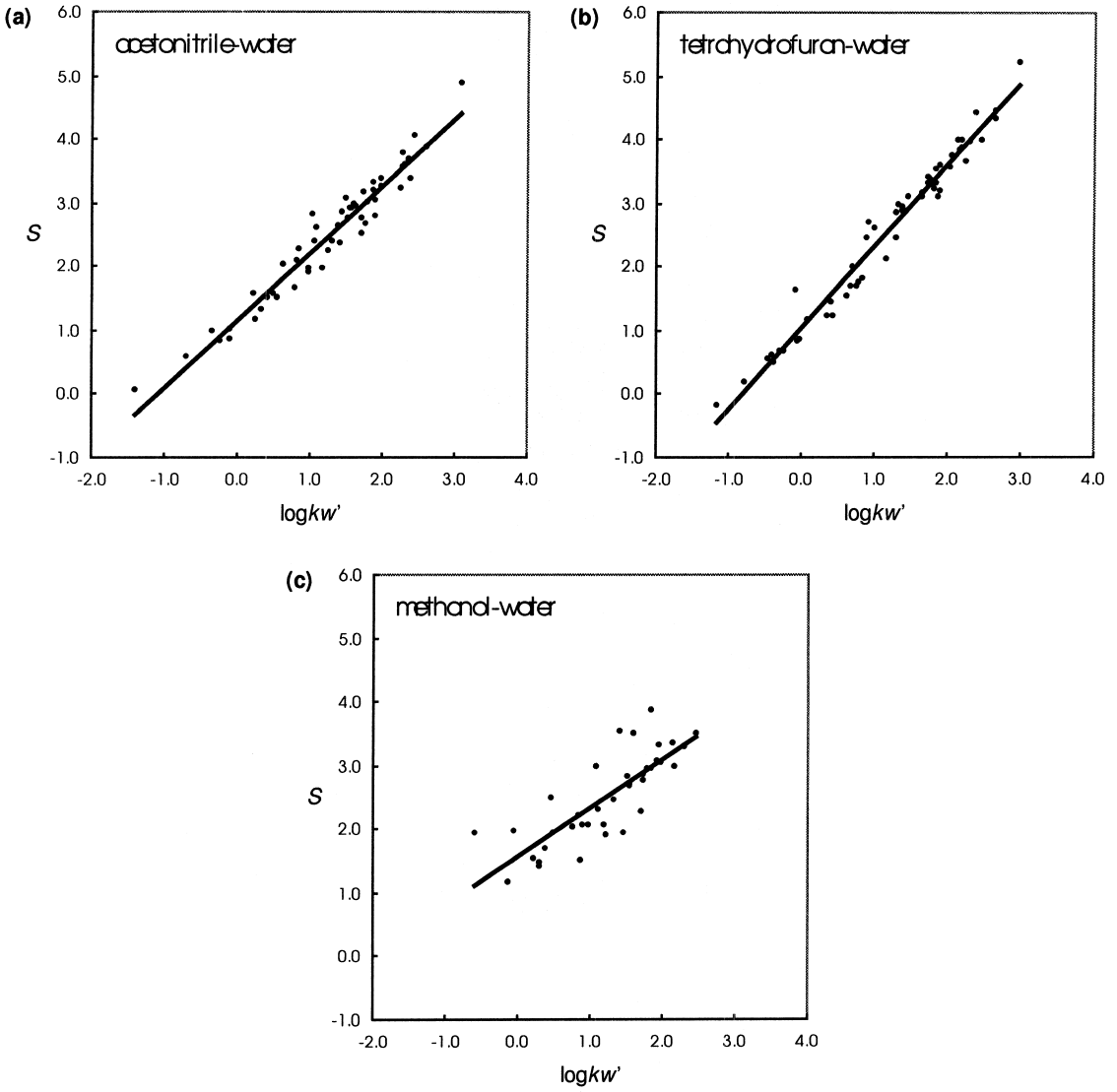

Fig. 4. Plots of S vs. log k'_w value for each solute calculated from the global LSER fit extrapolated to unity and zero ϕ. (a) Acetonitrile–water ($S=1.06 \log k'_w+1.16$). (b) Tetrahydrofuran–water ($S=1.28 \log k'_w+1.05$). (c) Methanol–water ($S=0.76 \log k'_w+1.58$).

Many more coefficients would be required if the same data were fitted using a series of local LSERs. Once calibrated with a set of standard solutes at two mobile phase compositions, the global LSER model can be used to predict the retention of any other solute whose LSER descriptors are known at any mobile phase composition within the range of mobile phase compositions for which the LSST model that is valid.

The global LSER model was tested with retention data obtained in acetonitrile–water, tetrahydrofuran–water and methanol–water mobile phases each at four or five mobile phase compositions for a large number of highly variegated solutes. The results show that the residuals of the global LSER fits are due mainly to the local LSER model rather than to the LSST model. Therefore, it should be possible to improve the global LSER model by refining the local

LSER model and/or solute's descriptor values. This improvement should reduce the residuals contributed by the local LSER model and make the global LSER model more practically useful as a basis of method development.

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