Journal of Chromatography, 214 (1981) 21–34
Elsevier Scientific Publishing Company, Amsterdam — Printed in The Netherlands

CHROM. 13,944

SOLVENT STRENGTH OF MULTICOMPONENT MOBILE PHASES IN LIQUID–SOLID CHROMATOGRAPHY

MIXTURES OF THREE OR MORE SOLVENTS

J. L. GLAJCH
Central Research and Development Department, E. I. du Pont de Nemours and Company, Wilmington, DE 19898 (U.S.A.)
and
L. R. SNYDER*
Technicon Instruments Corp., Tarrytown, NY 10591 (U.S.A.)
(Received April 24th, 1981)

SUMMARY

The recently improved theory for the calculation of solvent strength in binary-solvent liquid–solid chromatography (LSC) systems has been extended to ternary and higher order solvent systems. It has been shown that these new approaches result in greatly improved predictions of solvent strength in ternary- and quaternary-solvent systems, especially those involving strong polar solvents which can localize. This current method is more general and exact than previous approximations of solvent strength and facilitates development of solvent optimization schemes in LSC which use multiple solvents.

INTRODUCTION

The optimization of separation or resolution in high-performance liquid chromatography (HPLC) is a practical goal which is receiving increasing attention (*e.g.*, refs. 1–5). The usual strategy[1] is to separately optimize column efficiency (plate number N), solvent strength and separation selectivity. The choice of column will normally be dictated by the application, so that primary emphasis is given to optimizing solvent strength and selectivity. The general approach is to vary the composition of a particular binary-solvent mixture A–B for the best solvent strength, such that solute capacity factor k' values fall within a range of roughly 1–10. Solvent selectivity can then be further improved by substituting other strong solvents C, D, ... for the strong solvent B in the original mixture A–B. However, after each substitution, the proportions of individual solvents in the mixture must be reoptimized in terms of solvent strength.

In the past decade (*e.g.*, refs. 5–10) there has been increasing emphasis given to the use of ternary or quaternary solvent mixtures as mobile phases in HPLC. These more complex mobile phases offer further opportunities for invoking additional chemical effects that can alter separation selectivity to advantage, and allow better "fine-tuning" of the final separation. Because of the requirement that solvent strength be maintained constant throughout a series of solvents chosen for different selectivity, the ability to predict solvent strength as a function of composition greatly simplifies the process of selectivity optimization.

In this paper we consider a general approach to the prediction of solvent strength for ternary and quaternary mobile phases in liquid–solid chromatography (LSC). Little previous work in this area has been reported, except for one study[11] that proposed an approximate relationship for ternary-solvent mixtures. We will show that it is possible to predict the solvent strength of mobile phases that contain any number of solvent components, but specifically we will examine the case of ternary- and quaternary-solvent mixtures in detail. Later papers[12,13] will apply the present approach to the development of a systematic practical scheme for optimizing solvent strength and selectivity in LSC for any sample mixture.

THEORY

The theory of solvent strength in LSC separations has been examined in detail for the case of binary solvent mobile phases[14–17]. In particular, the previous paper on binary-solvent systems[17] serves as an introduction to the more general case of mobile phases which contain three or more solvent components. A simple model of solute retention can be developed, based on two simple physical phenomena: a displacement model of solute retention, and the localization of polar molecules of solvent or solute on the adsorbent surface. The application of this model then results in simple expressions for solvent strength as a function of mobile phase composition and the properties of individual solvent components. A comparison of experimental and calculated values of solvent strength ε^0 for 93 solvent binaries in ref. 17 showed agreement within ± 0.017 units (1 standard deviation, S.D.) which is adequate for the proper control of solvent strength while optimizing the LSC separation.

Binary-solvent mobile phases

Solvent strength ε^0 in LSC can be defined in terms of the relationship derived in ref. 14:

$$\log (k_1/k_2) = \alpha' A_s(\varepsilon_2 - \varepsilon_1) \tag{1}$$

Here, k_1 and k_2 are capacity factor values (k') for a solute when using solvents 1 and 2 as mobile phases (see ref. 1), ε_1 and ε_2 are ε^0 values for the two solvents, α' is an adsorbent activity parameter, and A_s refers to the cross-sectional area of the solute molecule. We desire to relate the solvent strength ε_{AB} of a binary-solvent mobile phase to its composition. If the mobile phase is a mixture of solvents A and B, where B is the stronger solvent, it can be shown (as in ref. 17) that

$$\varepsilon_{AB} = \varepsilon_A + \frac{\log N_B(10^{\alpha' n_b(\varepsilon_B - \varepsilon_A)} + 1 - N_B)}{\alpha' n_b} \tag{2}$$

where ε_A and ε_B are the ε^0 values of the pure solvents, n_b is the cross-sectional area of a molecule of B, and N_B refers to the mole fraction of B in the mobile phase.

Solvent localization and eqn. 2. For less polar solvents B (so-called class-N solvents), eqn. 2 is a reliable relationship for predicting values of ε_{AB} when values of ε_A and ε_B are known. For more polar B-solvents (class P), however, it has been shown[17] that no single value of ε_B applies for all values of N_B. The reason is that more polar solvents B can adsorb with *localization*, or attachment to a specific adsorption site. As a result, the adsorption energy and value of ε_B will be larger for B at low values of N_B and θ_B, because all molecules of B can localize when the adsorbent surface is not largely covered by adsorbed B. With increasing values of θ_B, however, the filling of the remainder of the adsorbent surface by molecules of B will not allow localized adsorption, and values of ε_B progressively decline with increase in θ_B. If the value of ε_B is ε'_B for $\theta = 0$, and ε''_B for $\theta = 1$, then a localization function $\%_{\text{olc}}$ can be defined such that

$$\%_{\text{olc}} = (\varepsilon_B - \varepsilon''_B)/(\varepsilon'_B - \varepsilon''_B) \tag{3}$$

It was found in ref. 17 for binary-solvent mobile phases and alumina or silica as adsorbents that a single relationship, $\%_{\text{olc}} = f(\theta_B)$, is valid for over twenty different B-solvents. The relationship is shown in Fig. 1 as the solid curve. Use of the latter relationship for $\%_{\text{olc}}$ with eqn. 10 of ref. 17 allows calculation of ε_B for any value of N_B, which in turn allows the calculation of values of ε_{AB} from eqn. 2. For a more complete discussion see ref. 17.

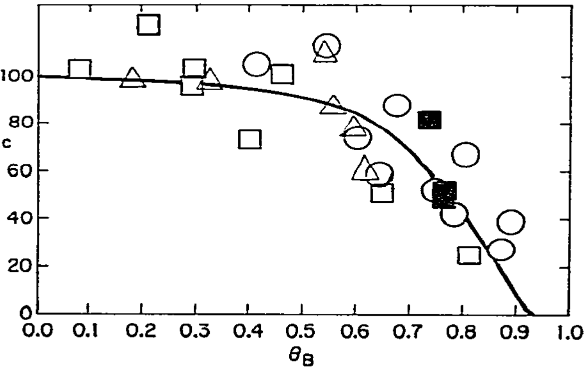

Fig. 1. Experimental solvent localization parameters $\%_{\text{olc}}$ plotted against values of θ for mobile phases of Tables I–III. ○, Dioxane in Table I; □, MTBE in Table II; △, acetonitrile in Table III, ■, MTBE in Table III.

Mobile phases containing three or more solvent components

The approach followed here for predicting the solvent strength of a mobile phase which contains more than two solvent components is conceptually the same as for the derivation of eqn. 2 for binary-solvent mobile phases. Again, it is assumed that a Langmuir-type equilibrium exists for the adsorption of the various pure solvent components A, B, C, etc. onto the adsorbent surface, with formation of an adsorbed monolayer. The following reactions can then be written corresponding to adsorption of one solvent molecule and displacement of some number n molecules of another solvent (solvent strength for the pure solvents is assumed to increase in the order A, B, C, ...):

$$B_n + A_a \rightleftharpoons B_a + A_n \tag{4}$$
$$C_n + B_a \rightleftharpoons C_a + B_n \tag{4a}$$
$$D_n + C_a \rightleftharpoons D_a + C_n \tag{4b}$$
$$\ldots$$

Subscripts n and a refer as earlier to a molecule in the non-sorbed and adsorbed phases, respectively. The approximation is again made that the various molecules A, B, ... have approximately constant molecular areas, so that one molecule of A displaces exactly one molecule of B, etc. Equilibrium constants K_{AB}, K_{BC}, etc. can be defined for eqns. 4–4b (*cf.* eqn. 4 of ref. 17):

$$K_{AB} = \theta_B N_A / \theta_A N_B \tag{5}$$
$$K_{BC} = \theta_C N_B / \theta_B N_C \tag{5a}$$
$$K_{CD} = \theta_D N_C / \theta_C N_D \tag{5b}$$
$$\ldots$$

Here, θ_i again refers to the mole fraction of solvent i in the adsorbed phase, and N_i is its mole fraction in the mobile phase.

As for eqn. 5b of ref. 17:

$$K_{AB} = 10^{\alpha' n_b (\varepsilon_B - \varepsilon_A)} \tag{6}$$
$$K_{BC} = 10^{\alpha' n_b (\varepsilon_C - \varepsilon_D)} \tag{6a}$$
$$K_{CD} = 10^{\alpha' n_b (\varepsilon_D - \varepsilon_C)} \tag{6b}$$
$$\ldots$$

The value of n_b assumed in eqns. 6–6b must be constant for the various solvents B, C, ... The approach used here is to simply take the average of the n_b values of the individual solvents, as determined from their molecular dimensions[14]. Thus, for dichloromethane ($n_b = 4.1$) and dioxane ($n_b = 6.0$) as polar solvents in various ternary-solvent mobile phases containing these solvents (see discussion of Table I), an average value of $n_b = 5.1$ is assumed. Actually the exact value of n_b assumed does not have a large effect on final calculated values of solvent strength for multicomponent mobile phases.

The sum of the adsorbed-phase mole fractions equals one:

$$\theta_A + \theta_B + \theta_C + \theta_D + \ldots = 1 \tag{7}$$

Eqns. 5–7 allow the calculation of values of θ_A, θ_B, ... (*e.g.*, see below).

As for eqn. 7 of ref. 17, the capacity factor k' of a given solute in a multicomponent mobile phase can be written:

$$k' = k_A \theta_A + k_B \theta_B + k_C \theta_C + k_D \theta_D + \ldots \tag{8}$$

with the various pure-solvent k' values (k_A, k_B, ...) related (*cf.* eqn. 7b of ref. 17) as

$$k_A = K_{AB} k_B \tag{9}$$
$$k_B = K_{BC} k_C \tag{9a}$$
$$k_C = K_{CD} k_D \tag{9b}$$

The quantity k_A/k' is then determined and used to calculate ε^0 for the multicomponent mobile phase as in eqn. 6a of ref. 17:

$$\varepsilon^0 = \varepsilon_A + \left(\frac{\log (k_A/k')}{\alpha' n_b}\right) \tag{10}$$

In this paper the specific cases of three- and four-component mobile phases will be discussed in greater detail, although the approach above is completely general for any number of solvent components.

Note from eqns. 4a and 8 of ref. 17 that it is possible to express the strength of a binary-solvent mobile phase as

$$\varepsilon_{AB} = \varepsilon_A + \left(\frac{\log (N_A/\theta_A)}{\alpha' n_b}\right) \tag{11}$$

It is shown in Appendix I that the same expression applies also to the strength of mixtures of any number of components. Since the application of eqn. 11 somewhat simplifies the calculation of ε^0 values for multi-component mixtures, its use is illustrated in Appendix II for such a calculation.

Ternary-solvent mobile phases

First define the mole fraction ratios: $r_{AB} = N_B/N_A$, $r_{BC} = N_C/N_B$, $r_{CD} = N_D/N_C$, etc. Then from eqns. 5, 5a and 7 there are three equations and three unknowns, allowing solution for θ_A, θ_B and θ_C (*cf.* similar derivation of Jaroniec and Patrykiejew):

$$\theta_A = 1/[1 + r_{AB}K_{AB} (1 + r_{BC}K_{BC})] \tag{12}$$
$$\theta_B = \theta_A r_{AB} K_{AB} \tag{12a}$$
$$\theta_C = \theta_B r_{BC} K_{BC} \tag{12b}$$

Eqns. 8–10 then yield a final value of ε^0.

Quaternary-solvent mobile phases

As for eqns. 12–12b:

$$\theta_A = 1/[1 + r_{AB}K_{AB} (1 + r_{BC}K_{BC} (1 + r_{CD}K_{CD}))] \tag{13}$$
$$\theta_B = \theta_A r_{AB} K_{AB} \tag{13a}$$
$$\theta_C = \theta_B r_{BC} K_{BC} \tag{13b}$$
$$\theta_D = \theta_C r_{CD} K_{CD} \tag{13c}$$

The derivation of ε^0 then proceeds as for the ternary solvent mixture, using eqns. 4–4b and 6–6b.

EXPERIMENTAL

All measurements were done on a DuPont Model 850 liquid chromatograph (DuPont Analytical Instruments Division, Wilmington, DE, U.S.A.) equipped with a Model 870 pump, a 254-nm UV absorbance detector and a Model 845 refractive index detector. Samples were introduced with a Model 725 Micromeritics Auto-Sampler (Micromeritics Instrument, Norcross, GA, U.S.A.) using a 25-μl sampling loop. A 15 × 0.46 cm column packed with Zorbax-SIL chromatographic packing, was used for all studies.

All solvents were distilled-in-glass grade (Burdick & Jackson Labs., Muskegon, MI, U.S.A.) except n-hexane, which was Spectrograde (Phillips Petroleum, Bartlesville, OK, U.S.A.). The mobile phases were 50% water-saturated using the procedure described in ref. 1. The solvents were all degassed individually and then mixed before the water saturation procedure. The substituted naphthalenes were dissolved in hexane.

All retention measurements and k' calculations were carried out with a PDP-10 computer system[18]. Other calculations were performed on a PDP 11/60 minicomputer (Digital Equipment, Maynard, MA, U.S.A.) programmed in FORTRAN. The measurement of column dead-time, t_0, for accurate determination of k' as done by injecting a small aliquot of the mobile phase which had already passed through the column, but which had been diluted slightly with hexane. This had the effect of injecting a sample which was slightly weaker than the mobile phase into the system. Both short- and long-term reproducibility measurements of k' values were shown to have a standard deviation of less than 2%. (One specific case for long-term reproducibility is included in Table II for mobile phases 1 and 10.)

RESULTS AND DISCUSSION

Ternary-solvent mobile phases and alumina

Only limited data are available from the literature for ε^0 values of ternary-solvent mobile phases in well-defined LSC systems. One such study[11] is summarized in Table I, for alumina as adsorbent and ternary-solvent mixtures which include pentane, benzene, methylene chloride and/or dioxane as solvents. Since dioxane is capable of solvent-localization, the values of ε^0 are first determined for dioxane in these mixtures in Table I, by trial-and-error application of the procedure of the preceding section for calculating ε^0 of the ternary mixture. These values of ε^0 ($= \varepsilon_B$) were used to determine values of ε'_B and ε''_B for dioxane (best fit to eqn. 3 as in ref. 17). The resulting $\%_{\mathrm{olc}}$ values from eqn. 3 are plotted in Fig. 1 as circles. The fit of these data to the $\%_{\mathrm{olc}}$ *vs.* θ_B curve for binary-solvent mixtures is seen to be reasonable. That is, in ternary-solvent mobile phases containing a single class P[17] solvent that is capable of localization, the ε^0 value of the class P solvent is calculable as a function of θ (eqn. 10; ref. 17) for that solvent, as in the case of binary-solvent mobile phases.

The scheme of the preceding section can now be used for the calculation of ε^0 values of the ternary-solvent mobile phases of Table I, as illustrated in Appendix II. Resulting values of ε^0 calculated in this fashion are listed in Table I as the first column of ε^0 (calc.) values; the overall agreement between experimental and calculated values is ±0.022 units (1 S.D.). Since the corresponding agreement between experimental and calculated values for 93 binary-solvent mixtures is ±0.017 units, the present scheme for ternary-solvent mobile phases seems to be about as accurate as the scheme for calculating the strength of binary-solvent mixtures.

TABLE I

EXPERIMENTAL VERIFICATION OF PRESENT APPROACH FOR CALCULATION OF SOLVENT STRENGTH FOR TERNARY-SOLVENT MOBILE PHASES

Elution from alumina, data of ref. 11.

Mobile phase composition (%, v/v)				*Avg.* n_b	ε^0		
Pentane	*Benzene*	*CH_2Cl_2*	*Dioxane*		*Expt.*	*Calc.**	*Calc.***
60	30	10	0	5.1	0.22	0.266	0.266
30	30	40	0	5.1	0.32	0.348	0.344
60	38	0	2	6.0	0.35	0.365	0.365
60	35	0	5	6.0	0.40	0.404	0.404
60	30	0	10	6.0	0.44	0.431	0.431
60	0	38	2	5.1	0.39	0.389	0.382
60	0	35	5	5.1	0.43	0.433	0.439
60	0	30	10	5.1	0.47	0.467	0.472
60	0	20	20	5.1	0.52	0.489	0.493
20	0	75	5	5.1	0.48	0.460	0.458
20	0	70	10	5.1	0.51	0.496	0.499
20	0	60	20	5.1	0.55	0.530	0.531

* Assumes $\alpha' = 0.65$, values of pure-solvent ε^0 values as in ref. 11, and n_b is the average of the polar solvents present in the mobile phase (avg. n_b values above).

** Same as in *, except n_b determined from eqn. 14.

The use of a simple average value of n_b for the polar solvents of the mobile phase (as noted in Table I) presents some conceptual difficulty, although it appears to work in practice. Thus, as the concentration of any solvent in the mobile phase approaches zero, it would be expected that the effect of the n_b value for that solvent on the average value of n_b calculated for the mixture would be less. A more fundamental basis for the estimation of an average n_b value would reflect the differing concentrations of various solvents in the adsorbed phase, *i.e.*, the average value $\bar{n}_b$ should be given as

$$n_b = \sum_{B}^{i} (n_b)_i \, \theta_i / \sum_{B}^{i} \theta_i \qquad (14)$$

i.e., the summation excludes n_b for the weakest solvent A. Values of $\bar{n}_b$ can be calculated during the calculation of ε^0 values for ternary solvents as in Table I, and a successive approximation approach then leads to revised values of ε^0, as shown in the second column of ε^0 values in Table I; the resulting agreement of experimental and calculated ε^0 values for these mobile phases is improved from ±0.022 (first column) to ±0.021 (second column). Thus, a slight increase in the accuracy of calculated values is achieved by the use of eqn. 14, as expected. However, this approach to estimating n_b values is considerably more complex than simple averaging, and we have not used it in further calculations of ε^0 values for ternary- and quaternary-solvent mobile phases. It should be noted that eqn. 14 will find its greatest use when the n_b values of the individual solvents in a multicomponent mobile phase differ by wider margins than in Table I.

TABLE II

EXPERIMENTAL DATA FOR THREE- AND FOUR-SOLVENT MOBILE PHASES WITH SILICA AS ADSORBENT

*Solute**	A_s	k'**													
N_A =		0.422	0.248	0.956	0.7165	0.5875	0.331	0.502	0.574	0.474	0.422	0.542	0.841	0.978	0.913
N_B =		0.000	0.752	0.000	0.000	0.399	0.399	0.286	0.244	0.053	0.000	0.053	0.071	0.000	0.000
N_C =		0.578	0.000	0.000	0.270	0.000	0.270	0.204	0.176	0.470	0.576	0.402	0.048	0.000	0.000
N_D =		0.000	0.000	0.044	0.0135	0.0035	0.000	0.008	0.0064	0.0017	0.000	0.0033	0.038	0.022	0.087
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*
2-OCH_3	12.7	0.58	0.70	0.23	0.20	0.39	0.48	0.32	0.46	0.53	0.58	0.46	0.26	0.64	0.31
1-NO_2	15.6	0.85	0.91	1.01	0.45	0.63	0.71	0.50	0.68	0.77	0.85	0.68	0.71	1.74	1.03
1,2-$(OCH_3)_2$	17.3	1.11	1.30	0.49	0.45	0.68	0.84	0.53	0.80	0.98	1.11	0.80	0.47	1.17	0.49
1,5-$(NO_2)_2$	23.1	2.25	2.30	2.45	1.65	1.91	1.79	1.33	2.02	–	2.26	–	–	5.14	1.63
1-CHO	16.4	2.68	2.58	1.55	1.43	1.58	1.84	1.29	1.89	2.35	2.66	1.93	1.30	3.20	1.23
2-CO_2CH_3	16.2	3.10	3.00	1.75	1.73	1.82	2.18	1.45	2.19	–	3.10	–	–	3.97	1.25
1-CO_2CH_3	16.2	3.10	3.17	1.90	1.81	1.95	2.28	1.51	2.31	2.81	3.10	2.30	1.53	4.47	1.33
2-CHO	16.4	3.81	3.51	2.05	1.98	2.06	2.49	1.69	2.52	3.30	3.81	2.65	1.66	4.56	1.49
1-CH_2CN	17.8	3.86	3.38	4.65	2.99	2.79	2.63	2.05	3.16	3.60	3.81	3.15	3.13	9.86	3.16
1-OH	15.7	4.09	5.04	4.22	4.12	5.11	4.49	3.76	5.21	4.59	4.13	4.56	3.38	10.32	2.38
1-$COCH_3$	17.3	4.92	4.60	2.29	2.43	2.51	3.19	2.05	3.13	4.19	4.91	3.27	1.90	5.04	1.63
2-$COCH_3$	17.3	7.01	6.03	3.15	3.43	3.23	4.20	2.70	4.19	5.90	6.97	4.56	2.49	7.10	2.06
2-OH	15.7	7.26	8.80	7.00	7.39	8.79	7.56	6.39	9.12	8.15	7.32	8.04	5.65	18.31	3.75
ε_B***		–	–	0.728	0.85	0.85	–	0.863	0.864	0.87	–	0.867	0.77	0.765	0.620
ε^0 (expt.)[§]		0.223	0.222	0.241	0.248	0.240	0.236	0.252	0.234	0.225	0.223	0.233	0.250	0.219	0.273
ε^0 (calc.)[§§]		0.223	0.222	0.242	0.237	0.263	0.223	0.247	0.225	0.225	0.223	0.221	0.277	–	–

* Substituted naphthalenes; see Experimental for details.

** For mobile phases of indicated composition; N_A, mole fraction of hexane; N_B, mole fraction of chloroform; N_C, mole fraction of dichloromethane; N_D, mole fraction of MTBE.

*** Value of ε_B for MTBE, calculated from experimental ε^0 value of mobile phase from eqn. 2.

[§] Calculated from eqn. 15, using $\alpha' = 0.57$ as in ref. 11 and values of A_s from Table II (ref. 14).

[§§] Calculated as described in text and Appendix I; assumes ε^0 (hexane) = 0.00; ε^0 (chloroform) = 0.256; ε^0 (dichloromethane) = 0.30; ε' (MTBE) = 0.87; ε'' (MTBE) = 0.58; n_b = 4.1 (1), 5.0 (2), 4.5 (3, 6–12), 4.3 (4), 4.7 (5).

Ternary- and quaternary-solvent mobile phases and silica

Data were obtained in order to define the solvent strength values of several multicomponent mobile phases with silica as adsorbent, as described in the Experimental section. Resulting k' values for several solutes are summarized in Table II. From these data it was possible to calculate best (average) values of ε^0 for each of the mobile phases of Table II as follows. First, the solvent strength for mobile phase 1 (dichloromethane–hexane) of Table II could be calculated from the data presented in ref. 17: $\varepsilon^0 = 0.223$. Second, values of ε^0 for other mobile phases in Table III could be determined by means of eqn. 1, which for several different solutes as in Table II can be expressed:

$$\varepsilon_2 = \varepsilon_1 + [\overset{n}{\Sigma} \log (k_1/k_2)]/\alpha' \overset{n}{\Sigma} A_s \tag{15}$$

Here, the summations are over the n (equal 13) solutes represented in Table II. The quantity ε_2 refers to ε^0 for a mobile phase of interest, and ε_1 is the ε^0 value for mobile phase 1 (dichloromethane–hexane). The ratio (k_2/k_1) refers to k' values for a given solute in the two mobile phases being compared. The summation over A_s yields the sum of A_s values listed in Table II (equal to 217.7).

TABLE III

EXPERIMENTAL *VS.* CALCULATED ε^0 VALUES FOR 3- AND 4-SOLVENT SYSTEMS WITH HEXANE, CH_2Cl_2, MTBE and CH_3CN

N_a, N_b, N_c and N_d are mole fractions of hexane, CH_2Cl_2, MTBE and CH_3CN, respectively. $\Sigma \log k'$, are experimental values based on 13 solutes in Table II. ε^0 expt. as calculated by eqn. 2. ε^0 calc. as in Appendix II.

Mobile phase	N_a	N_b	N_c	N_d	$\Sigma \log k'$	ε^0 *expt.*	ε^0 *calc.*
15	0.422	0.578	–	–	5.887	0.223	(0.223)
16	0.958	–	0.042	–	5.578	0.226	0.223
17	0.870	0.100	–	0.03	5.447	0.227	0.224
18	0.686	0.300	–	0.014	5.812	0.224	0.222
19	0.565	0.4305	0.0045	–	5.429	0.227	0.223
20	0.555	0.442	0.003	–	6.314	0.220	0.215
21	0.553	0.440	–	0.007	5.765	0.224	0.222
22	0.680	0.310	0.006	0.005	5.727	0.225	0.222
23	0.710	0.280	0.010	–	5.196	0.229	0.223
24	0.881	0.096	–	0.023	6.336	0.218	(0.218)
25	0.849	0.094	–	0.057	3.350	0.242	(0.242)
26	0.818	0.092	–	0.090	1.917	0.254	(0.254)

For the mobile phases of Table II, the solvent methyl *tert.*-butyl ether (MTBE) is the only localizing solvent, and values of ε^0 for this (pure) solvent in the various mobile phases of Table III are listed in the table. From the latter values we can determine ε_B' and ε_B'' by application of eqn. 3 as for the preceding system (dioxane) in Table I. The values derived from this calculation were $\varepsilon_B' = 0.87$ and $\varepsilon_B'' = 0.58$. This approach also yields values of $\%_{\text{lc}}$ for MTBE, and these values are plotted *vs.* θ_B in Fig. 1 (squares). The values obtained from three binary-solvent systems of MTBE–

hexane (2.0, 4.0 and 8.0%, v/v) are also plotted in Fig. 1 and are found to follow the relationship (solid curve) found for binary-solvent systems[17]. Finally, using these values of ε^0 for the various solvent components of Table II (listed there), the values of ε^0 for each of the ternary- or quaternary-solvent mobile phases of Table II can be calculated. These are compared with the experimental values in Table II, and the resulting agreement (±0.016 units; 1 S.D.) is comparable to that found for binary solvents in ref. 17 (±0.017) and the ternary-solvent system of Table I (±0.022).

A second set of solvent systems was studied experimentally to further test ternary- and quaternary-solvent strength calculations and as a preliminary effort toward selectivity optimization in LSC. Selectivity effects will be discussed in more detail in ref. 12, but the solvent strength data are presented in Table III. The four solvents hexane, dichloromethane, MTBE and acetonitrile were chosen on the basis of solvent selectivity effects and nine solvent systems were run with the substituted naphthalenes as solutes. Acetonitrile is immiscible with hexane, so it was necessary to add 5% (v/v) dichloromethane to achieve total miscibility in these concentration ranges.

Since acetonitrile can delocalize, it was first necessary to calculate the $\varepsilon'_{\mathrm{B}}$ and $\varepsilon''_{\mathrm{B}}$ values for this solvent as with dioxane and MTBE above. Using the approach outlined in ref. 17 and solvent systems containing 1.0, 2.5 and 4.0% (v/v) acetonitrile, it was possible to estimate values of $\varepsilon'_{\mathrm{B}} = 0.9$ and $\varepsilon''_{\mathrm{B}} = 0.4$ for acetonitrile. These values, along with the other information previously obtained for MTBE, allowed the calculation of solvent strength for all nine solutions in Table III. The calculated values are compared with the experimental values of ε^0 and very good agreement is obtained (±0.004; 1 S.D.). These mobile phase systems of Tables II and III validate the present approach for three- and four-component solvent systems with silica as adsorbent.

For a multi-solvent mobile phase (A–B–C–D) where two solvents (C, D) can localize, our analysis of solvent localization and $\%_{\mathrm{olc}}$ in ref. 17 suggests that the value of $\%_{\mathrm{olc}}$ for solvents C and D in the mobile phase can be given as follows. It is assumed that solvent D localizes more strongly than C, where localization is greater for a solvent with a larger value of $(\varepsilon'/\varepsilon'')$.

(solvent D) $\%_{\mathrm{olc}}$ = value from Fig. 1 for $\theta_{\mathrm{B}} = \theta_{\mathrm{D}}$
(solvent C) $\%_{\mathrm{olc}}$ = value from Fig. 1 for $\theta_{\mathrm{B}} = (\theta_{\mathrm{C}} + \theta_{\mathrm{D}})$

Comparison vs. older method for solvent strength calculation

An equation for estimating the solvent strength of ternary- and quaternary-solvent mixtures has been previously described[14]:

$$\varepsilon^0 = \varepsilon_{\mathrm{g}} + \left(\frac{\log(N_{\mathrm{h}}\, 10^{\alpha' n_{\mathrm{h}}(\varepsilon_{\mathrm{h}} - \varepsilon_{\mathrm{g}})} + N_{\mathrm{g}})}{\alpha' n_{\mathrm{h}}}\right) \tag{16}$$

Solvent H is assumed to be stronger than solvent G, N_{g} and N_{h} refer to the mole fractions of G and H, respectively, in the solvent mixture, n_{h} is the molecular area value for H, and ε_{g} and ε_{h} are the ε^0 values for G and H, respectively, and G and H are stronger than other solvents (A, B, ...) in the mobile phase. There are two major problems with the use of eqn. 16 for the accurate prediction of solvent strength in ternary- or higher-order solvent systems. First, eqn. 16 should hold only if the combined concentrations of G and H are greater than 10% (v/v) and secondly, the strengths of G and H must be substantially greater than the other solvents in the system. In many cases of interest, these two assumptions cannot be met and another method of estimating solvent strength must be found. This is especially true for quaternary- and higher order-solvent mixtures where, as the number of solvent components increases, it becomes less likely that the combined concentrations of the strongest two components will be sufficient to determine solvent strength.

Although retention data for ternary-solvent systems in LSC have been limited, it is possible to compare eqn. 16 to the method described in Appendix II for the data in Table I from the literature, and the data generated in this work (Tables II and III). This comparison is shown in Table IV, where the values in the first column were calculated using eqn. 16 and those in the second column were calculated using the approaches in Appendix II, including solvent-localization effects, where necessary.

TABLE IV

CALCULATED ε_{AB}

a = Calculated using eqns. 810b from ref. 14, $\varepsilon_B'' = \varepsilon_B'$. b = Calculated using method described in Appendix II. Al–A12, solvents from Table I (alumina); S1–S23, solvents from Tables II and III (silica).

Solvent	*a*	*b*	*Solvent*	*a*	$(N_G + N_H)$	*b*	*Solvent*	*a*	$(N_G + N_H)$	*b*
A1	0.241	0.266	S1	–	–	0.223	S15	–	–	0.223
A2	0.352	0.344	S2	–	–	0.222	S16	–	–	0.223
A3	0.290	0.365	S3	–	–	0.242	S17	−0.094	(0.03)	0.224
A4	0.342	0.404	S4	0.118	0.284	0.237	S18	0.040	(0.014)	0.222
A5	0.395	0.431	S5	0.135	0.402	0.263	S19	0.166	(0.0045)	0.223
A6	0.369	0.382	S6	0.200	0.669	0.223	S20	0.168	(0.003)	0.215
A7	0.390	0.439	S7	0.062	0.212	0.247	S21	0.111	(0.007)	0.222
A8	0.420	0.472	S8	0.035	0.182	0.225	S22	−0.517	(0.011)	0.222
A9	0.465	0.493	S9	0.175	0.472	0.225	S23	0.117	(0.010)	0.223
A10	0.427	0.458	S10	–	–	0.223				
A11	0.445	0.499	S11	0.153	0.405	0.221				
A12	0.476	0.531	S12	0.067	(0.086)	0.277				
			S13	–	–	0.219				
			S14	–	–	0.273				

The binary solvents S1-S3 and S13-S14 have been excluded. It is evident from the comparison of these results that eqn. 16 only gives reasonable results when the concentrations of G and H are high, such as is the case in some of the solvent systems in the first column of Table IV. In the case of the data generated here (the second and third columns of Table IV), the calculated results from eqn. 16 are poor compared with both the experimental values (*cf.*, Tables II and III) and the calculations of Appendix II. In two cases, S17 and S22, the absurd result of a negative solvent strength is obtained. It should be pointed out that poor correlation could have been expected for solvent systems S7–9, 11–12 and 22, since these involve cases where the combined concentrations of G and H are less than 10% (v/v). In other cases, however, (*e.g.*, S4), this is not the case, and we might expect better results from eqn. 16 if it indeed were valid.

CONCLUSION

The approach of ref. 17 for calculating solvent strength in LSC has been extended to ternary- and quaternary-solvent systems, and should be general for higher order-solvent mixtures. Again, solvent localization effects have been shown to be important in these higher order systems, especially since the concentration of any one component is more likely to be low. A more general and exact method has been described to replace the older, less accurate calculation for ternary- and higher order-solvent mixtures.

These improvements in the calculation of solvent strength are of particular importance since they form the basis for the use of multicomponent solvent systems in LSC, especially for optimization of solvent selectivity. This will be described more fully in future work[12,13]. The present study also provides added insight into the details of retention in LSC systems, and this will prove applicable to future studies of solvent selectivity.

ACKNOWLEDGEMENTS

The technical assistance of P. Hollins is greatly appreciated along with the many useful suggestions by J. J. Kirkland.

APPENDIX I

Proof of eqn. 18 for any number of solvents in a mixture

First, define $r_{\mathrm{ba}} = (N_{\mathrm{b}}/N_{\mathrm{a}})$, $r_{\mathrm{cb}} = (N_{\mathrm{c}}/N_{\mathrm{b}})$, $\ldots$ $r_{m(l)} = (N_m/N_l)$. Similarly, for K values, $K_{\mathrm{ba}} = 10^{\alpha n(\varepsilon_{\mathrm{b}}-\varepsilon_{\mathrm{a}})}$, $K_{\mathrm{cb}} - 10^{\alpha n(\varepsilon_{\mathrm{c}}-\varepsilon_{\mathrm{b}})}$, $\ldots$ $K_{m(l)} = 10^{\alpha n(\varepsilon_m-\varepsilon_l)}$. It then follows from arguments similar to those for eqn. 5–7 and 12 (see similar derivation of ref. 17) that

$$\begin{aligned}\theta_{\mathrm{a}} &= 1/[1 + r_{\mathrm{ba}}K_{\mathrm{ba}}\,(1 + r_{\mathrm{cb}}K_{\mathrm{cb}}\,(1 + \ldots (1 + r_{m(l)}\,K_{m(l)}))))] \\ &= 1/(1 + r_{\mathrm{ba}}K_{\mathrm{ba}} + r_{\mathrm{ca}}K_{\mathrm{ca}} + \ldots + r_{ma}K_{ma}) \qquad \text{(i-1a)}\end{aligned}$$

$$\theta_{\mathrm{b}} = \theta_{\mathrm{a}}r_{\mathrm{ba}}K_{\mathrm{ba}} \qquad \text{(i-1b)}$$

$$\theta_{\mathrm{c}} = \theta_{\mathrm{a}}r_{\mathrm{ba}}K_{\mathrm{ba}}r_{\mathrm{cb}}K_{\mathrm{cb}} = \theta_{\mathrm{a}}r_{\mathrm{ca}}K_{\mathrm{ca}} \qquad \text{(i-1c)}$$

$$\ldots$$

$$\theta_m = \theta_{\mathrm{a}}r_{ma}K_{ma} \qquad \text{(i-2)}$$

Similar to eqns. 8 and 9:

$$k' = k_{\mathrm{a}}\theta_{\mathrm{a}} + k_{\mathrm{b}}\theta_{\mathrm{b}} + k_{\mathrm{c}}\theta_{\mathrm{c}} + \ldots k_m\theta_m \qquad \text{(i-3)}$$

where k_i refers to the pure k' value in solvent i:

$$k_{\mathrm{a}} = K_{\mathrm{ab}}k_{\mathrm{b}} \qquad \text{(i-4a)}$$

$$k_{\mathrm{b}} = K_{\mathrm{bc}}k_{\mathrm{c}} \qquad \text{(i-4b)}$$

$$k_{\mathrm{c}} = K_{\mathrm{cd}}k_{\mathrm{d}} \qquad \text{(i-4c)}$$

$$\ldots$$

$$k_m = K_{(l)m}k_m \qquad \text{(i-4m)}$$

Eqns. i-1–4 can be combined to give

$$\begin{aligned} k' &= \theta_a k_{ml} \, (1 + r_{ba} + r_{cb} + r_{dc} + \ldots + r_{ml}) \\ &= \theta_a k_{ml} \, (N_a + N_b + N_c + \ldots + N_m)/N_a \\ &= \left(\frac{\theta_a}{N_a}\right) k_{ml} \end{aligned} \tag{i-5}$$

Now, since

$$k_{ml} = 10^{\alpha n_b(\varepsilon_m - \varepsilon_l)} \tag{i-6}$$

Similar to eqn. 1, the solvent strength ε^0 of the mixture is related to the k' values in the multi-solvent mixture (k') and solvent m ($k' = 1$) as

$$\log (k'/1) = \alpha' n_b(\varepsilon_m - \varepsilon^0) \tag{i-7}$$

The above equation rearranges to

$$\varepsilon^0 = \varepsilon_m - (\log (k')/\alpha' n_b) \tag{i-8}$$

Combination of eqns. i-5 and i-8 and rearrangement yields

$$\varepsilon_{abc\ldots m} = \varepsilon_a + \left(\frac{\log (N_a/\theta_a)}{\alpha' n_b}\right) \tag{i-9}$$

APPENDIX II

Examples of the calculation of solvent strength for ternary mixtures

Case A. No solvent delocalization. In the first example, we take the mobile phase given as the second entry of Table I: pentane–benzene–dichloromethane (30:30:40, v/v/v) (alumina adsorbent). None of these solvents is capable of localization (Table I), so the input values are as follows: $\alpha' = 0.65$, n_b (avg., see text) $= 5.0$, ε_A (pentane) $= 0.00$, ε_B (benzene) $= 0.32$ and ε_C (CH_2Cl_2) $= 0.42$. First calculate mole fraction ratios r: $r_{AB} = 1.296$, $r_{BC} = 1.851$. Next values of K are calculated from eqns. 6 and 6a: $K_{AB} = 12.66$, $K_{BC} = 2.211$. Values of θ from eqns. 12 and 12a are then: $\theta_A = 0.01183$, $\theta_B = 0.1940$, $\theta_C = 0.7941$. From eqn. 11, the solvent strength ε^0 is then 0.364. This compares to the experimental value of 0.32 in this instance.

Case B. Solvent delocalization. Take as example the third entry of Table I: pentane–benzene–dioxane (60:38:2, v/v/v). Of these solvents, only dioxane localizes. The following input values can be used: $\alpha' = 0.65$, n_b (avg.) $= 6.0$, ε_A (pentane) $= 0.00$, ε_B (benzene) $= 0.32$ and for dioxane, $\varepsilon'_C = 0.79$ and $\varepsilon''_C = 0.61$. This procedure is exactly as in the above example for case A, except that an estimated value of ε_C for dioxane must first be obtained. If initially a value of $\%_{\mathrm{olc}} = 0.50$ is assumed, then $\varepsilon_C = 0.70$ (eqn. 9 of ref. 17). Proceeding as for case A above, we then obtain $\theta_C = 0.608$, for which $\%_{\mathrm{olc}}$ (by Appendix I of ref. 17) is 0.850. Next an average is taken of the assumed (0.500) and calculated (0.850) values of $\%_{olc}$, equal to 0.675, and repeat the calculation for our second approximation. The table below summarizes the results for each successive approximation:

Assumed $\%_{olc}$	*Value of* ε_C *from* $\%_{olc}$	θ_C*	$\%_{olc}$**	ε^0
0.500	0.700	0.608	0.850	0.340
0.675	0.731	0.672	0.758	0.360
0.716	0.739	0.687	0.729	0.365
0.723	0.740	0.689	0.725	0.366
0.724	0.740	0.689	0.725	0.366

* Eqns. 12–12b.
** Table III.

It is seen that this successive approximation process converges on a final value of $\varepsilon^0 = 0.366$. This compares favorably with the experimental value from Table I of 0.35.

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