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Review

Column selectivity from the perspective of the solvation parameter model

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Abstract

The solvation parameter model is a useful tool for delineating the contribution of defined intermolecular interactions to retention of neutral molecules in separation systems based on a solute equilibrium between a gas, liquid or fluid mobile phase and a liquid or solid stationary phase. The free energy for this process is decomposed into contributions for cavity formation and the set up of intermolecular interactions identified as dispersion, electron lone pair, dipole-type and hydrogen bonding. The relative contribution of these interactions is indicated by a series of system constants determined by the difference of the defined interaction in the two phases. The interpretation of these system constants as a function of experimental factors that affect retention in the chromatographic system provides the connection between relative retention (selectivity) and the control variables for the separation system. To aid in the understanding of these processes we perform an analysis of system constants for gas chromatography, liquid chromatography, supercritical fluid chromatography and micellar electrokinetic chromatography as a function of different experimental variables as a step towards gaining a theoretical understanding of selectivity optimization for method development.

Keywords: Reviews; Solvation parameter model; Stationary phases; Selectivity; Retention

Contents

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1. Introduction

The solvation parameter model describes retention in chromatographic systems in terms of the difference in solvent–solvent and solute–solvent intermolecular interactions in the mobile and stationary phases. Transfer of a solute from one phase to another requires the formation of a cavity in the acceptor phase of a suitable size to accommodate the solute with the solvent molecules in the same arrangement as in the bulk solvent. The energy consumed by this process depends on the strength of solvent–solvent interactions (cohesion) and the size of the solute. In the second step the solvent molecules are reorganized into their equilibrium position around the solute. The free energy for this process is small and is not explicitly considered in the solvation parameter model. Finally, the solute is inserted into the cavity and establishes various solute–solvent interactions identified as dispersion, induction, orientation and hydrogen bonding for non-ionic solutes. If two condensed phases are involved in the separation then the difference in cavity formation and solute–solvent interactions in each phase gives the free energy change characterized by an equilibrium constant. When one phase is an ideal gas the free energy change at equilibrium is equal to the difference in free energy of cavity formation in the solvent and the strength of solute–solvent interactions.

To move from a qualitative picture to a numerical description the contribution of the individual free energy processes to the solvation model must be delineated in a quantitative form. Within the framework of the solvation parameter model these contributions are represented as the sum of product terms, each one composed of solute factors (descriptors) and complementary solvent factors (system constants) [1–4]. Thus, a solute has a certain capacity for a defined intermolecular interaction indicated by its descriptor value. The contribution of this interaction to the total solvation free energy, however, is dependent on the solvent possessing a complementary capacity for the same interaction. The sum of each product term for all possible interactions and for cavity formation is equal to the total free energy change for the characterized process.

The solvation parameter model for distribution between two condensed phases, Eq. (1), and transfer from the gas phase to a solvent, Eq. (2), are set out below in the form generally used in chromatography:

$$\log SP = c + vV_X + rR_2 + s\pi_2^H + a\sum\alpha_2^H + b\sum\beta_2^H \quad (1)$$

$$\log SP = c + rR_2 + s\pi_2^H + a\sum\alpha_2^H + b\sum\beta_2^H + l\log L^{16} \quad (2)$$

SP is some free energy related solute property such as a distribution constant, retention factor, specific retention volume, relative adjusted retention time, or retention index value. Although when retention index values are used in gas–liquid chromatography the system constants will be different to models obtained for the other dependent variables. Retention index values, therefore, can be used to estimate solute descriptor values, but should not be used to determine system properties. The right-hand side of Eqs. (1) and (2) contains the system constants (r, s, a, b, l, v) and the solute descriptors (R_2, π_2^H, $\Sigma\alpha_2^H$, $\Sigma\beta_2^H$, $\log L^{16}$, V_X).

Abraham has suggested a change in the symbols for the different interactions in Eqs. (1) and (2) to simplify the model expressions [5,6]. This is reasonable now that the properties of the model are well established and further changes are not expected. The reader should be aware that a new model is not being proposed by Eqs. (3) and (4) and that the identity of the solute descriptors and system constants is revealed by a one-to-one comparison of Eqs. (1) and (2) with Eqs. (3) and (4):

$$\log SP = c + vV + eE + sS + aA + bB \quad (3)$$

$$\log SP = c + eE + sS + aA + bB + lL \quad (4)$$

The contributions of cavity formation and dispersion interactions are highly correlated with solute size and cannot be separated if a volume term, such as the characteristic volume [V_X in Eq. (1) or V in Eq. (3)], is used as a solute descriptor. The transfer of a solute between two condensed phases will occur with little change in the contribution from dispersion interactions and the absence of a specific term in Eqs. (1) and (3) to represent dispersion interactions is not a serious problem. For transfer of a solute from the gas phase to a condensed phase this is no longer the case and the solvation equation must be set up to account for the contribution of dispersion interactions to the free energy of solute transfer. Abraham handled this problem by defining a second descriptor for the contribution of cavity formation and dispersion interactions [$\log L^{16}$ in Eq. (2) or L in Eq. (4)]. This term includes not only solute–solvent dispersion interactions, but also the cavity effect making the V_X term in Eq. (1) or V term in Eq. (3) redundant.

1.1. Solute descriptors

The solute descriptors in Eqs. (1) and (2) must be free energy related properties to correlate with chromatographic retention. It is also important that the solute descriptors are accessible for a wide range of compounds by either calculation or simple experimental techniques, otherwise the models would lack practical utility. McGowan's characteristic volume, V_X (or V) in units of $cm^3\ mol^{-1}/100$, can be calculated for any molecule whose structure is known by simple summation rules (Table 1) [4,7]. $\text{Log}\, L^{16}$ (or L) is the solute gas–liquid distribution constant (also referred to as the Ostwald solubility coefficient) in hexadecane at 298 K. For volatile solutes it can be determined directly [8]. For all compounds of low volatility, it is determined by back calculation from gas chromatographic retention measurements on non-polar stationary phases at any convenient temperature [9–12]. Suitable stationary phases are those for which the system constants $a \approx b \approx s \approx 0$ in Eq. (2).

The solute excess molar refraction, R_2 (or E), models polarizability contributions from n- and π-electrons. The solute molar refraction is too closely related to solute size to be used in the same correlation equation as V_X. To avoid correlation between the molar refraction and V_X, Abraham defined an excess molar refraction, R_2, as the molar refraction for the given solute, less the molar refraction for an *n*-alkane of the same characteristic volume [13,14]. The excess molar refraction is simply calculated from the refractive index as indicated in Table 1. The calculation of the excess molar refraction is straightforward for liquids but, even for solids, refractive index values are easily estimated using available software for molecular property estimations. In addition, R_2, like the molar refraction, is almost an additive quantity, and values for solids can be estimated through addition of fragments with known R_2 values [3,15,16].

In the early stages of the development of the solvation parameter model, Abraham and coworkers commenced the process by defining descriptors for solute hydrogen-bond acidity (α_2^{H}) and solute hydrogen-bond basicity (β_2^{H}). The superscript (H) indicates the origin of the scale and the subscript (2) that the descriptors are solute properties. Initially, these solute descriptors were determined from 1:1 complexation constants measured in an inert solvent [5,17,18]. These studies also led to scales that had a zero origin. A problem still remained, however, when these descriptors were used to characterize distribution processes. The influence of solute structure on the distribution process will be a consequence of hydrogen bonding of the solute to any surrounding solvent molecules, not just to one. This required scales of ''summation'' or ''overall'' hydrogen bonding that refer to the propensity of a solute to

Table 1
Calculation of solute descriptor values for use in the solvation parameter model

Calculation of McGowan's characteristic volume, *V*, for toluene. Atomic volumes: C = 16.35, H = 8.71, N = 14.39, O = 12.43, F = 10.48, Si = 26.83, P = 24.87, S = 22.91, Cl = 20.95, B = 18.23, Br = 26.21, I = 34.53. Subtract 6.56 for each bond of any type. Toluene = 7 carbon atoms + 8 hydrogen atoms − 15 bonds = 114.45 + 69.68 − 98.40 = 85.73 in $cm^3\ mol^{-1}$. After scaling $V = 0.857$ in $cm^3\ mol^{-1}/100$. For complex molecules the number of bonds, *B*, is easily calculated from the algorithm $B = N - 1 + R$, where *N* is the total number of atoms, and *R* is the number of rings

Calculation of the excess molar refraction, *E*, for toluene using $E = 10V_x[(\eta^2 - 1)/(\eta^2 + 2)] - 2.832V + 0.526$.
The refractive index for toluene (η) at 20°C (sodium D-line) = $1.496E = 8.57(0.292) + 0.5255 - 2.832(0.857) = 0.601$ in $cm^3\ mol^{-1}/10$

Estimation of solute descriptors for 2,6-dimethoxyphenol from liquid–liquid distribution constants. *V* and *E* were calculated as above giving 1.174 and 0.840, respectively. Other solute descriptors were obtained as the best-fit values from the distribution systems given below

Distribution system	log *K*(calc.)	log *K*(exp.)	Best-fit values		
			S	*A*	*B*
Water–octanol	1.10	1.15	1.41	0.13	0.71
Water–ether	0.79	0.74			
Water–olive oil	0.56	0.57			
Water–hexadecane	−0.35	−0.36			
Water–cyclohexane	−0.15	−0.15			

interact with a large excess of solvent molecules. These hydrogen-bond descriptors are denoted as $\Sigma\alpha_2^H$ (or *A*) and $\Sigma\beta_2^H$ (or *B*) to distinguish them from the 1:1 solute descriptors. New values of the effective hydrogen bonding solute descriptors are now determined in conjunction with other solute descriptors using liquid–liquid distribution and chromatographic measurements [1,19]. A minor complication is that certain solutes (sulfoxides, anilines, pyridines) show variable hydrogen-bond basicity in distribution systems where the organic phase absorbs appreciable amounts of water. A new solute descriptor $\Sigma\beta_2^0$ was defined for these solutes and should be used for reversed-phase and micellar electrokinetic chromatography. For the same solutes, $\Sigma\beta_2^H$ should be used for all other applications and always for gas chromatography. Except for the solute types indicated above, the two hydrogen-bond basicity scales are identical. It should also be noted that the scales of hydrogen-bond acidity and basicity are unrelated to proton transfer acidity and basicity expressed by the pK_a scale.

It would be useful to have descriptors that were related to the propensity of a solute to engage in dipole–dipole and induced dipole–dipole interactions. In the event, it proved impossible to separate out descriptors for the two types of interactions, and Abraham [13] constructed a solute descriptor for dipolarity/polarizability, π_2^H (or *S*), combining the two interactions. The dipolarity/polarizability descriptor was initially determined through gas chromatographic measurements on polar stationary phases [9,19–21], but is now more commonly determined in combination with the hydrogen-bonding solute descriptors from liquid–liquid distribution constants and chromatographic measurements [1,3,16].

Solute descriptors are available for about 3500 compounds, with some large compilations reported [1,12–24]. The largest database is the University College London (UCL) database with other smaller collections maintained by other research groups that are derived from the UCL database. For compounds not in the database, estimation methods using fragment constants are available [3–5,15,16,25,26]. An early version of a software program to estimate solute descriptors from structure has appeared [26]. In all other cases it is possible to calculate V_X and R_2

and determine the other descriptors from experimental distribution constants and chromatographic measurements. If data are available for a particular solute in three systems with significantly different system constants then π_2^H, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ can be determined as the solution to three simultaneous equations. If the number of equations is larger than the number of descriptors to be determined, the descriptor values that give the best-fit solution (i.e. the smallest standard deviation in the observed and calculated log *SP* values) are taken.

1.2. System constants

The system constants reflect the difference in solute interactions in the two phases, except for gas chromatography, where the system constants reflect stationary phase properties alone. The *r* (or *e*) system constant indicates the tendency of the phases to interact with solutes through π- and n-electron pairs; the *s* system constant for the tendency of the phases to interact with solutes through dipole-type interactions; the *a* system constant denotes the difference in hydrogen-bond basicity between phases (because acidic solutes will interact with a basic phase); and the *b* system constant is a measure of the difference in hydrogen-bond acidity between phases (because basic solutes will interact with an acidic phase). The *l* system constant is a measure of the energy required for cavity formation and the strength of dispersion interactions in gas chromatography. The *v* system constant is a measure of the difference in cavity formation in the two condensed phases together with any residual dispersion interactions that are not self-canceling. System constants with a positive sign indicate that the characterized interaction is more favorable for the stationary phase and leads to an increase in retention. The corollary is also true with a negative sign indicating more favorable interactions in the mobile phase. For gas chromatography the system constants must be positive, since interactions in the gas phase are negligible, and chemical sense indicates that interactions in the gas phase cannot exceed those in a condensed phase. The exception is the *r* system constant for fluorine-containing compounds. This anomaly arises from the selection of *n*-alkanes as the zero values for the excess molar refraction scale. The strongly electronegative fluorine atoms make electrons on neighboring carbon atoms less available for electron lone pair interactions than electron lone pairs in typical *n*-alkanes. The system constants can of course be zero, representing either no capability for a particular interaction in gas chromatography (e.g. *n*-alkanes have no hydrogen-bonding properties) or the defined interaction is equal in both phases in condensed-phase systems. The *l* system constant represents the opposing contributions from cavity formation and dispersion interactions to the solvation process. Depending on the relative magnitude of these terms the *l* system constant could be positive or negative, but in all systems studied so far the *l* system constant is negative for water [24] and positive for all other gas–liquid-phase systems.

1.3. Model requirements

The system constants in Eqs. (1) to (4) are obtained by multiple linear regression analysis for a number of solute property determinations for solutes with known descriptors. The solutes used should be sufficient in number and variety to establish the statistical and chemical validity of the model [27,28]. In particular, there should be an absence of significant cross-correlation among the descriptors, clustering of either descriptor or dependent variables should be avoided, and the number of solute property determinations should be sufficient to obtain an exhaustive fit. The overall correlation coefficient, standard error in the estimate, Fischer *F*-statistic, and the standard deviation in the individual system constants are used to judge whether the results are statistically sound. An exhaustive fit is obtained when small groups of solutes selected at random can be deleted from the model without statistically significant changes in the system constants. Alternatively, cross-validation can be used to test the stability of a model. Arranging the system constants in histogram form is a convenient tool for observing the distribution of a descriptor within the selected descriptor space. The optimum selection of descriptor values will provide a uniform distribution in the histogram. Clustering of descriptors into a few columns in the histogram with most of the descriptor space unoccupied is a possible cause of a local fit or unstable model. The residuals from the model fit

(difference between the experimental and predicted dependent variable), when plotted against the individual independent variables (solute descriptors), should be randomly distributed. Correlation or trends in the residuals associated with individual solute descriptors is an indication that the model is likely to be unreliable [29].

A minimum number of seven solutes are needed to do multiple linear regression for six unknowns (five system constants and an intercept). To statistically control the model, three to five varied values for each solute descriptor and the intercept is a reasonable minimum, but since individual solutes express several interactions simultaneously, the number of required solutes can be reduced from about 18 to possibly nine [30–32]. These purely statistical arguments require that the error in the dependent and independent variables are small and randomly distributed and that the solute descriptors evenly occupy the descriptor space. These conditions are unlikely to be fulfilled for typical chromatographic data sets. To aim to achieve the minimum number of solutes for system characterization seems unwise and rather foolish for column chromatography, since the time required to generate data is favorable for the collection of larger data sets with minimal additional effort. Solutes can be separated as mixtures, of course, and since only identification of the position in the chromatogram is required, structure-specific detectors make complete separation unnecessary. A more worthy philosophy is to over-determine the statistical requirements of Eqs. (1)–(4) to ensure an exhaustive fit. This can usually be achieved using 20 to 40 varied solutes. The actual number of solutes required in an individual case depends on the error distribution in the dependent variable. In chromatographic experiments the error distribution is unlikely to be even. Larger errors are associated with small retention factor values, and since these by definition represent minimal interactions with the stationary phase, even large data collections with a clustering of small values for the dependent variable are unlikely to provide acceptable models. For micellar electrokinetic chromatography, larger than average errors are associated with large retention factors (solutes migrating close to the micelle marker) as well.

A varied collection of solute descriptors may be assembled and found to be inadequate if significant cross-correlation exists between descriptors or the numerical values for the descriptors are clustered. Cross-correlation results from the unintentional correlation between different descriptor properties and leads to a loss in the capability of the multiple linear regression algorithms to distinguish between the correlated solute descriptor properties. Clustering is easily identified by inspection. Many solute descriptors have similar values (particularly compounds in a homologous series) which can produce a narrow range of descriptor values and diminished accuracy in the determination of the complementary system constants. This is most common for $\Sigma\alpha_2^H$ since the number of solutes with significant hydrogen-bond acidity is limited.

The system constants are more than mere regression constants and contain important chemical information about the system. It is important that the interpretation of the system constants is chemically sensible as well as statistically sound. Local models may provide an acceptable arithmetic model for the correlated data with abstract system constants that are physically impossible. The system constants, particularly in small data sets, are strongly influenced by statistical outliers (the difference between the model estimated value and experimental value is greater than twice the standard error in the estimate for the complete data set). These occasional outliers should be removed if the descriptor values are in doubt or the experimental result reconfirmed. Data sets containing a significant number of statistical outliers suggest that the error distribution in the dependent variable is not under statistical control and it is unlikely that reliable quantitative models will be obtained.

1.4. Data sources and scope

Previous reviews describe the initial development of the solvation parameter model [1–4] and its applications to gas chromatography [4,33], micellar electrokinetic chromatography [27,34], solid-phase extraction [35,36], thin-layer chromatography [37] and the identification of surrogate chromatographic models for biopartitioning processes [38,39]. In this article we will update the earlier reviews on gas and micellar electrokinetic chromatography and provide

an overview of contemporary studies in liquid and supercritical fluid chromatography with an emphasis on column selectivity. Contemporary studies in chromatography are generally focused on the determination of solute descriptors or revelation of retention mechanisms and their relationship to system variables. At this time the use of the solvation parameter model for systematic selectivity optimization is only poorly developed with most applications to structure-driven, computer-aided method development described for thin-layer chromatography [37,40–42] and solid-phase extraction [35,43]. These studies are not explicitly discussed in this review, which is limited in coverage to column chromatography. However, the structure of the article is such that it prepares the way for the development of structure-driven method development strategies for column chromatography in anticipation that this will become a major application of the solvation parameter model at some future time.

The solvation parameter model is often confused with the solvatochromic model. Although these two models have a similar general structure they use different solute descriptors. The solute descriptors for the solvatochromic model are based on the measurement of spectral energy differences, that is the difference of solvent effects on the ground and excited states of the selected indicator compounds, which are not free energy processes per se. In order to construct a correlation equation that has a sound physical interpretation, it is necessary that the various descriptors should be related to Gibbs free energy [4]. Thus we do not consider the solvatochromic model in this review or discuss its applications in chromatography [28,44,45]. To maintain a central focus on the solvation parameter model, other models that have since been abandoned, articles in which solute descriptors of mixed origin are used, and models that are statistically flawed based on considerations presented in Section 1.3 are excluded from discussion. Several of these topics are discussed in Ref. [4].

2. Gas chromatography

In many respects gas chromatography provides an ideal technique for studies involving the solvation parameter model. It provides accurate retention values that can safely be assumed to result from interactions in a single phase for normal operating conditions and a high peak capacity that allows quite complex mixtures to be used for system evaluation. Model statistics are generally superior to other chromatographic techniques and theoretical interpretation of the system constants is usually straightforward. Most initial studies employed packed columns to support fundamental research of the general retention mechanism for a wide range of stationary phase types. These studies are now complemented by recent work employing open-tubular column stationary phases that will be emphasized in this report.

2.1. Update on packed column studies

An earlier review provides a comprehensive account of the role played by packed columns in the development of the solvation parameter model and a comprehensive collection of system constants for more than 100 stationary phases at a reference temperature of 120°C, in most cases [4]. The system constants for the 77-phase McReynolds data set have been recalculated using updated solute descriptors [46] and Ballantine and co-workers have provided further values for the system constants of four cyano- [47], three olefinic- [48] and four amine-functionalized [49] stationary phases. Santiuste and Garcia-Dominguez have reported the system constants for four hydrocarbon, 14 industrial polymers and seven poly(methyltrifluoropropylsiloxane) stationary phases (in the case of the siloxane phases open-tubular columns were used) for several temperatures in the range 60 to 180°C for each stationary phase [50,51]. There are a few reported applications of the solvation parameter model in gas–solid chromatography for porous polymer and graphitized carbon black adsorbents [4,52]. These are extended by recent studies of industrial materials such as coal [53] and an open-tubular column coated in situ with a layer of poly(pyrrole) [54]. These latter studies are an indication of the increasing use of the solvation parameter model for material characterization.

The revised system constants for the McReynolds 77-phase data set highlights two interesting aspects of packed column stationary phase chemistry [46]. The system constants for squalane and other hydro-

carbon stationary phases have small but statistically significant values for polar interactions. In the absence of polar impurities, hydrocarbon phases are not expected to exhibit such properties. Surprisingly, McReynolds paper contains scant information for the experimental conditions employed. However, in an earlier publication for a smaller number of stationary phases, which were probably incorporated into the larger database, columns were prepared by adding 2% of a wetting agent (poly-tergent J-300) to the stationary phase [55]. This is one possible explanation for the unexpected weak polar interactions for these stationary phases. In a recent study employing squalane, these weak polar interactions were absent [12].

Analysis of the McReynolds database confirms that there are no significant hydrogen-bond acid stationary phases among those stationary phases commonly used in gas–liquid chromatography. Small *b* system constants were identified for a few phases containing hydroxyl groups (e.g. docosanol, diglycerol and sorbitol) and for poly(ester)-type stationary phases ($b = 0.07–0.19$). The poly(ester) stationary phases contain no hydrogen-bond acid functional groups and are not expected to behave as hydrogen-bond acids. Other studies have confirmed the presence of a small hydrogen-bond acidity for these materials [56,57]. It was speculated that impurities commonly found in poly(ester) stationary phases or generated in use when the poly(esters) are subjected to elevated temperatures are the most likely cause of their weak hydrogen-bond acidity. The limited number of suitable stationary phases with significant hydrogen-bond acidity suggests an obvious target to extend the selectivity range of existing phases, particularly since variable hydrogen-bond basicity is a characteristic property of many compounds. So far this observation has received little attention from column manufacturers. Martin et al. [58] synthesized a high-temperature hydrogen-bond acid stationary phase with a poly(siloxane) backbone containing hexafluoro-2-hydroxypropyl substituent groups. This phase had good chromatographic properties, low cohesion, moderate dipolarity, and virtually no hydrogen-bond basicity. Its selectivity characteristics were shown to complement those of common poly(siloxane) stationary phases used in gas chromatography.

The system constants for a varied group of packed column stationary phases at 120°C are summarized in Table 2. The system constants are only loosely scaled to each other so that changes in magnitude in any column can be read directly, but changes in magnitude along rows must be interpreted cautiously. Most stationary phases possess some capacity for electron lone pair interactions (*e* constant), but selectivity for this interaction is rather limited among common stationary phases. Fluorine-containing stationary phases have negative values of the *e* system constant, representing the tighter binding of electron pairs in fluorocarbon groups compared with hydrocarbon groups. Electron lone pair interactions do not usually make a significant contribution to retention in gas–liquid chromatography and are not considered as a primary means of selectivity optimization. The most striking feature of Table 2 is the paucity of stationary phases with significant hydrogen-bond acidity (*b* constant) as discussed above. Many stationary phases contain hydrogen-bond acid groups such as hydroxyl, amide or phenol groups that are expected to behave as hydrogen-bond acids. These groups are also significant hydrogen-bond bases and prefer to self-associate, forming inter- and intramolecular hydrogen-bond complexes to the exclusion of hydrogen-bond acid interactions with basic solutes.

In the general absence of stationary phases with suitable properties for exploiting electron lone pair interactions or hydrogen-bond acidity that leaves the most important stationary phase properties for selectivity optimization as their cohesive energy and capacity for dipole-type and hydrogen-bond base interactions. The cavity/dispersion term for the hydrocarbons, poly(dimethylsiloxanes) and poly(methylphenylsiloxanes) are all similar, indicating roughly equal difficulty in forming a cavity in these stationary phases. Stationary phases with dipolar and hydrogen bonding functional groups are considerably more cohesive and the additional free energy required for cavity formation is reflected in the smaller values for the *l* system constant. From an interpretive point of view the *l* system constant indicates the spacing between members of a homologous series. There is generally a good correlation between the *l* system constant and the partial molar Gibbs free energy of solution for a methylene group. The liquid

Table 2
System constants for packed column stationary phases at 121°C (dependent variable, log K_L)

Stationary phase	System constant					
	e	*s*	*a*	*b*	*l*	*c*
(*i*) *Hydrocarbon phases*						
Squalane	0.138	0	0	0	0.584	−0.221
Apolane-87	0.170	0	0	0	0.549	−0.221
(*ii*) *Ether and ester phases*						
Poly(phenyl ether) five rings PPE-5	0.230	0.829	0.337	0	0.527	−0.395
Carbowax 20M CW20M	0.317	1.256	1.883	0	0.447	−0.560
Poly(ethylene glycol) Ucon 50 HB 660	0.372	0.632	1.277	0	0.499	−0.184
1,2,3-Tris(2-cyanoethoxypropane) TCEP	0.116	2.088	2.095	0.261	0.370	−0.744
Didecylphthalate DDP	0	0.748	0.765	0	0.560	−0.328
Poly(ethylene glycol adipate) EGAD	0.132	1.394	1.820	0.206	0.429	−0.688
Poly(diethylene glycol succinate) DEGS	0.230	1.572	2.105	0.171	0.407	−0.650
(*iii*) *Liquid organic salts*						
Tetrabutylammonium 4-toluenesulfonate QBApTS	0.156	1.582	3.295	0	0.459	−0.686
Tetrabutylammonium tris(hydroxymethyl)-methylamino-2-hydroxy-1-propanesulfonate QBATAPSO	0.266	1.959	3.058	0	0.317	−0.860
Tetrabutylammonium 4-morpholinepropane-sulfonate QBAMPS	0	1.748	3.538	0	0.550	−0.937
Tetrabutylammonium methanesulfonate QBAMES	0.334	1.454	3.762	0	0.435	−0.612
(*iv*) *Poly*(*siloxane*) *phases*						
Poly(dimethylsiloxane) SE-30	0.024	0.190	0.125	0	0.498	−0.194
Poly(dimethylmethylphenylsiloxane) OV-3 (10 mol% phenyl)	0.033	0.328	0.152	0	0.503	−0.181
Poly(dimethylmethylphenylsiloxane) OV-7 (20 mol% phenyl)	0.056	0.433	0.165	0	0.510	−0.231
Poly(dimethylmethylphenylsiloxane) OV-11 (35 mol% phenyl)	0.097	0.544	0.174	0	0.516	−0.303
Poly(methylphenylsiloxane) OV-17	0.071	0.653	0.263	0	0.518	−0.372
Poly(methylphenyldiphenylsiloxane) OV-22 (65 mol% phenyl)	0.201	0.664	0.190	0	0.482	−0.328
Poly(methylphenyldiphenylsiloxane) OV-25 (75 mol% phenyl)	0.277	0.644	0.182	0	0.472	−0.273
Poly(cyanopropylmethyldimethylsiloxane) (10 mol% cyanopropylmethylsiloxane) OV-105	0	0.364	0.407	0	0.496	−0.203
Poly(cyanopropylmethylphenylmethylsiloxane) (50 mol% cyanopropylmethylsiloxane) OV-225	0	1.226	1.065	0	0.466	−0.541
Poly(dicyanoalkylsiloxane) OV-275 (70 mol% dicyanopropyl and 30 mol% dicyanoethyl)	0.206	2.080	1.986	0	0.294	−0.909
Poly(trifluoropropylmethylsiloxane) QF-1	−0.449	1.157	0.187	0	0.419	−0.269
Poly(dimethylsiloxane)–poly(ethylene glycol) copolymer OV-330	0.104	1.056	1.419	0	0.481	−0.430
PSF6	−0.360	0.820	0	1.110	0.540	−0.510
(*v*) *Miscellaneous*						
Bis(3-allyl-4-hydroxyphenyl)sulfone H10	−0.051	1.323	1.266	1.457	0.418	−0.568

Compiled from Refs. [4,56,58,59].

organic salts with non-associating anions have surprisingly large *l* system constants compared with non-ionic polar stationary phases, 0.44 to 0.55, and are unique among polar stationary phases in their ability to separate compounds belonging to a homologous series [59]. For anions believed to be associated as hydrogen-bond complexes the *l* system constants are significantly smaller, 0.26 to 0.37, and equivalent to the values observed for the most polar non-ionic stationary phases.

The stationary phases in Table 2 differ significantly in their capacity for dipole-type interactions (*s* system constant) and in their hydrogen-bond basicity (*a* system constant). The results from principal component analysis for 52 non-hydrogen-bond acid stationary phases with their system constants entered as variables are shown in Fig. 1 [4,59,60]. The first two principal components account for about 95% of the total variance with the first principal component (PC 1) strongly associated with the hydrogen-bond basicity of the stationary phases (*a* system constant). The second principal component (PC 2) is strongly associated with dipole-type interactions and the phase cohesive energy (*s* and *l* system constants). The stationary phases are classified into three dis-

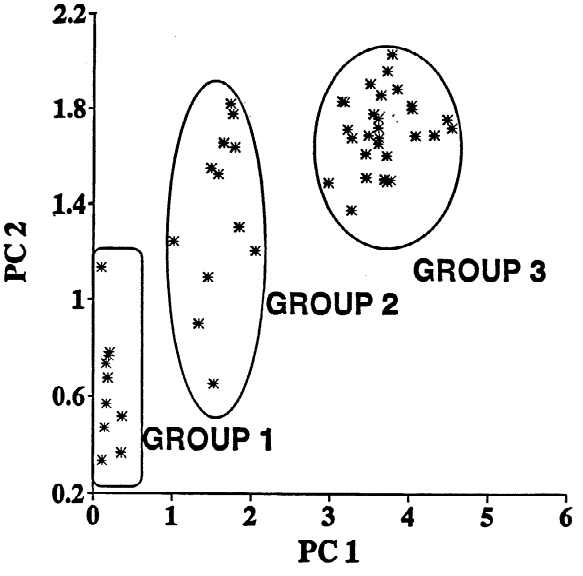

Fig. 1. Principal component score plot with the system constants from the solvation parameter model as variables for 52 non-hydrogen-bond acid stationary phases at 121°C. (From Ref. [50]. ©The Royal Society of Chemistry.)

perse groups. Group 1 stationary phases (e.g. squalane, SE-30, OV-3, OV-7, OV-105, OV-11, OV-17, OV-22, OV-25, PPE-5, QF-1) are weak hydrogen-bond bases with a weak and variable capacity for dipole-type interactions. Differences in cohesive energy are small. Group 2 contains the polar and cohesive non-ionic stationary phases and some liquid organic salts with highly delocalized anions (e.g. U50HB, OV-225, OV-275, OV-330, TCEP, CW 20M, EGAD, DEGS, tetrabutylammonium picrate). These phases have a narrow range of hydrogen-bond basicity and are distinguished mainly by differences in their capacity for dipole-type interactions and their cohesive energy. Group 3 contains only liquid organic salts, which are all dipolar ($s = 1.4$ to 2.1) and strong hydrogen-bond bases ($a = 1.4$ to 5.4) with variable cohesive energy. Anion size and the extent of charge delocalization govern the hydrogen-bond basicity of the liquid organic salts. Charge delocalizing anions (e.g. picrate, perfluorobenzenesulfonate) are weaker hydrogen-bond bases and less dipolar than the other salts. Small non-delocalizing anions (e.g. chloride, bromide) are the most hydrogen-bond basic.

Cluster analysis provides an alternative approach to principal component analysis for the classification of stationary phases by multivariate analysis. The outputs for clustering algorithms are dendrograms. The complete link dendrogram for the stationary phases listed in Table 2 are shown in Fig. 2. Stationary phases with similar selectivity are located next to each other and are connected. Connections at the extreme left-hand side of the dendrogram occur for phases with similar properties and those towards the right-hand side with greater degrees of difference. Stationary phases with no paired descendents are singular phases with properties that cannot be duplicated by other phases in the data set. The stationary phases in Table 2 are classified into six groups with three phases behaving independently. Group 1 contains squalane, Apolane-87, OV-3, OV-7, SE-30 and OV-105. These phases have low cohesive energy and a minimal capacity for polar interactions. The second group of stationary phases contains OV-22, OV-25, OV-11, OV-17, PPE-5 and DDP. These phases have low cohesive energy and are weakly dipolar and hydrogen-bond basic. QF-1 is loosely connected to this group but is significantly more

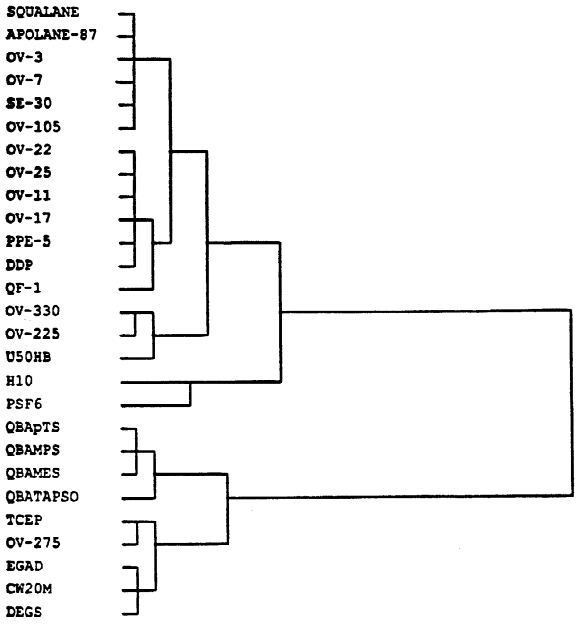

Fig. 2. Complete linkage cluster dendrogram for the stationary phases in Table 2. The system constants from the solvation parameter model were used as variables.

dipolar and has a different capacity for electron lone pair interactions. The third group contains OV-330 and OV-225 with UH50B loosely connected to this group. Compared to the second group these stationary phases are more dipolar and hydrogen-bond basic and slightly more cohesive. They represent an increase in the intensity of the same range of interactions as the larger group of stationary phases. The fourth group contains H10 and PSF6. These are strong hydrogen-bond acid stationary phases but in other respects quite different from each other. The fifth group contains the liquid organic salts with QBATAPSO distinguished within this group by its greater cohesive energy. Phases in this group are dipolar and strong hydrogen-bond bases as discussed earlier. The sixth group of solvents is divided into two subgroups. TCEP and OV-275 are strongly dipolar, hydrogen-bond basic and have high cohesive energy. EGAD, CW20M and DEGS have a similar range of polar interactions, but not quite as intense, and have a lower cohesive energy than TCEP and OV-275. For selectivity optimization in packed column gas chromatography a single phase is initially selected from each group. Subsequently for fine tuning, additional phases are selected from within the group identified as possessing the desired separation properties. Stationary phase selection must consider the temperature operating range for the phases as well as their selectivity.

There is only a limited amount of information for the influence of temperature on selectivity in packed column gas–liquid chromatography [4,50,58,61]. In general, polar interactions are expected to decrease with increasing temperature, and cavity formation should be easier at higher temperatures, but for individual stationary phases the magnitude of these temperature-induced changes will not be the same. In the solvation parameter model, each product term representing a defined interaction can be regarded as made up of a solute factor, a stationary phase factor and a coefficient. In theory, all three contributions could be temperature dependent. Out of practical necessity the solute descriptors are considered temperature invariant (otherwise a new set of descriptors would be needed for each temperature used). It is found experimentally that system constants alter quite regularly with temperature, and plots of system constants against temperature (or reciprocal temperature) are linear or shallow curves. The *s*, *a*, *b*, and *l* system constants are found to decline with increasing temperature while the *e* system constant is less predictable and often increases with increasing temperature. The use of a hydrocarbon reference phase instead of the gas phase for the *E* solute descriptor is the likely reason for this difference. Fig. 3 provides examples of the influence of temperature on the system constants and the contribution of intermolecular interactions (product terms) to the retention of octan-2-one for the hydrogen-bond acid stationary phase PSF6 [58]. There is a significant decline in the contribution of hydrogen-bond acid and electron lone pair repulsion interactions for the stationary phase but only a modest decline in dipole-type interactions with increasing temperature. By extrapolation, PSF6 would be expected to show zero hydrogen-bond acidity at about 210°C ($b = 0$) while remaining significantly dipolar ($s > 0$). Hydrogen-bond interactions exhibit a greater temperature dependence than dipole-type interactions for octan-2-one, such that hydrogen-bond interactions are more important as polar contributions to retention at lower temperatures and dipole-type interactions at higher

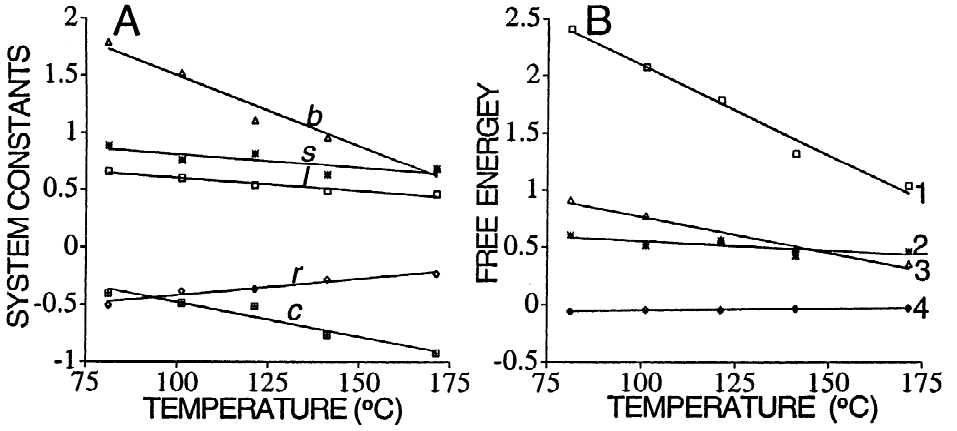

Fig. 3. Influence of temperature on the system constants (A) and contributions of individual intermolecular interactions to the retention of octan-2-one (B) for the hydrogen-bond acid stationary phase PSF6. For (A), $a = 0$. For (B), $1 = lL$, $2 = sS$, $3 = bB$, and $4 = eE$. (From Ref. [49]. ©Elsevier.)

temperatures. Throughout the temperature range investigated the cavity/dispersion contribution to retention is the most important for octan-2-one with electron lone pair repulsion interactions of minor significance. Consequently, the capacity of a stationary phase for specific intermolecular interactions determined at a single reference temperature can be quite misleading for selectivity optimization at other temperatures. When stationary phases are ranked in order of their capacity for individual intermolecular interactions at different temperatures, crossovers occur. Also, selectivity differences between individual stationary phases are enhanced at low temperatures with phases becoming more alike at higher temperatures. Information on the contribution of polar interactions to retention at high temperatures is unavailable. These contributions could be small and stationary phase selectivity differences rather limited at high temperatures.

Partitioning is the dominant retention mechanism for virtually all compounds at intermediate temperatures and moderate to high phase loadings in gas–liquid chromatography [62]. Any refined retention model, however, must also take into account contributions from interfacial adsorption, which includes interactions at the gas–solid (support) interface and gas–liquid interface. The relative contributions of absorption and adsorption to retention can be isolated from a plot of (V_N^*/V_L) against $1/V_L$, where V_N^* is the net retention volume per gram of column packing and V_L the volume of liquid per gram of column packing using standard data treatments [4,12,33,57,63]. Interfacial adsorption by the support usually results from polar interactions between the solute and support functional groups, typically silanol groups, which are inadequately masked by the deactivation steps during column preparation [12]. Interfacial adsorption at the liquid interface is generally observed for solutes with limited solubility in the stationary phase, and is most important for non-polar solutes on polar stationary phases, and to a lesser extent polar solutes on non-polar stationary phases [57,63]. It is generally more significant for all types of compounds on highly cohesive stationary phases and makes a greater contribution to the retention mechanism at low phase loadings due to a combination of a larger accessible liquid surface area and a smaller bulk liquid volume. The Δ function, defined by Eq. (5), provides a semi-quantitative index of the relative contribution of interfacial adsorption to retention on a packed column:

$$\Delta(\%) = 100[\log K_S - \log K_L]/\log K_L \quad (5)$$

where K_S is the observed distribution constant for sorption of a solute in a particular chromatographic

system and K_L is the gas–liquid partition coefficient. When retention occurs exclusively by gas–liquid partitioning, $\log K_S = \log K_L$ and $\Delta = 0\%$. For a varied group of solutes on poly(diethylene glycol succinate) Δ values of 0–35% [57], on Carbowax 20M Δ values of 0–10% [63] and on squalane Δ values of 0–12% [12] were observed for stationary phase loadings between about 8 and 20% (w/w) and temperatures within the range 60–140°C. The relative contribution of interfacial adsorption to retention is both a system property (temperature, stationary phase cohesion, and volume-to-surface area ratio) and a solute property (compatibility of solvent and solute for intermolecular interactions). An example of the effect of system properties on the relative importance of interfacial adsorption as a retention mechanism for *n*-dodecane and 1-octanol on poly(diethylene glycol succinate) is shown in Fig. 4.

There are three common uses of the solvation parameter model in gas–liquid chromatography that might be affected by interfacial adsorption: the calculation of system constants; the calculation of solute descriptors; and the prediction of retention for computer-aided method development. The system constants for the sorption models ($\log K_S$ as the dependent variable) are different to those determined for pure partitioning ($\log K_L$ as the dependent variable). Only in the case of the partition model can the results be interpreted in an exact manner. Data collected at high phase loadings and intermediate temperatures should provide useful (near pure partitioning) qualitative models, and should be identified as such. Qualitative models should not be used to infer mechanistic details for phase differences unless these differences are large enough that they are unlikely to be the product of differences in retention mechanisms.

Since the standard errors in the estimate of individual system constants are (slightly) higher for sorption models than for the partition models, some (small) loss in accuracy is anticipated when columns exhibiting a mixed retention mechanism are used for the estimation of solute descriptor values. The largest errors, however, are found for relatively non-polar solutes on cohesive phases, for which the value of polar solute descriptors will be small in any case. The properties of these solutes could be estimated using less cohesive phases where the general evidence suggests limited involvement of interfacial adsorption as a retention mechanism.

Sorption models provide a more reliable prediction of retention compared to a partition model when interfacial adsorption contributes to retention, but are only useful for an individual characterized column,

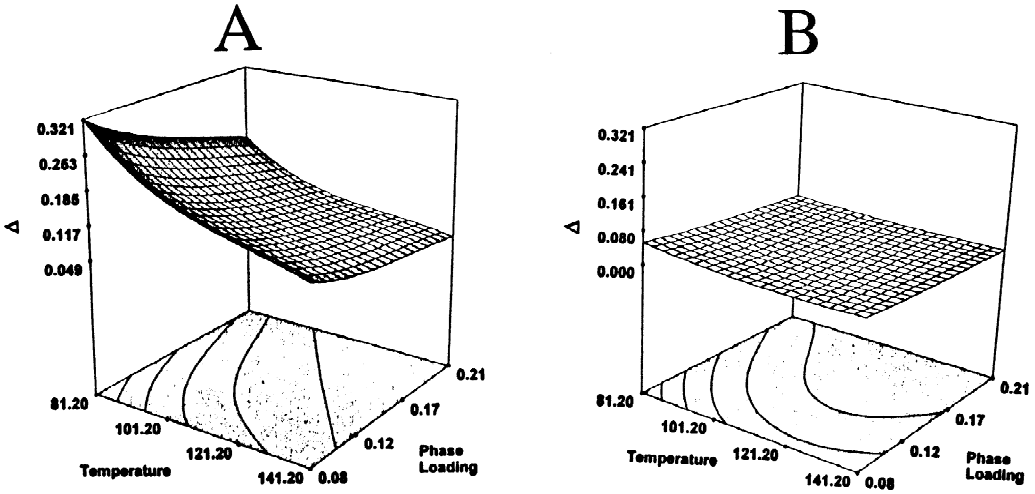

Fig. 4. Three-dimensional surface of the influence of phase loading (% w/w) and temperature (°C) on the relative contribution of interfacial adsorption ($\Delta\%/100$) to retention for *n*-dodecane (A) and 1-octanol (B) on DEGS.

and do not allow for simulation of retention in further chromatographic systems. In general, interfacial adsorption is an additional source of uncertainty to the general model error in the prediction and simulation of retention based on partition models.

2.2. Open-tubular columns

An extensive database of system constants for open-tubular column stationary phases is now available [12,63–67]. This database currently contains system constants for 22 columns representing 16 stationary phase chemistries determined at 20°C intervals over the temperature range 60–140°C. The system constants at 120°C are summarized in Table 3 to permit a comparison with the packed column results discussed above. Additional data for glass open-tubular columns coated with six poly-

Table 3
System constants for open-tubular column stationary phases at 120°C (dependent variable log k)

General abbreviation	Column identity	System constants ($b = 0$ in all cases)				Ref.
		l	e	s	a	
Poly(dimethylsiloxane)						
PMS	DB-1	0.504	0	0.207	0.185	[12]
Poly(methyloctylsiloxane)						
PMOS	SPB-Octyl	0.615	0	0.232	0	[12]
Poly(dimethyldiphenylsiloxane)						
PMPS-5	DB-5	0.513	0	0.280	0.193	[65]
	HP-5	0.518	0	0.309	0.205	[65]
	OV-5	0.503	0	0.286	0.223	[65]
	SPB-5	0.504	0	0.293	0.212	[65]
	PTE-5	0.505	0	0.293	0.210	[65]
PMPS-20	Rt_x-20	0.549	0	0.564	0.259	[a]
PMPS-35	DB-35	0.540	0	0.695	0.314	[a]
PMPS-50	HP-50+	0.474	0.160	0.623	0.281	[66]
	Rt_x-50	0.519	0.057	0.796	0.339	[a]
PMPS-65	Rt_x-65	0.531	0.108	0.839	0.358	[a]
Arylene–siloxane copolymer (nominally similar to HP-5)						
AS-5	HP-5TA	0.595	0	0.350	0.284	[65]
Poly(methyltrifluoropropylsiloxane)						
PMTS-20	DB-200	0.464	−0.340	1.010	0.203	[67]
PMTS-50	DB-210	0.439	−0.343	1.278	0.077	[66]
Poly(cyanopropylmethylsiloxane)						
PCM-50	DB-23	0.438	0	1.537	1.468	[a]
Poly(cyanopropylphenyldimethylsiloxane)						
PCPM-14	DB-1701	0.487	0	0.593	0.636	[66]
PCPM-50	DB-225	0.438	0	1.208	1.175	[66]
Poly(cyanopropylsiloxane)						
PCPS	SP-2340	0.418	0	1.993	1.960	[66]
Poly(ethylene glycol)						
PEG	HP-INNOWax	0.458	0.219	1.351	1.882	[63]
	HP-20M	0.452	0.209	1.335	2.014	[63]
	AT-Wax	0.440	0.225	1.318	1.889	[63]
NPEG	DB-FFAP	0.428	0.214	1.424	2.077	[63]
Poly(siloxane) of unknown composition						
VRX	DB-VRX	0.543	0	0.304	0.159	[67]

[a] W. Kiridena, W.W. Koziol, C.F. Poole, M.I. Nawas, Chromatographia (in press).

(methyltrifluoropropylsiloxane) and a cyanopropyl-containing poly(siloxane) stationary phase are given in Ref. [50].

The inclusion of additional stationary phases, interpretation of selectivity differences associated with stationary phase chemistry and prediction of separations by computer simulations for structure-driven method development is an on-going project. Among the findings indicated so far, it was demonstrated that five poly(dimethyldiphenylsiloxane) stationary phases containing 5% diphenylsiloxane groups (PMPS-5 in Table 3) possess virtually equivalent selectivity with minor differences in their hydrogen-bond basicity [65]. Selectivity differences between the arylene–siloxane copolymer (AS-5 in Table 3) and the PMPS-5 phases are somewhat larger, with the copolymer stationary phase being less cohesive and more hydrogen-bond basic than the poly(dimethyldiphenylsiloxane) stationary phases. Small, though significant, selectivity differences were noted among the poly(ethylene glycol) stationary phases (PEG and NPEG in Table 3) [63]. These selectivity differences were indicated to result from chemical differences for the stationary phases and from differences in the relative contribution of interfacial adsorption to the retention mechanism. The latter depends on both system properties (film thickness and column radius) and solute characteristics. The volume-to-surface area ratio of packed and open-tubular columns are of comparable magnitude and interfacial adsorption is likely to affect retention on open-tubular columns in a similar manner to that discussed for packed columns.

Most of the stationary phase types in Table 3 were derived from popular packed column stationary phases and subsequently modified to allow immobilization and improved column performance and thermal stability. Their selectivity equivalence can be ascertained by comparison of system constants for stationary phases with nominally similar chemical composition in Tables 2 and 3 at 120°C [66]. There are small differences in selectivity for the polar phases and the description ''of similar'' rather than ''equivalent'' selectivity is justified. Some of these differences have a chemical origin, but a part of these differences might be explained by contributions from interfacial adsorption. The data in Table 2 are corrected for interfacial adsorption while the results in Table 3 are not.

The range of the system constants in the packed column stationary phase database at 120°C is: $l = 0.67–0.24$; $e = -0.49–0.40$; $s = 0–2.1$; and $a = 0–5.7$ [4,46,56,59]. If we compare these values with the system constants in Table 3 there is good coverage of the upper range for the l system constant, limited coverage of the e system constant, and near complete coverage of the range for the s system constant [66]. There is near complete coverage of the range for the a system constant if only non-ionic packed column stationary phases are considered ($a = 0–2.4$).

The poly(siloxane) stationary phases in Table 3 span a wide range of selectivity, which is generally engineered by replacing dimethylsiloxane monomer groups by monomer groups containing diphenylsiloxane (PMPS), 3,3,3-trifluoropropylmethylsiloxane (PMTS) and various monomers containing a cyanoalkyl substituent (PCM, PCPM and PCPS). Introduction of diphenylsiloxane monomer groups results primarily in an increase in the dipolarity/polarizability (s system constant) for the phase with a smaller change in hydrogen-bond basicity and cohesion. The substitution of monomers containing the 3,3,3-trifluoropropylmethylsiloxane group produces a large change in the dipolarity/polarizability of the phase without increasing hydrogen-bond basicity, resulting in a unique change in the s/a system constant ratio. A characteristic of fluorine-containing phases is electron lone pair repulsion (e system constant is negative), which is different to all other phases. The substitution of monomers containing cyanoalkyl groups increases the capacity of the phase for both dipole-type interactions and its hydrogen-bond basicity with a different value of the s/a system constant ratio compared with the 3,3,3-trifluoropropylmethylsiloxane group. For all phases the introduction of monomers containing polar substituents is accompanied by a simultaneous increase in the cohesion of the stationary phases, reflected in a smaller value for the l system constant. The poly(ethylene glycol) stationary phases are also significantly dipolar/polarizable and roughly equivalent to the poly(siloxane) phases containing slightly more than about 50 mol% of 3-cyanopropylphenylsiloxane or 3,3,3-trifluoropropylmethylsiloxane groups.

Hierarchical cluster analysis (Fig. 5) provides a convenient tool to visualize the selectivity grouping of the stationary phases in Table 3. Two large

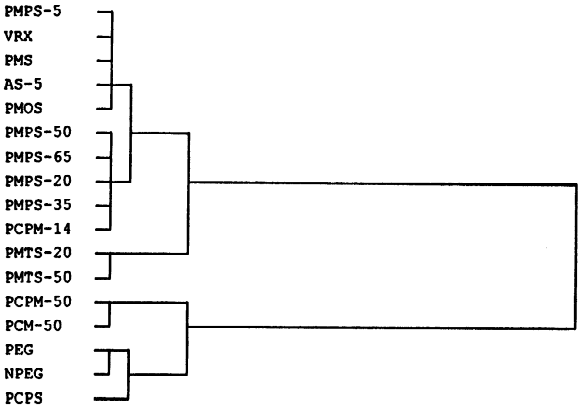

Fig. 5. Complete linkage dendrogram for the stationary phases in Table 3. An average value for the system constants was used to represent the PMPS-5 and PEG phases. For PMPS-50 the value for the Rt_x-50 phase was entered.

clusters contain the phases (PMPS-5, VRX, PMS, AS-5 and PMOS) and (PMPS-50, PMPS-65, PMPS-50, PMPS-20, PMPS-35 and PCPM-14). The first cluster contains the low polarity phases with a limited capacity for selectivity adjustment. The second cluster contains all the poly(dimethyldiphenylsiloxane) stationary phases containing more than 5% diphenysiloxane monomer groups and PCPM-14. These phases have a larger capacity for dipole-type and hydrogen-bond base interactions compared with the first group. Their nearest neighbors are the moderately polar PMTS-20 and PMTS-50 phases, which are more dipolar/polarizable and cohesive than the second group with a different selectivity for electron lone pair interactions. PCM-50 and PCPM-50 are cohesive, dipolar and hydrogen-bond basic stationary phases with more in common with NPEG and PEG than the phases in group 1 and 2. PCPS is the most cohesive, dipolar and hydrogen-bond basic of the stationary phases in Table 3 and is indicated as behaving independently. For method development, PMS (or PMOS, PMPS-5), PMPS-50, PMTS-50, PEG, PCPM-50 and PCPS are suitable phases for selectivity screening. Phases within a group can then be evaluated for selectivity optimization once a suitable general selectivity has been identified. Note that phases within a group are of a similar general kind, but not of equivalent selectivity. Therefore, exploring different phases within a group is not a redundant approach for optimizing band spacing.

The database contains system constants measured at a series of temperatures over the temperature range 60–140°C [12,63–67]. This allows an assessment of the effect of temperature on selectivity to be made. General trends are similar to those discussed for packed column stationary phases and need not be repeated here. Of note is the change in the order of the system constants for different stationary phases with temperature. The change in the a system constant with temperature is steep compared with the s system constant, such that variation in the a/s system constant ratios with temperature vary significantly for individual stationary phases. This is true particularly for PCPS, PCPM-50, PEG and NPEG stationary phases. Although the l system constant values for individual stationary phases at a single temperature are different, their slopes against temperature are closely grouped. This suggests that temperature-induced changes in cohesion and capacity for dispersion interactions are not a strong function of the identity of the stationary phase.

3. Liquid chromatography

The solvation parameter model has steadily gained acceptance as a general tool to explore the contribution of individual intermolecular interactions to the retention mechanism of non-ionic compounds in reversed-phase liquid chromatography and to a lesser extent liquid–solid or normal-phase chromatography. The model coefficients for these systems represent the difference in the characterized property for the stationary and mobile phases. Consequently, the general interpretation of system constants is not as straightforward as was the case for gas–liquid chromatography. Fundamental problems are the limited understanding of the influence of the mobile phase on the equilibrium stationary phase composition and the spatial heterogeneity of the stationary phase structure. Some comments on how these factors influence retention models in reversed-phase liquid chromatography will help explain the speculative nature of some interpretations of system constants summarized subsequently.

3.1. Reversed-phase liquid chromatography

3.1.1. Selection of a dependent variable

For separations employing binary mobile phase mixtures the change in solute retention factors with composition can be adequately described by Eq. (6) [38,68–70]. For a restricted composition range, a simple linear equation will often suffice, Eq. (7):

$$\log k = \log k_W + a\phi + b\phi^2 \quad (6)$$

$$\log k = \log k_W - S\phi \quad (7)$$

In the above equations, k is the solute retention factor for any volume fraction of organic solvent ϕ, and a and b are regression coefficients obtained by fitting the experimental data to a second-order polynomial model. The intercept, k_W, of the linear model, Eq. (7), is notionally related to the solute retention factor for water alone as the mobile phase. The S-value in Eq. (7) is the slope of the experimental data obtained by fitting to a linear regression model. Assuming that the composition and volume of the stationary phase is unaffected by the change in composition of the binary mobile phase over the linear portion of the plot, then the S-value is equivalent to the free energy of transfer of the solute from water to the organic solvent. If this were the case the S-value would be independent of the stationary phase identity. These considerations led to the general use of the S-value as a measure of solvent strength and its use to identify mobile phase compositions of similar solvent strength but different selectivity for method development. S-Values, however, are known to vary with structure, tending to increase with solute size and decreasing polarity. S-Values, therefore, are only approximate descriptors of solvent strength.

In practice, plots of $\log k$ against volume fraction of organic solvent are often curved when the volume fraction of organic solvent at either extreme of the composition range ($\phi \rightarrow 0$ or $\phi \rightarrow 1$) is included in the plot (Fig. 6) [38,71,72]. For individual solutes, linear, convex or concave plots are observed for the same system. Across different systems the shape of the plots may change for the same solute. For the intermediate mobile phase composition range, an approximate linear relationship based on Eq. (7) can almost always be found, but the intercepts obtained by linear extrapolation are generally different from the intercepts found by curve fitting the whole range of experimental data (Table 4) [38]. Also, the intercept obtained by linear extrapolation is usually dependent on the identity of the organic modifier and often on the composition range employed for retention factor measurements. Where reliable values of $\log k_W$ are available, there is only a poor correlation with the values obtained by linear extrapolation based on Eq. (7) [38].

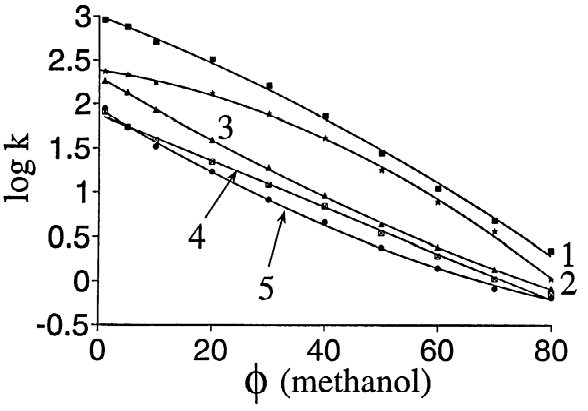

Fig. 6. Plot of the retention factor as a function of the volume fraction (% v/v) of methanol in reversed-phase liquid chromatography. Stationary phase is an octadecylsiloxane-bonded silica sorbent with methanol–water as the mobile phase. Solute identification: 1 = naphthalene; 2 = bromobenzene; 3 = acetophenone; 4 = 2-phenylethanol; and 5 = benzamide.

For the purpose of model development, Eqs. (6) and (7) suggest the possibility of using any of three free energy related parameters, $\log k$, $\log k_W$ and the S-value, as the dependent variable. The use of $\log k$ is unambiguous but suffers from the problem that the composition for the mobile phase must be stated for each model and a new model is required for each mobile phase composition of interest. $\log k_W$ and the S-value are attractive because they suggest that column and mobile phase properties could be specified separately and by a single model in each case. Some authors have adopted $\log k_W$ as the preferred parameter for characterizing column properties using the solvation parameter model [73–76].

Table 4
Comparison of experimental and extrapolated log k_w values for an octadecylsiloxane-bonded silica sorbent

Solute	Organic solvent	Log k_w		Experimental
		Quadratic[a] Eq. (6)	Linear[b] Eq. (7)	
2-Phenylethanol	Methanol	2.36	2.00	2.45
	Acetonitrile	2.05	1.27	
	Tetrahydrofuran	1.65	1.32	
Acetanilide	Methanol	2.19	1.60	2.52
	Acetonitrile	1.92	1.03	
	Tetrahydrofuran	1.39	1.04	
Acetophenone	Methanol	2.81	2.26	3.01
	Acetonitrile	2.33	1.71	
	Tetrahydrofuran	1.99	1.59	
Benzaldehyde	Methanol	2.43	1.87	2.56
	Acetonitrile	1.94	1.66	
	Tetrahydrofuran	1.74	1.56	

[a] From 1 to 100% (v/v) methanol and acetonitrile and 1 to 70% (v/v) tetrahydrofuran.
[b] From 40 to 70% (v/v) methanol and acetonitrile and 30 to 60% (v/v) tetrahydrofuran.

Our concern with the use of either log k_w or the *S*-value as a dependent variable in the solvation parameter model is that neither term has a clear thermodynamic definition [38] and no rigorous experimental protocol exists for the determination of accurate and self-consistent values. Different experimental conditions result in a dispersion of extrapolated log k_w values, the extent of which depends on the solute and the range of mobile phase compositions used for the extrapolation. This additional error source must compromise the accuracy of the information deduced from models based on log k_w. Qualitatively, this is revealed by poorer statistical fits for models based on log k_w than is typical for models based on experimental retention factors at a fixed mobile phase composition [38,73,74,77,78]. Wang et al. combined the linear solvent strength model, Eq. (5), with the solvation parameter model to develop a global model for the prediction of retention in reversed-phase liquid chromatography [77]. This approach assumes that a linear relationship exists between log k and ϕ as represented by Eq. (7) and the existence of a linear relationship between the system constants of the solvation parameter model and ϕ for binary mobile phases. The usefulness of such an approach is compromised by the fact that neither assumption is necessarily true for all experimental conditions. It may prove useful for a limited composition range where both requirements for a linear dependence on ϕ might be met approximately.

3.1.2. System considerations

Because of selective solvation the structure and composition of the stationary phase depends on the properties of the mobile phase it is in contact with in a rather complex manner. Any meaningful interpretation of the system constants must accommodate what is known about the influence of mobile phase composition on stationary phase sorption properties

The stationary phase in reversed-phase liquid chromatography is poorly defined. It has a fluid structure and composition and volume that depend on the equilibrium mobile phase composition, the identity and bonding density of surface-restrained ligands, the number and type of accessible silanol groups, and temperature [79–83]. The selective sorption of mobile phase components and their influence on chain conformation results in a film of associated solvent molecules and surface-restrained ligands with a thickness and composition that changes with solvent type and mobile phase composition. In predominantly aqueous solutions the surface-restrained ligands are most likely in a collapsed state with intercalated solvent trapped within

their structure. Access to surface silanol groups may be sterically restricted and the thickness of the stationary phase layer minimized. In predominantly organic mobile phases the surface-restrained ligands will be solvated and fully extended perpendicular to the surface. Mobile phase components will have greater access to the layer with penetration of solvent restricted by the ligand bonding density and the strength of ligand–ligand interactions. Water molecules are likely to preferentially interact with silanol groups and organic solvent molecules to the organic ligands. A gradient of solvent composition from the silica surface to the bulk mobile phase is possible with the organic solvent preferentially localized at the chain ends most distant from the surface. Solvents with a preference for hydrogen-bond interactions, such as methanol, are likely to drag associated water molecules with them into the stationary phase. This fluid stationary phase structure is sometimes referred to as an interphase with a permanent boundary provided by the surface of the silica substrate and a fluctuating boundary as an imaginary plane projected above the silica surface beyond which resides the mobile phase. It should be noted that all the above interactions take place within the porous structure of the silica substrate, where some types of interactions might be promoted by local confinement

Conceptual models of the structure of solvated porous polymer and porous graphitic carbon stationary phases are not as well developed as those for silica-based chemically bonded phases. Porous polymer sorbents of the type used in liquid chromatography have macroporous (or mesoporous) structures constructed from an agglomeration of extensively fused microspheres, which are themselves microporous materials. Reversed-phase retention on porous polymers is presumed to occur through solute interactions with the solvated surface of the polymer matrix lining the macropores, as well as with solvent imbibed by the micropores of the solvent-swollen matrix [78,84,85]. The selective uptake of mobile phase components by the micropores has a significant influence on the overall retention and selectivity of the separation, but in a manner that is incompletely understood. In the case of porous graphitic carbon an adsorption mechanism is generally presumed with solvent effects controlling retention through mobile phase interactions [86,87]. The solvent layer adsorbed at the graphite surface is possibly no more than a few monolayers thick with selective adsorption of mobile phase components controlled by dispersion and polarization interactions with the graphite surface.

At the microscopic level, binary mixtures of water and organic solvents are heterogeneous containing clusters of associated water molecules, water–organic solvent aggregates, and associated organic solvent molecules with an equilibrium composition that depends on the volume fraction of organic solvent and its identity [88,89]. Although the existence of solvent clusters is well established, the absolute relationship between the bulk solution composition and the size and composition of the clusters is still debatable. In terms of retention it is assumed that solutes distribute themselves selectively between the stationary phase and individual solvent clusters characterized by different distribution constants. The overall solute distribution constant is an average of these different preferences.

3.1.3. Analysis of system constants

Most studies in reversed-phase liquid chromatography attempt to establish a relationship between the system constants of the solvation parameter model and properties of either the mobile or stationary phase. The most useful representation of these relationships is a system map (Fig. 7) [38,43,78,90–97]. For chemically bonded phases the dominant contribution to retention in reversed-phase liquid chromatography is the cavity and dispersion interaction term (v system constant) sometimes with a small contribution from electron lone pair interactions (e system constant). As the volume fraction of organic solvent increases the v system constant decreases, indicating a smaller difference in the cohesion and dispersion interactions between the mobile and stationary phases. This is the basis of the observation that increasing the volume fraction of organic solvent in the mobile phase generally results in reduced retention in reversed-phase liquid chromatography. Polar interactions are more favorable in the mobile phase and reduce retention (system constants have a negative sign). The most important characteristic property of the mobile phase is its hydrogen-bond acidity. Since water is the most cohesive and hydrogen-bond acidic of the common solvents used

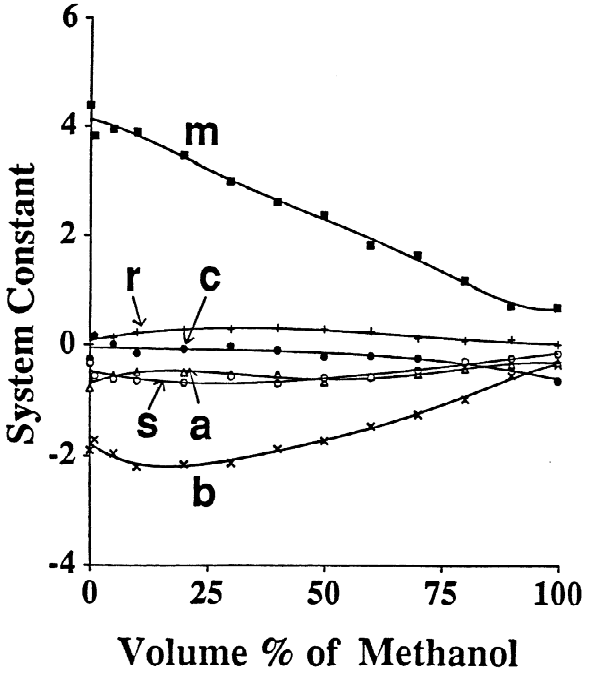

Fig. 7. System map for an octadecylsiloxane-bonded silica sorbent with a methanol–water mobile phase.

in reversed-phase liquid chromatography the dominant trends illustrate the pivotal role of water in the retention mechanism. Other interactions represented by the *e*, *s* and *a* system constants rarely, if ever, compete effectively with the *v* and *b* system constants in controlling retention except for mobile phases containing a low volume fraction of water [98]. The general trends illustrated in Fig. 7 are independent of the organic solvent type except for numerical differences in the system constants representing the solvent's ability to selectively modify system properties (Table 5) [90].

A number of studies report stationary phase properties at a single solvent composition or over a narrow range of solvent compositions [38,43,72,93–101]. These are somewhat difficult to summarize in a global sense since either the identity or composition of the mobile phase is different in many of these studies. It is also important not to become fixated on the properties of the column packing alone. Any reasonable explanation of the variation in system constants requires consideration of the mobile phase components sorbed by the stationary phase. Also,

Table 5
Influence of solvent type on the system constants of the solvation parameter model in reversed-phase liquid chromatography for a cyanopropylsiloxane-bonded silica sorbent

Solvent	Volume fraction (% v/v)	System constant			
		v	*e*	*a*	*b*
Methanol	50	0.84	0.21	−0.20	−0.88
	40	1.09	0.24	−0.22	−1.15
	30	1.45	0.32	−0.24	−1.36
2-Propanol	50	0	0.15	−0.27	−0.10
	40	0.29	0.16	−0.27	−0.41
	30	0.84	0.20	−0.29	−1.05
Acetonitrile	50	0.40	0.05	−0.18	−0.54
	40	0.64	0.09	−0.21	−0.80
	30	0.98	0.15	−0.24	−1.06
Tetrahydrofuran	50	0.47	0	−0.11	−0.67
	40	0.70	0	−0.06	−0.93
	30	1.18	0	0	−1.45

$s = 0$ in all cases.

since the system constants represent the difference in sorption interactions for the solute in the mobile and solvated stationary phase, any meaningful comparison must be made for the same mobile phase composition. Most data are available for the mobile phase methanol–water (50:50) (Table 6) [41,77,78,90,91,102–105], and acetonitrile–water (30:70) (Table 7) [43,77,78,90,91,106,107]. Individual system constants vary significantly with the identity of the stationary phase and the choice of organic solvent modifier. Selectivity differences between separation systems, however, are preferably correlated through the differences in their system constant ratios (e/v, s/v, a/v and b/v) [72,99,107–109]. There must be a significant difference in at least two system constant ratios for effective changes in band spacing on any compared sorbents. The octadecylsiloxane-bonded phases in Tables 6 and 7 show a significant variation in the b/m ratio but a close grouping of other system constant ratios. In broad terms they show little selectivity dispersion. Taking a closer look at the identity of the individual phases it can be seen that the modern endcapped octadecylsiloxane-bonded phases based on high purity silica with a high bonding density have remarkably similar system constant ratios suggesting near selectivity equivalence, while traditional octa-

Table 6
System constant ratios for several stationary phases with methanol–water (50:50) as the mobile phase

Stationary phase	System constant ratios					Ref.
	v	e/v	s/v	a/v	b/v	
(*i*) *Dimethylsiloxane-bonded phases*						
Methyl	1.25	0	−0.10	−0.21	−0.79	[102]
Cyclohexyl	1.85	0	−0.15	−0.12	−0.76	[a]
Octyl	2.29	0.03	−0.26	−0.09	−0.79	[103]
Decyl	1.65	0	−0.08	−0.22	−0.76	[102]
$(CH_2)_3OC_3F_7$	1.47	−0.09	0	−0.29	−0.92	[102]
$(CH_2)_2C_6F_{13}$	1.64	−0.17	0	−0.30	−0.85	[102]
Phenyl	1.13	0	0	−0.38	−0.78	[102]
Pentafluorophenyl	1.56	0	0	−0.22	−0.80	[102]
(*ii*) *Octadecylsiloxane-bonded phases*						
Hypersil ODS	2.46	0.07	−0.27	−0.08	−0.75	[38]
Zorbax ODS	2.68	0.14	−0.31	−0.11	−0.81	[38]
Spherisorb ODS-2	2.14	0.17	−0.32	−0.22	−0.86	[38]
Capcell Pak C_{18}	2.23	0.08	−0.21	−0.34	−0.91	[93]
J.T. Baker ODS	2.03	0.08	−0.20	−0.17	−0.74	[43]
Nucleosil C_{18}	1.78	0.11	−0.29	−0.25	−0.91	[38]
Nucleosil C_{18} (HD)	2.37	0.08	−0.16	−0.08	−0.85	[109]
Partisil ODS	2.28	0.20	−0.47	−0.21	−0.91	[105]
(*iii*) *Other phases*						
Porous graphitic carbon (Hypercarb)	3.21	0.30	0.08	−0.07	−0.52	[112]
Porous polymer (PLRP-S 100)	2.77	0.16	0	−0.40	−1.01	[78]
Horizontally polymerized C_{18}/C_3	2.59	0.17	−0.45	−0.21	−0.91	[105]
J.T. Baker Butyl (WP)	1.65	0	−0.15	−0.16	−0.81	[92]
J.T. Baker $(CH_2)_3CN$	0.84	0.25	0	−0.24	−1.05	[90]
J.T.Baker $(CH_2)_3OCH_2CH(OH)CH_2(OH)$	0.80	0.26	0	−0.20	−1.18	[91]

[a] A.D. Gunatilleka, C.F. Poole, unpublished results.

decylsiloxane-bonded phases show greater selectivity diversity. On the other hand, selectivity differences between the octadecylsiloxane-bonded phases and the porous polymers, porous graphitic carbon and fluorocarbon-containing siloxane-bonded phases show greater differences in their system constant ratios. These phases should be considered as complementary to the octadecylsiloxane-bonded phases for the purpose of method development. Selectivity differences between octadecylsiloxane-bonded and octylsiloxane-bonded phases are small by comparison and enable only small selectivity differences to be explored. The polar bonded phases are less retentive than the alkylsiloxane-bonded phases due to their smaller v system constants (cavity formation and/or dispersion interactions with the solvated stationary phase are less favorable for retention). At the same time they exhibit useful selectivity differences reflected in their system constant ratios compared with those for the octadecylsiloxane-bonded phases. Some further refinement in our understanding of the stationary phase contribution to retention could be realized if sorbent characteristics such as bonding density, chain length, ligand type, surface area, etc., were studied in a systematic fashion in conjunction with retention modeling using the solvation parameter model. In one case it was shown that individual system constants for octadecylsiloxane-bonded and butylsiloxane-bonded silica sorbents of similar bonding density were linearly related over a wide range of binary mobile phase compositions containing methanol or acetonitrile [92]. Increased retention for the octadecylsiloxane-bonded sorbent was the result of a more favorable contribution from

Table 7
System constant ratios for several stationary phases with acetonitrile–water (30:70) as the mobile phase

Stationary phase	System constant ratios					Ref.
	v	e/v	s/v	a/v	b/v	
(*i*) *Octadecylsiloxane-bonded phases*						
LiChrospher 100 RP-18e	1.95	0.16	−0.25	−0.30	−1.00	[107]
LiChrospher 100 RP-18	1.84	0.14	−0.25	−0.31	−1.00	[107]
Purospher RP-18e	1.95	0.16	−0.26	−0.32	−1.01	[107]
Purospher	1.89	0.14	−0.18	−0.32	−1.09	[107]
LiChrospher PAH	1.76	0.16	−0.29	−0.31	−0.92	[107]
SymmetryShield RP-C_{18}	2.01	0.19	−0.22	−0.26	−1.04	[107]
Aquapore OD-300	1.62	0.14	−0.25	−0.30	−0.98	[107]
Synchropak RP-C_{18}	1.38	0.13	−0.25	−0.32	−0.94	[107]
J.T. Baker ODS	2.11	0.08	−0.13	−0.23	−0.90	[43]
Inertsil ODS2	1.78	0.05	−0.18	−0.23	−0.97	[125]
(*ii*) *Siloxane-bonded phases*						
SymmetryShield RP-C_8	1.89	0.18	−0.17	−0.18	−1.05	[107]
LiChrosorb RP-select B	1.63	0.14	−0.23	−0.33	−0.99	[107]
LiChrospher 100 RP-8	1.58	0.13	−0.22	−0.31	−0.97	[107]
Zorbax SB 300 C_8	1.22	0.13	−0.22	−0.28	−0.96	[107]
Zorbax C_8	2.35	0	−0.11	−0.20	−1.06	[77]
Aquapore Butyl	1.15	0.13	−0.25	−0.27	−0.95	[107]
Synchropak RP-C_4	1.13	0.13	−0.26	−0.29	−0.97	[107]
J.T. Baker Butyl (WP)	1.99	0	−0.10	−0.16	−0.91	[92]
J.T. Baker CN	0.98	0.15	0	−0.24	−1.08	[90]
Zorbax SB 300 CN	0.83	0.18	−0.23	−0.21	−1.12	[107]
J.T. Baker DIOL	0.56	0.23	0	−0.16	−1.25	[91]
(*iii*) *Other phases*						
PLRP-S 100	2.40	0.11	−0.06	−0.40	−1.16	[78]
PS-ZrO_2	1.79	0.20	−0.12	−0.12	−1.15	[106]
PBD-ZrO_2	2.23	0.07	−0.20	−0.13	−1.16	[106]

cavity formation and dispersion interactions as well as a more favorable phase ratio with only minor differences due to changes in selectivity for dipole-type and hydrogen-bond interactions. The solvation parameter model was able to predict separation factor values for a varied group of compounds with an average error of 5 to 20% for a wide range of binary mobile phase compositions containing methanol or acetonitrile [108]. Since system constants contain some degree of uncertainty, it is reasonable to assume that the solvation parameter model is blind to small differences in selectivity for sorbents identified as equivalent through use of the system constant ratios. The solvation parameter model does not contain a term for shape selectivity nor does it consider specific interactions such as electrostatic interactions that are known to contribute to the retention of some bases on silica-based phases.

Retention of neutral molecules on porous graphitic carbon with aqueous mobile phases demonstrates properties that are characteristic of reversed-phase mobile phases and more specific properties characteristic of adsorption on a polarizable adsorbent [110–112]. The dominant contribution to retention is the cavity formation and dispersion interaction term, composed of favorable interactions in the mobile phase (hydrophobic effect) and additional contributions from adsorption on the graphite surface. Electron lone pair and dipole-type interactions in the adsorbed state result in increased retention and are more important than similar interactions for typical octadecylsiloxane-bonded silica-based phases. Hydrogen-bonding interactions are more favorable in the mobile phase resulting in lower retention. The changes in the system constants for cavity formation and dispersion interactions (v system constant) and

hydrogen-bond interactions (*a* and *b* system constants) are roughly linearly related to the volume fraction of water in methanol–water mobile phase compositions [112]. The solvation parameter model poorly predicted the retention properties of angular molecules (e.g. diphenylmethane, benzophenone, etc.), attributed to a failure of the characteristic volume to correctly model the contact surface area for the interaction of angular molecules with the flat graphite surface. It has been speculated that interactions for porous polymers result from a combination of adsorption and absorption interactions, but whether there is a shape dependence of the type observed for porous graphitic carbon is unclear [78].

3.1.4. Temperature

The majority of liquid chromatographic separations are carried out at ambient temperature for convenience and because ambient temperature provides reasonable column efficiency for low molecular mass solutes. Elevated temperatures usually improve the kinetic performance of columns and modify column selectivity. The simultaneous optimization of temperature and mobile phase composition is considered desirable for method development in liquid chromatography, although the possibility of exploiting temperature as an optimization variable is often ignored [113,114]. Variation in temperature and composition show similar trends in retention, but within the easily accessible range for both variables the capacity to change retention is greater for composition variation [114,115]. The predominant influence of higher temperatures in reversed-phase liquid chromatography is to decrease retention by a reduction in the difference in cohesive energy and dispersion interactions between the mobile and stationary phases and to decrease the hydrogen-bond acidity of the mobile phase relative to the stationary phase (Fig. 8) [114]. Changes in other polar interactions are less significant. Temperature optimization in reversed-phase liquid chromatography, therefore, will have the largest effect on peak spacing of compounds that differ in size and hydrogen-bond basicity.

The use of very high temperatures in liquid chromatography is quite recent, as embodied, for example, in separations employing hot pressurized water as a mobile phase [115] and separations on

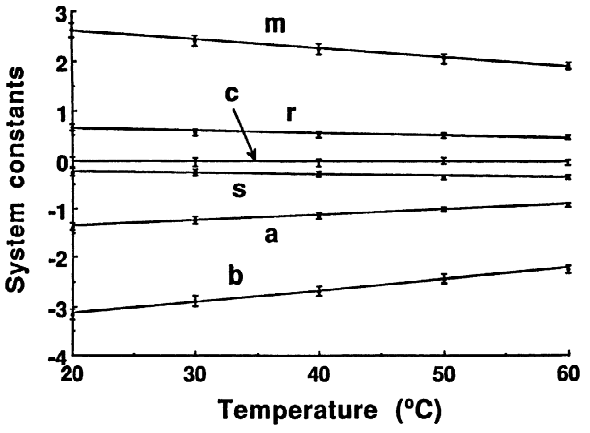

Fig. 8. Variation of the system constants with temperature for a mobile phase of 2-propanol–water (37:63) on a porous polymer sorbent PLRP-S 100. (From Ref. [114]. ©Royal Society of Chemistry.)

polymer encapsulated sorbents at up to 200°C [116]. Here the main interest has been to exploit water as a mobile phase or to obtain fast separations without loss of efficiency at high flow-rates. The dominant effect of increasing temperature on the solvation properties of water is to diminish its cohesive energy and capacity for hydrogen-bond interactions [115]. Even so, at 180°C hot pressurized water is a relatively weak solvent for reversed-phase liquid chromatography. Its solvent strength is similar to 50–60% (v/v) methanol in water at 20°C. On the other hand, temperature-induced changes in selectivity for hot pressurized water are different to selectivity changes observed for composition variation of binary mobile phases containing acetonitrile, methanol or propan-2-ol. The complementary nature of these selectivity differences suggests that hot pressurized water should be considered as a viable mobile phase for method development in reversed-phase liquid chromatography for the separation of polar compounds.

3.1.5. Ternary solvents

Binary mobile phase compositions provide adequate control of solvent strength for reversed-phase liquid chromatography but rather limited opportunities for simultaneous selectivity optimization. Ternary and higher order solvent mixtures are usually required for the simultaneous optimization of

solvent strength and selectivity for moderately complex mixtures. For method development using binary mobile phases, individual system constants usually change smoothly with composition and can be fit to simple linear or polynomial functions of the volume fraction of organic solvent. Retention maps can be simulated from these system maps for any solute with known or estimated solute descriptor values. A statistical mixture-design approach was successful in extending this method to ternary mobile phase compositions [117,118]. Three-dimensional system surface maps now replace the two-dimensional system maps (Fig. 9), which allow the simulation of three-dimensional retention surfaces as a continuous function of mobile phase composition. The system surfaces are smooth without irregular features and are modeled by the general equation:

$$y = a_1\phi_1 + a_2\phi_2 + a_3\phi_w + a_4\phi_1\phi_2 + a_5\phi_1\phi_w + a_6\phi_2\phi_w \quad (8)$$

where y is an individual system constant, ϕ_1, ϕ_2 and ϕ_w are the volume fractions of the two organic solvents and water, respectively, and a_1, a_2, a_3, a_4, a_5 and a_6 are model constants obtained by regression analysis. The regression constants may be abstract values but were consistent with a physical interpretation of the solvation properties of the ternary systems. The mixture-design approach was able to predict retention at compositions other than those used to construct the system surface maps with a similar accuracy to models obtained by the solvation parameter model at the new compositions.

3.1.6. Ionizable solutes

The solvation parameter model described by Eq. (1) is set up to model the retention of neutral compounds and ionizable compounds in their neutral form. Changes in mobile phase pH are not expected to have a significant influence on the retention of neutral compounds under typical reversed-phase conditions, but the same cannot be said of ionizable compounds. The ionic form of a compound generally exhibits weaker retention than the neutral form under

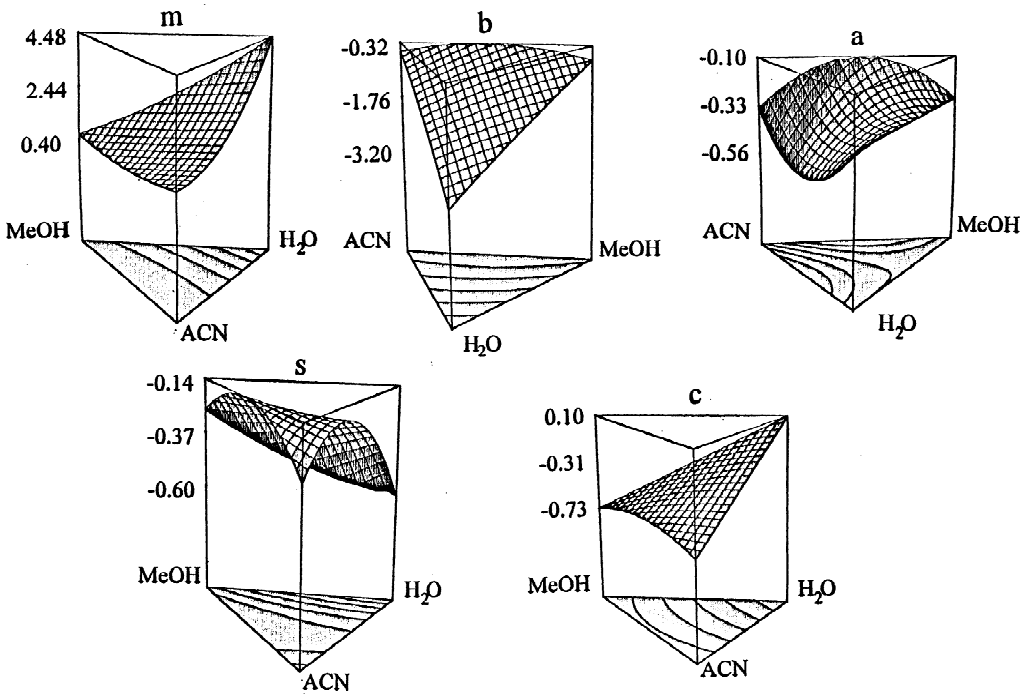

Fig. 9. System surfaces for the variation of the system constants with composition for the ternary mobile phase methanol–acetonitrile–water on an octadecylsiloxane-bonded silica sorbent. The *e* system constant was zero at all compositions. (Adapted from Ref. [117]. ©Friedr. Vieweg and Sohn.)

reversed-phase separation conditions, as well as variable retention related to the composition, ionic strength and pH of the mobile phase. These changes in retention are generally too large for predictions made for the neutral form of a compound to be a useful estimate of its retention in an appreciably ionized form. In addition, the inclusion of retention data for partially ionized compounds in the solvation parameter model is an additional source of model error.

The solvation parameter model has been modified for the conjoint prediction of retention of neutral and ionic compounds by the addition of either of two new solute descriptors derived from the acid dissociation constant for the solutes in the mobile phase [119,120]. The scaled effective acid dissociation descriptor, P, is defined as $P = (14 - \mathrm{p}K^{*})/10$, where $\mathrm{p}K^{*}$ is the effective acid dissociation constant for the solute in the mobile phase, and is usually different to the $\mathrm{p}K_a$ in water. The degree of ionization descriptor is defined as $\log[1 - D(1 - f)]$, where $D = 10^{(\mathrm{pH}^{*} - \mathrm{p}K^{*})}/[1 + 10^{(\mathrm{pH}^{*} - \mathrm{p}K^{*})}]$ and $f = k_{X^-}/k_{HX}$. The f value should be different for each solute, but applications using the degree of ionization descriptor are considerably simplified if an average value of f is used. For the conjoint prediction of the retention of phenols and neutral compounds an average value of $\log f = -1.80$ was found to be suitable. The degree of ionization descriptor has the advantage that it allows the same model to be used for any pH^{*}, the effective pH for the mobile phase composition. This is not possible with the P solute descriptor because it is not pH dependent and the p system constant changes with the pH^{*} value of the mobile phase. Both extended models provided good agreement between experimental and predicted retention factors for neutral compounds and phenols over the pH range 2–12 in a methanol–water mobile phase. In deriving the new solute descriptors it was assumed that the S and A solute descriptors were unchanged by the extent of ionization. This simplifying assumption is likely the most significant contributing factor to the slightly larger prediction error for the conjoint models. Both the P and degree of dissociation descriptor are limited by the need to know the pH^{*} value for the mobile phase and $\mathrm{p}K^{*}$ values for each ionizable solute in the mobile phase. These values are not always available or easy to estimate and may require additional experimental work for their determination.

3.1.7. Gradient elution

Gradient elution methods provide faster and more convenient separation conditions for compounds with a wide range of retention properties. Gradient elution methods are also more suitable for high-throughput solute property estimations, such as the determination of solute descriptors [121,122], and can be used for column characterization [123,124]. For a typical linear solvent strength gradient the gradient retention time, t_g, is related to solute properties through [125,126]:

$$t_g = I + v'V + e'E + s'S + a'A + b'B \quad (9)$$

where the system constants depend on the initial mobile phase composition and the experimental conditions (t_M/b). The variable b in this case refers to the gradient steepness parameter. The coefficients for the gradient model are given by $v' = v_0(t_M/b)$, etc. The intercept $I = C + (t_M/b)\log k_0$, where t_M is the column hold-up time, k_0 the retention factor for the solute in the mobile phase at the start of the gradient, and C is a constant for the gradient system. The derivation of Eq. (9) assumes that the S-value in Eq. (7) is constant for all solutes and that $k_0 \gg \frac{1}{2}3b$. The latter is generally the case but the S-value will likely vary over a narrow range for different solutes, as discussed in Section 3.1.1. The coefficients determined by gradient elution (e.g. v') are usually systematically smaller than those calculated by $v_0(t_M/b)$, where v_0, etc., are the system constants for the mobile phase at the start of the gradient [126]. Because gradient retention times are unsuitable parameters for interlaboratory reference data, and to allow for column changes over time, a chromatographic hydrophobicity index (CHI) was recommended as a reference calibration scheme [121–125]. The gradient retention times are placed on the CHI scale by correlation with a calibration set of compounds with defined CHI values. It was demonstrated that both the gradient retention times and the derived CHI values are free energy related parameters suitable for use in the solvation parameter model in the same way as $\log k$ is used for isocratic separations [123].

The gradient elution method was used to identify a limited number of system types (columns and mobile phases) with significantly different separation properties suitable for the high-throughput determination of solute descriptors, which should also be useful for method development (Table 8) [123,124]. The octadecylsiloxane-bonded sorbent with methanol and acetonitrile and the porous polymer sorbent with acetonitrile were selected for their interactions with dipolar/polarizable solutes with significant hydrogen-bond basicity. The octadecylsiloxane-bonded sorbent with 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoropropan-2-ol and the alkyl fluoroalkylsiloxane-bonded sorbent with 2,2,2-trifluoroethanol were chosen for their interactions with dipolar/polarizable solutes with significant hydrogen-bond acidity. The 3-cyanopropylsiloxane-bonded phases with acetonitrile and methanol were selected for their weak interactions with hydrogen-bond acids.

3.2. Normal-phase liquid chromatography

Application of the solvation parameter model to retention in liquid–solid chromatography has received less attention than reversed-phase liquid chromatography [91,127–130]. This is understandable given the limited use of liquid–solid chromatography for analysis today, but another important consideration is that the solute descriptors were developed from partition properties and are not necessarily suitable for adsorption interactions. With certain reservations, identified presently, the latter concern does not appear to be an overriding difficulty. Some selected data for different adsorbents are summarized in Table 9. Retention on all phases results from polar interactions of a dipole-type and through hydrogen bonding. Increasing solute size generally reduces retention and electron lone pair interactions are unimportant for many applications. For the weak solvent hexane the 3-cyanopropylsiloxane-bonded phase (CYANO) is more cohesive and less hydrogen-bond basic than the 3-aminopropylsiloxane-bonded (AMINO) and the spacer bonded propanediol (DIOL) phases. The AMINO and DIOL phases are similar to each other with a slightly different blend of polar interactions. The addition of 1% (v/v) methanol to hexane causes a significant change in selectivity for all bonded

Table 8
System constant ratios for reversed-phase gradient elution systems selected to provide varied separation properties

System	System constant ratios				
	v'	e'/v'	s'/v'	a'/v'	b'/v'
Column: Inertsil ODS2 Solvent B: methanol	5.15	0.11	−0.20	−0.21	−0.91
Column: Inertsil ODS2 Solvent B: 2,2,2-trifluoroethanol	5.67	0.12	−0.35	−0.55	−0.69
Column: Inertsil ODS2 Solvent B: 1,1,1,3,3,3-hexafluoroisopropanol	4.47	0.14	−0.31	−1.06	−0.89
Column: Inertsil ODS2 Solvent B: acetonitrile	4.80	0.09	−0.22	−0.33	−0.22
Column: alkyl fluorooctyl Solvent B: 2,2,2-trifluoroethanol	3.11	−0.04	−0.18	−1.18	−0.61
Column: 3-cyanopropyl Solvent B: acetonitrile	3.68	0.05	−0.08	−0.15	−1.13
Column: 3-cyanopropyl Solvent B: methanol	5.42	0.15	−0.19	−0.13	−0.83
Column: PLRP-S 100 Solvent B: acetonitrile	4.38	−0.15	−0.10	−0.57	−1.29

Gradient conditions: 0–1.5 min 0% B, 1.5–10.5 min 0→100% B, 10.5–11.5 min 100% B, 11.5–12 min 100→0% B and 12–15 min 0% B. Flow-rate 1.0 ml/min.

Table 9
System constants for separations by liquid–solid chromatography

Stationary phase[a]	Mobile phase	System constants					Ref.
		v	*e*	*s*	*a*	*b*	
DIOL	Hexane	−1.05	0	1.63	2.10	3.86	[129]
AMINO		−0.85	0	1.40	1.65	3.81	[129]
CYANO		−0.37	0	1.88	2.47	0.99	[129]
Silica	Hexane–methanol	−0.83	0	1.06	2.23	1.56	[128]
DIOL	(99:1)	−0.85	0	1.07	2.37	1.47	[128]
AMINO		−0.72	0	0.94	2.94	1.20	[128]
CYANO		−0.61	0	0.95	1.86	1.15	[128]
Silica	Hexane–methyl	0	−0.86	1.67	1.84	3.00	[127]
CYANO	*t*-butyl ether (95:5)	−1.20	0	1.43	1.10	2.80	[127]
Silica	Hexane–methyl	−0.46	−0.21	1.10	1.16	3.02	[127]
CYANO	*t*-butyl ether (80:20)	−1.08	0	1.01	0.53	2.26	[127]

[a] AMINO, 3-aminopropylsiloxane-bonded silica; CYANO, 3-cyanopropylsiloxane-bonded silica; DIOL, spacer bonded propanediol siloxane-bonded silica.

phases. The apparent hydrogen-bond acidity of the chemically bonded stationary phases is significantly reduced but the difference in capacity of these systems for dipole-type interactions is reduced to a lesser extent. The hydrogen-bond basicity of the AMINO phase is increased significantly and the DIOL phase slightly. For this mobile phase the selectivity of the DIOL phase is similar to silica gel. With hexane–methyl *t*-butyl ether as a mobile phase the apparent stationary phase hydrogen-bond acidity is increased and the hydrogen-bond basicity is significantly reduced. Compared with reversed-phase liquid chromatography the range of selectivity variation is greater for liquid–solid chromatography and more significantly dependent on both the choice and composition of the mobile phase. Consequently, it is unwise to try to reduce retention properties to a stationary phase effect alone. A meaningful comparison can only be made for specific stationary and mobile phase combinations, since the same stationary phase can exhibit very different chromatographic properties with different mobile phases.

The data in Table 9 provide an effective illustration of the complementary nature of liquid–solid and reversed-phase separations. In reversed-phase liquid chromatography, solute size is the most important parameter for effective retention with polar interactions tending to reduce retention, the exact opposite of that observed for liquid–solid chromatography. The negative effect of solute size on retention in liquid–solid chromatography is probably related to the additional work required to displace an increasing number of solvent molecules from the adsorbent surface to establish the solute in the adsorbed solvent layer. Without compensation by an increase in dispersion interactions for the adsorbed solute compared with the solvated solute this will result in an unfavorable free energy contribution to retention. The data in Table 9 also indicate that for solutes with a limited capacity for polar interactions it will be difficult to obtain useful retention in liquid–solid chromatography.

There seem to be few problems in modeling retention on polar chemically bonded phases when solute selection is performed correctly (exclusion of nitrogen-containing bases that might be retained by electrostatic interactions in addition to sorption interactions). For silica gel, solute size effects and site-specific interactions on the heterogeneous adsorbent surface reduce the predictive accuracy of general models built with the solvation parameter model [127]. In an effort to improve the model fit for adsorption on inorganic oxides the simple competition model was used to separate the retention factor into contributions from solvent and solute interactions with the adsorbent surface [131,132]. First of all, it was shown that the solvent strength parameter (the free energy of adsorption of the solvent per unit area of the standard activity surface), ε^{o}, could be fit to the solvation parameter model with an average prediction error similar to the experimental error for the dependent variable:

$$\varepsilon^{o}_{Silica} = 0.27 - 0.26V + 0.20S + 0.38A + 0.54B$$
$$\rho = 0.986 \quad SE = 0.04 \quad F = 150 \quad n = 21 \qquad (10)$$

$$\varepsilon^{o}_{Alumina} = 0.23 - 0.23V + 0.36S + 0.94A + 0.48B$$
$$\rho = 0.985 \quad SE = 0.05 \quad F = 289 \quad n = 38 \qquad (11)$$

The statistical parameters are ρ the multiple correlation coefficient, SE the standard error in the estimate, F Fischer's statistic, and n the number of solvents included in the model. These results show that alumina is significantly more hydrogen-bond basic and less hydrogen-bond acidic than silica, while both adsorbents are reasonably dipolar/polarizable.

The simple competition model describes retention in liquid–solid chromatography [132]:

$$\log k = c + \alpha'(S^{o} - A_S\varepsilon^{o}) \qquad (12)$$

The constant term in Eq. (12) depends largely on the phase ratio, α' is the adsorbent activity parameter, S^{o} the free energy of solute adsorption on a standard adsorbent ($\alpha' = 1$) and A_S the adsorbent cross section of the solute. For a particular set of experimental conditions the equation constant term and α' are fixed and Eq. (12) can be rearranged to allow calculation of the S parameter, which is proportional to S^{o}:

$$S = p + qS^{o} = \log k + A_S\varepsilon^{o} \qquad (13)$$

where p and q are regression constants. The S parameter provided a suitable fit to the solvation parameter model for a number of mobile phase compositions on silica gel [132], for example the model indicated by Eq. (14) for 30% (v/v) methyl *t*-butyl ether in hexane:

$$S = -1.73(\pm0.17) - 0.45(\pm0.15)V - 0.63(\pm0.13)E + 3.48(\pm0.14)S + 1.79(\pm0.13)A + 6.19(\pm0.22)B$$
$$\rho = 0.993 \quad SE = 0.20 \quad F = 519 \quad n = 44 \qquad (14)$$

The S parameter was not entirely independent of the mobile phase composition and therefore is not totally suitable as a surrogate parameter for the free energy of solute adsorption on the bare silica surface. The solvent contribution to the competition model is contained in the $A_S\varepsilon^{o}$ term. It was shown that the solute cross section is more than a size parameter and contains chemical information by application of the solvation parameter model:

$$A_S = 1.81(\pm0.41) - 2.40(\pm0.43)E + 8.67(\pm0.49)S + 3.74(\pm0.40)A + 11.16(\pm0.56)B$$
$$\rho = 0.986 \quad SE = 0.81 \quad F = 464 \quad n = 55 \qquad (15)$$

With individual models for A_S and S to hand it was possible to test the validity of Eq. (13) to estimate retention in liquid–solid chromatography. For separations on silica with different mobile phase compositions the average error in the prediction of $\log k$ was 0.17. These results are encouraging but fall somewhat short of what is required for method development applications. The approach is probably sound but the definition of the S parameter and A_S terms remains ambiguous. It is likely that there is a commingling of solute and solvent properties between the two parameters leading to additional uncertainty in model predictions. Advanced models may also need to consider solute interactions in the mobile phase, which are not canceled by similar interactions in the adsorbed state.

4. Micellar electrokinetic chromatography

The separation system in micellar electrokinetic chromatography (MEKC) consists of a homogeneous distribution of charged surfactant micelles in an electrolyte solution. Provided that the velocity of the micelles in a defined direction is different to the velocity of the bulk electrolyte solution in an electric field a separation of neutral solutes is possible. An acceptable separation depends on differences in solute distribution constants between the micelles and aqueous electrolyte (selectivity), favorable kinetic properties (efficiency), an adequate migration window (peak capacity) and a reasonable total separation time. Mass transfer and diffusion properties are generally favorable for high efficiency in MEKC (ca. $>200\,000$ plates per column). The difference in velocity of the bulk electrolyte and the micelles in the direction of the detector establishes the migration window, and to some extent this can be optimized by pH manipulation. Selectivity in MEKC is controlled mainly by the choice of surfac-

tant. Fine-tuning of selectivity is obtained using solvent modifiers and additives to adjust the solvation properties of either the bulk electrolyte or the micelles [27,34]. Recommendations for the selection of experimental conditions and suitable solutes to determine surfactant selectivity in MEKC are given in Ref. [27] with additional comments in Ref. [28].

4.1. Surfactant selection

System constant ratios for common surfactants are summarized in Table 10. For convenience the surfactants are grouped into alkyl sulfates and sulfonates [27,133–139], bile acids [27,133,140,141], miscellaneous anionic surfactants [135,136,142], cationic surfactants [27,28,133] and a microemulsion [140,143]. In those cases where multiple entries are indicated for the same surfactant there is conflict in the literature as to the true value. In other cases where multiple values are available we have indicated a consensus value taking the uncertainty of individual system constants into account. It should be noted that the sorption properties of micelles are influenced by properties of the electrolyte solution, particularly its ionic strength, choice of buffer ions, pH and temperature [27]. For typical operating conditions these effects are usually small and the system constant ratios in Table 10 will provide a reliable guide to the selection of surfactants with different sorption characteristics for method development. In the region of the critical micelle concentration, variation in micelle properties can be significant. Whenever practical the surfactant concentration should be significantly ($\approx 5\times$) greater than the critical micelle concentration for the surfactant in the buffer (which is usually less than the critical micelle concentration in water commonly found in handbooks). In the usual concentration range for MEKC surfactant concentration influences retention through changes in the phase ratio with little effect on selectivity.

Method development in MEKC usually begins with sodium dodecyl sulfate (SDS) because of its favorable kinetic and chromatographic properties. Other surfactants are selected based on their complementary selectivity to SDS. The system constant ratios for alkane sulfates and sulfonates are not very sensitive to changes in the identity of the surfactant counter-ion or the alkyl chain length [134,139] and provide only small changes in selectivity compared with SDS. On the other hand, the perfluorooctanesulfonate and alkyl-*N*-methyltaurine surfactants provide significant changes in selectivity [28,133,138]. Lithium perfluorooctanesulfonate (LPFOSu) has different selectivity for electron lone pair interactions (the only negative *e* system constant), it is the most dipolar (the only positive *s* system constant) and is the strongest hydrogen-bond acid and weakest hydrogen-bond base of the surfactants in Table 10. The *N*-alkyl-*N*-methyltaurine surfactants are stronger hydrogen-bond bases and weaker hydrogen-bond acids than SDS. Their properties are similar to the cationic surfactants, although TTAB is a stronger hydrogen-bond base than the *N*-alkyl-*N*-methyltaurine surfactants. In this case the *N*-alkyl-*N*-methyltaurine surfactants are likely to be selected for convenience. The bile acids are similar as a group with different selectivity to SDS. They are more cohesive, stronger hydrogen-bond bases and weaker hydrogen-bond acids [27,133]. Sodium cholate is a suitable representative example of this group. The microemulsion has similar separation properties to sodium cholate and could be substituted for it in many applications, except for estimation of $\log P$ (the octanol–water distribution constant) [140]. The *N*-alkylsarcosinates have similar selectivity to the *N*-alkyl-*N*-methyltaurine surfactants, and both groups are not required for selectivity optimization. The dodecylcarboxylate and dodecylphosphate surfactants are slightly more hydrogen-bond basic than SDS and could be useful for optimizing the peak position of solutes differing in their hydrogen-bond acidity.

From the information available a working list of surfactants for selectivity optimization in MEKC would include sodium dodecyl sulfate, the microemulsion (or a bile acid such as sodium cholate), lithium perfluorooctanesulfonate, sodium *N*-dodeconyl-*N*-methyltaurine (or an *N*-alkylsarcosante or cationic surfactant), and sodium dodecylphosphate. Having selected the preferred surfactant type, selectivity can be fine-tuned by selecting further surfactants within a similar selectivity group or by using solvent modifiers or additives.

Considering the anionic surfactants in Table 10 as

Table 10
Surfactant system constant ratios for micellar electrokinetic chromatography

Surfactant	Abbreviation	System constant ratios					Ref.
		v	e/v	s/v	a/v	b/v	
(*i*) *Alkane sulfates and sulfonates*							
Sodium octyl sulfate	SOS	2.85	0.16	−0.11	−0.04	−0.66	[139]
Sodium decyl sulfate	SDecS	2.69	0.12	−0.09	0	−0.59	[139]
Sodium dodecyl sulfate	SDS	2.98	0.12	−0.14	−0.08	−0.64	[133]
(36°C)		2.86	0.09	−0.11	−0.05	−0.59	[136]
Lithium dodecyl sulfate	LDS	2.81	0.13	−0.15	−0.07	−0.55	[138]
(35°C)		3.01	0.10	−0.12	−0.07	−0.59	[134]
Magnesium dododecyl sulfate							
(35°C)	$Mg(DS)_2$	3.02	0.09	−0.14	−0.09	−0.62	[134]
Copper dododecyl sulfate (35°C)	$Cu(DS)_2$	3.05	0.11	−0.17	−0.09	−0.63	[134]
Sodium dodecyl sulfonate (36°)	SDSu	2.84	0.12	−0.15	−0.01	−0.63	[136]
Sodium tetradecyl sulfate (35°C)	STS	3.01	0.09	−0.11	−0.06	−0.60	[135]
Lithium perfluorooctanesulfonate	LPFOSu	2.20	−0.11	0	−0.42	0	[138]
		2.36	−0.29	0.20	−0.34	−0.25	[133]
Sodium *N*-lauroyl-*N*-methyltaurine	SLMT	2.88	0.18	−0.12	0.14	−0.82	[142]
Sodium *N*-dodecanoyl-*N*-methyltaurine	SDMT	3.07	0.23	−0.16	0.07	−0.84	[133]
(*ii*) *Bile acids*							
Sodium cholate	SC	2.45	0.26	−0.19	0	−0.93	[133]
Sodium deoxycholate	SDC	2.67	0.25	−0.18	0	−0.93	[133]
Sodium taurocholate	STC	2.43	0.25	−0.14	0	−0.85	[133]
Sodium taurodeoxycholate	STDC	2.62	0.26	−0.17	0	−0.83	[133]
(*iii*) *Miscellaneous anionic surfactants*							
Sodium *N*-lauroylsarcosinate	SLN	2.98	0.14	−0.12	0.15	−0.78	[135]
Sodium *N*-myristoylsarcosinate	SMN	2.99	0.16	−0.14	0.15	−0.82	[135]
Sodium *N*-parmitoylsarcosinate	SPN	3.11	0.14	−0.14	0.15	−0.83	[135]
Sodium *N*-lauroyl-*N*-methyl-β-alaninate	ALE	2.92	0.15	−0.13	0.17	−0.83	[142]
Sodium dodecoxycarbonylvaline	SDCV	2.99	0.14	−0.19	0.05	−0.81	[28]
Sodium dodecylcarboxylate (36°)	SDCA	2.96	0.05	−0.13	0.08	−0.60	[136]
Sodium dodecylphosphate (36°)	SDP	3.01	0.08	−0.18	0.05	−0.66	[136]
Sodium lauryl sulfoacetate (36°)	SLSA	2.97	0.16	−0.13	0.04	−0.82	[136]
(*iv*) *Cationic surfactants*							
Tetradecyltrimethylammonium bromide	TTAB	2.99	0.10	−0.07	0.29	−0.91	[28]
Hexadecyltrimethylammonium bromide	CTMAB	3.40	0.18	−0.16	0.17	−0.91	[133]
(*vi*) *Microemulsion*							
1.44% (w/w) SDS + 6.49% (w/w)		3.05	0.09	−0.23	−0.02	−0.92	[143]
butan-1-ol + 0.82% (w/w) heptane		2.39	0.13	−0.22	0	−0.95	[140]

Temperature 20–25°C except where noted.

a single group, it is clear that both the identity of the surfactant head group and relatively small changes in structure in the region of the head group can significantly influence selectivity. These changes in selectivity for dipole-type and hydrogen-bond interactions are probably determined by the amount of water attracted into the interphase region and the ability of the charge density on the head group to modify the properties of neighboring water molecules through interactions with the head group [34].

Aqueous electrolyte solutions containing a surfactant mixture, organic solvent or additives provide an

alternative approach for selectivity control. Non-ionic surfactants as a component of mixed surfactant micelles allow changes in selectivity, phase ratio and separation time without affecting the operating current and usually without degrading efficiency in MEKC. Systematic studies of the influence of the mole ratio of the neutral surfactant polyoxyethylene (23) dodecyl ether (Brij® 35) on the selectivity of mixed surfactant micelles containing sodium dodecyl sulfate [137,144] or sodium *N*-dodeconyl-*N*-methyltaurine [145] produced similar trends with only a modest change in system constants, for example (Table 11). The addition of Brij® 35 results in small changes in the *v*, *e* and *s* system constants. In addition, increasing the mole fraction of the neutral surfactant in the mixed surfactant micelle results in a small increase in hydrogen-bond basicity but a more significant change in the hydrogen-bond acidity of the mixed surfactant micelle. Changes in the hydrogen-bond acidity of the mixed surfactant micelle are particularly noticeable for small mole fractions of the neutral surfactant. The capability of optimizing selectivity in this way is limited to relatively small, although predictable, changes. Mixed micelles formed from two anionic surfactants allow a wider range of selectivity optimization if the individual surfactants possess significantly different sorption properties [138,141]. The limiting values are the system constants for the individual surfactants. At intermediate mole fraction mixing ratios the system constants change in a linear or quadratic manner with surfactant composition. This approach is limited by the number of surfactants with sufficiently different sorption characteristics to provide a significant variation in system properties and the formation of separate rather than mixed micelles at high mixing ratios [138]. Typical water-miscible organic solvents (e.g. methanol, acetonitrile, tetrahydrofuran) have a similar effect on selectivity to that observed for reversed-phase liquid chromatography with chemically bonded phases [144,145]. The range of modifier concentration is restricted, however, to predominantly aqueous solutions by the instability of micelle aggregates at moderate (e.g. $>25\%$) volume fractions of organic solvent. This tends to suppress the range over which the system constants can be changed and results in a smaller range of selectivity differences between individual solvents. These results are consistent with the view that the organic solvent modifiers moderate the characteristic solvophobic properties of the aqueous electrolyte while having minimal effect on the micelle phase. The use

Table 11
Influence of the concentration of non-ionic surfactant (Brij® 35) and organic solvent on system selectivity

Concentration Brij® 35 (m*M*)	Solvent	(% v/v)	System constant ratios				
			v	*e*/*v*	*s*/*v*	*a*/*v*	*b*/*v*
(*i*) *Mixed micelle*							
0			3.07	0.23	−0.16	0.07	−0.84
1			3.05	0.24	−0.18	0.06	−0.82
5			3.07	0.25	−0.18	0.07	−0.89
12			3.20	0.23	−0.16	0.09	−0.90
20			3.08	0.23	−0.14	0.09	−0.92
30			3.17	0.22	−0.14	0.10	−0.92
40			3.00	0.19	−0.12	0.08	−0.94
50			3.09	0.19	−0.12	0.11	−0.96
(*ii*) *Solvent modifier*							
20	Acetonitrile	5	3.21	0.21	−0.15	0.10	−0.90
20		10	2.80	0.25	−0.16	0.10	−1.01
20		15	2.57	0.19	−0.18	0	−0.89
20		20	2.20	0.16	−0.13	0	−0.97
20	Methanol	20	2.64	0.21	−0.13	0.11	−0.95
20	Propan-2-ol	20	2.40	0.20	−0.18	0	−0.92
20	Tetrahydrofuran	20	2.34	0.27	−0.15	0	−1.00

Sodium *N*-dodeconyl-*N*-methyltaurine, 50 m*M*.

of alkyl polyols (e.g. 1,2-alkanediols with C_4–C_8 alkyl chains) as hydrophobic modifiers produced small changes in the system constants for SDS micelles without obvious trends related to the concentration or structure of the diols [146].

An interphase model is able to explain the influence of surfactant and solvent properties on selectivity in MEKC [34,145,147]. The interphase is defined as the region surrounding the core of the micelle containing the polar head groups and possibly neighboring segments of the surfactant tail, as well as components of the electrolyte solution, organized into a loose structure on account of their proximity and attraction to the micelle interface. The actual boundaries between the core of the micelle and the interphase region, and the interphase region and the bulk electrolyte solution, are not well defined and may change with the electrolyte composition. The composition of the interphase is probably spatially heterogeneous, but since the interphase region is thin, solutes can readily explore all regions, resulting in an average effect when macroscopic properties are determined. The electrolyte composition in the interphase is probably different to that of the bulk solvent, and is controlled by short-range surface electrostatic forces. Likewise, the concentration of organic modifiers and additives in the bulk electrolyte may be different to that in the interphase region due to selective sorption by micelle surface groups. Retention results from the difference in solvation interactions of the interphase region to those of the bulk electrolyte solution.

Supporting evidence for the interphase hypothesis comes from several sources. The ratio of solute molecules to micelle aggregates is low, so there is no mass balance effect to force deeper penetration into the micelle. The solute environment in the micellar phase is polar as indicated by a comparison of surfactant micelle system constants to those for water–organic solvent distribution systems [34,147]. It is also at least partly aqueous, as indicated by the significant hydrogen-bond acidity of anionic micelles, which lack suitable hydrogen atoms for this interaction. The retention data for varied solutes is homogeneous with respect to the construction of the solvation parameter models, suggesting a uniform average solvation environment for all solute types. The interphase model anticipates the small change in system constants with absorption of non-ionic surfactants to form mixed micelles and the sorption properties of organic solvents leading to solvophobic changes in the system constants [144,145]. The outer surface of mixed micelles is made up of the anionic surfactant head groups and some fraction of the non-ionic surfactant. Most of the non-ionic surfactant is lodged in the micelle core, causing an increase in the micelle volume, but having relatively little effect on the composition of the interphase region. As observed, the cohesive energy of the interphase region is not significantly influenced by the entry of the non-ionic surfactant into the core of the ionic micelle. The small change in hydrogen-bond acidity is the result of association of water molecules in the region of the anionic surfactant head groups with the hydrogen-bond basic non-ionic surfactant chains protruding into the interphase region. The addition of organic solvents to the buffer reduces retention by lowering the difference in cohesive energy between the interphase region and the bulk electrolyte solution, and modifying the capacity of the interphase region for polar interactions by the selective sorption of the solvent to the micelle surface.

5. Supercritical fluid chromatography

The solvation parameter model has been employed to study the retention mechanism in subcritical and supercritical fluid chromatography with mobile phases based on carbon dioxide in open-tubular columns [148,149] and packed columns containing chemically bonded phases [150–152] and porous polymers [153–155]. The primary goal of most packed column studies was to provide an understanding of the role of solvent modifiers and additives on the retention mechanism for polar compounds. Carbon dioxide is a weakly solvating mobile phase for polar compounds. In the absence of solvent modifiers and additives the chromatography of these compounds is often impossible. Polar solvents and additives are also suitable masking agents to mitigate the unfavorable interactions between polar compounds and silanol groups on silica-based sorbents. Apart from carbon dioxide there is limited information available for mobile phases based on super-

critical fluid heptane [154] and 1,1,1,2-tetrafluoroethane [154,155].

A number of reasons contribute to the difficulty over the interpretation of more than general trends in the system constants. Mobile phase densities can vary from dense gas-like to liquid-like in supercritical fluid chromatography. The fluid density can vary along the column length and no secure method has been devised to determine the column hold-up time. Mixed retention mechanisms may prevail on silica-based sorbents and the uptake of mobile phase components by all types of stationary phases can physically and chemically alter the sorption properties of the stationary phase. Some studies are possibly compromised by weak retention of most solutes [150] or inadequate selection of descriptors [151]. The wide range of possible mobile phase densities complicates selection of the model type. Eq. (4) using the *L* solute descriptor for the cavity formation and dispersion interaction term has been preferred over Eq. (3) using *V*, even for systems with liquid-like densities. In a few cases this was justified by the observation that Eq. (3) provided a poorer statistical model [148]. On the other hand, the numerical values of all system constants change with the choice of the model equation [153]. In virtually all studies, Eq. (4) provides good statistical models but the chemical interpretation of the system constants is not always logical without invoking special circumstances. A question remains whether the special circumstances are physically meaningful or the product of an abstract mathematical model. Some general trends seem relatively secure and are discussed below.

For supercritical fluid carbon dioxide at dense gas-like densities on an open-tubular column coated with a low polarity stationary phase, changes in selectivity with variation in temperature and pressure were small (Table 12) [148]. Increasing pressure (density) at a constant temperature reduces the *l* and *s* system constants and increases the *e* system constant in an approximately linear manner. Increasing temperature at a constant pressure (resulting in a decrease in density) reduces the *a* system constant and increases the *b* system constant (becomes less negative) in an approximately linear manner. Carbon dioxide is clearly a weak solvent and a significant portion of the value of the *s* and *a* system constants and their change with temperature can be accounted for by stationary phase properties, analogous to the observed system constants for similar poly(dimethylsiloxane) stationary phases in gas chromatography. Some of the observed changes could be accounted for by the uptake of carbon dioxide and change in volume of the stationary phase. The most likely contribution attributed to carbon dioxide at the prevailing mobile phase densities is changes in dispersion interactions in the mobile phase. There is some difficulty over the sign of the *b* system constant, which, although small, suggests that carbon dioxide is a stronger hydrogen-bond acid than the stationary phase. This is illogical of course, and was explained by attributing the negative value to weak hard Lewis acid interactions for carbon dioxide. Adding methanol to carbon dioxide at low densities resulted initially in a large decrease in the *s* system constant and a continuous reduction in the *l* and *b* system constants [149]. These results tend to indicate

Table 12
Effect of pressure and temperature in supercritical fluid chromatography on the system constants of the solvation parameter model with carbon dioxide as the mobile phase

Approximate pressure (atm.)	Temp. (°C)	System constants				
		l	*e*	*s*	*a*	*b*
75.7	100	0.361	0.05	0.16	0.21	−0.06
89.4	100	0.330	0.06	0.15	0.21	−0.06
103.2	100	0.299	0.08	0.13	0.19	−0.06
116.9	100	0.267	0.10	0.12	0.16	−0.08
89.4	60	0.315	0.04	0.16	0.27	−0.13
89.4	80	0.339	0.06	0.14	0.23	−0.08
89.4	120	0.316	0.08	0.13	0.16	−0.05

5 m×50 μm open-tubular column coated with the poly(methylsiloxane) stationary phase SB-Methyl-100.

that, for open-tubular columns, simultaneous modification of the solvation properties of the stationary and mobile phases by the modifier plays a larger role in changing selectivity than masking active silanol groups by the modifier, which is more important for packed columns containing silica-based sorbents [149–152].

The changes in system constants with composition of a binary mixture of carbon dioxide and 1,1,1,2-tetrafluoroethane on a column containing a porous polymer sorbent are illustrated by the results in Fig. 10 [155]. Adding 1,1,1,2-tetrafluoroethane to carbon dioxide influences selectivity by a nearly linear negative change in the *l*, *s* and *b* system constants and a modest increases in the *e* system constant. A significant portion of the magnitude of the system constants is certainly due to the sorption properties of the stationary phase. Also, it is likely that the variable uptake of mobile phase components by the stationary phase at different mobile phase compositions is a significant contributor to the change in system constants with mobile phase composition. Consequently, the mobile phase contribution to the change in system constants in Fig. 10 is difficult to isolate, but it seems likely that 1,1,1,2-tetrafluoroethane is more cohesive, dipolar and hydrogen-bond acidic than carbon dioxide and a very weak hydrogen-bond base. Note that in making these qualitative assessments that the density of the mixed mobile phase changes in a convex manner from 0.39 to 0.99 (g/ml) with a maximum value of about 1.11.

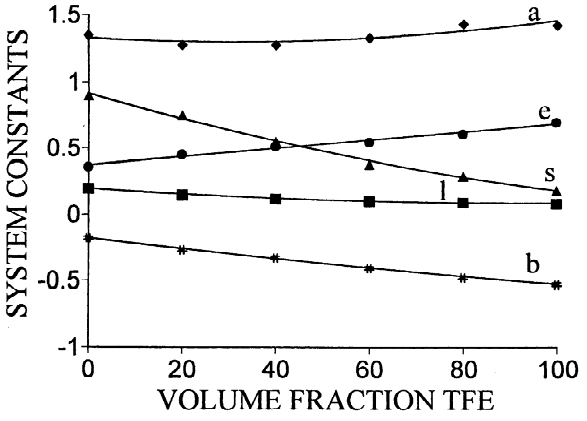

Fig. 10. System constants for a binary mixture of carbon dioxide and 1,1,1,2-tetrafluoroethane on a porous polymer stationary phase. Column 25 cm×4.6 mm I.D. Jordi-Gel RP-C_{18} with a 5 μm average particle diameter. The total fluid flow-rate was 1.0 ml/min, backpressure 200 bar and temperature 125°C.

6. Conclusions

In its short life the solvation parameter model has had a considerable impact on our understanding of the retention mechanism of non-ionic compounds in chromatography. Initial studies focused on the interpretation of the system constants of the solvation parameter model in terms of stationary and mobile phase properties and the use of chromatographic systems for the determination of solute descriptors. The use of the solvation parameter model for system selection and selectivity optimization is an emerging application for method development. Future studies are expected to build on these early developments with a view to create a general approach for structure-driven, computer-aided method development. A unique capability of this approach is the possibility to simulate separations in gas, liquid and micellar electrokinetic chromatography for the same mixture. This will allow method selection to be incorporated into the method development process. A number of factors need to be addressed in more detail before the solvation parameter model is likely to become a general tool in chromatography. More research groups need to gain experience in using the methodology. In liquid chromatography the importance of shape selectivity requires evaluation and more convenient methods of handling partially ionized compounds are needed. Improved methods of estimating solute descriptors from structure for complex molecules is required to lower the inertial barrier to the use of the solvation parameter model for predicting chromatographic properties for new or poorly characterized compounds encountered in industry. At the same time fundamental studies should continue to refine the relationship between controlled and systematic variations in stationary or mobile phase properties and their influence on changes in the contribution of intermolecular interactions to retention. For now a solid foundation has been built but a significant amount of work remains to be accomplished to claim either intellectual or procedural maturity.

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