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System Selectivity Cube: A 3D Visualization Tool for Comparing the Selectivity of Gas Chromatography, Supercritical-Fluid Chromatography, High-Pressure Liquid Chromatography, and Micellar Electrokinetic Capillary Chromatography Systems

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A three-dimensional visualization tool termed the system selectivity cube (SSC) has been developed to aid in the selection of chromatography systems. The most effective way to change the resolution of a complex mixture is to change the selectivity of the separation. The SSC allows efficient identification of systems of differing selectivity. Our approach is based on comparisons of the energetics of two systems and in this way is somewhat akin to the $\kappa-\kappa$ plots of Horvath et al. Our comparisons, however, are based on linear solvation energy relationships (LSERs) or other multiparameter models of retention. Our approach unifies LSERs, $\kappa-\kappa$ plots, and the "effective selectivity" concept introduced by Zhao and Carr. The utility and versatility of the SSC is demonstrated with LSERs for 74 micellar electrokinetic chromatography (MEKC) systems taken from the literature. The SSC groups those systems which provide little or no difference in selectivity and those systems which do differ in their selectivities. We anticipate that this approach will be useful for selecting replacement columns, systems that may offer better results for difficult separations, and orthogonal phases for 2D gas chromatography (GC) and reversed phase liquid chromatography (RPLC) separations.

In order to quantify components in a mixture, the compounds must be adequately resolved. Resolution (R_s) can be increased in several ways, guided by the general resolution equation:

$$R_s = \frac{\sqrt{N}}{4}\left(\frac{\alpha - 1}{\alpha}\right)\left(\frac{k_b}{1 + k_b}\right) \quad (1)$$

where N is the number of theoretical plates, α is the selectivity factor, and k_b is the retention factor of the more retained solute. It is possible to increase the resolution by increasing N via an increase in the length of the column, but this produces a concomitant increase in analysis time. Increasing the retention factor can also increase resolution, particularly if k_b is initially very small, but this again increases the analysis time. Therefore, one of the most useful ways to increase resolution is to improve selectivity, α. To do so, however, requires an ability to rapidly select chromatographic systems or conditions that produce different selectivities. We report here an efficient method for selecting systems that may provide different selectivities compared to a system that is failing to provide adequate resolution.

Homo-, Homeo-, and Heteroenergetic Retention. Horvath et al.[1] developed a method for comparing the energetics governing retention of solutes on two different chromatographic systems. Specifically, log k values for several solutes measured on one system are plotted and correlated against log k values for the same solutes on another system. This type of plot is called a $\kappa-\kappa$ plot. We note here that throughout the article we are taking the word "system" to be any combination of mobile and stationary phases in high-pressure liquid chromatography (HPLC), gas chromatography (GC), or supercritical-fluid chromatography (SFC) and any combination of buffer and pseudostationary phase in micellar electrokinetic chromatography (MEKC). Depending upon the results of the correlation, the relationship of the two systems is assigned to one of three categories: heteroenergetic, homeoenergetic, or homoenergetic. A poor correlation, with points exhibiting scatter from the best fit line, is said to exhibit a "heteroenergetic" relationship, indicating that the energetics governing retention of the two systems are different. Therefore, they would likely produce different selectivities, possibly even different elution orders, for a set of compounds. When the two systems produce a good correlation they are said to exhibit a "homeoenergetic" relationship. The systems may produce slightly different selectivities but would exhibit similar trends in elution order. They would likely result in similar resolution, or lack thereof, in problematic separations. The special case in which log k values of two systems are well correlated and the correlation has a unity slope is termed a "homoenergetic" relationship. Systems exhibiting homoenergetic

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(1) Melander, W.; Stoveken, J.; Horvath, Cs. *J. Chromatogr.* **1980**, *199*, 35–56.

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relationships operate on identical energetics of retention and will not produce useful differences in selectivities.

These energetic relationships can be used to guide system selection when confronted with a difficult separation or to aid in selecting "orthogonal" systems for use in 2D HPLC. Such comparisons, however, require the analysis of identical solute sets on every system of interest. It is unlikely that retention factors for the same test solutes recorded on the particular systems of interest under comparable conditions can be found in the literature, and measuring them could be time-consuming. Furthermore, comparisons are carried out on just two systems at a time, which does not allow for the simultaneous comparison of multiple systems.

Linear Solvation Energy Relationships. Retention models such as linear solvation energy relationships (LSERs)[2] and Snyder and Dolan's hydrophobic subtraction model (HSM)[3−6] do not require identical solute sets. They use large sets of solute retention factors (from dozens to hundreds of compounds) to quantify the impact of intermolecular interactions on solute retention, and thus general retention energetics, governing retention on the systems of interest. LSERs are of the form:[2]

$$\log k = aA + bB + eE + \mathrm{sS} + vV + c \qquad (2)$$

where k is the retention factor of a solute and A, B, S, E, and V quantify the potential of that solute to interact with the system via specific intermolecular interactions. The "A" parameter represents a solute's ability to donate a hydrogen bond (i.e., HB acidity). "B" is a measure of the solute's ability to accept a hydrogen bond (i.e., HB basicity). "E" represents the solute's polarizability in excess of that of a comparably sized *n*-alkane. "S" represents an indistinguishable blend of the solute's polarity and polarizability, and "V" is the McGowan volume[7] of the solute.

The coefficients a, b, e, s, and v represent the difference in the ability of the mobile and stationary phases to interact with solutes via specific intermolecular interactions. Consequently, they are complementary to the solute parameters they modify. For example, because "A" represents the solute hydrogen bond acidity, the a-coefficient reflects the difference in hydrogen bond basicity of the two phases. The b-, e-, and s-coefficients are interpreted in a similar manner. The v-coefficient represents the difference in interaction abilities of the two phases based on the volume of the solute. It is a blend of the energetics of cavity formation and dispersion forces. The c-coefficient is a solute independent term related to the phase ratio and other system constants.

LSERs and System Selectivity. Ishihama and Asakawa used LSER coefficients to construct vectors in five-dimensional space and used the angle between vectors to assess the similarity of two systems.[8] Abraham and Martins used the distance between vectors, L, as the metric for comparing two systems.[9] Lázaro et al. introduced the d-parameter, which is similar to L except it is defined using normalized vectors.[10] Fuguet et al. used principle component analysis of LSER coefficients along with radial distribution plots to assess the selectivity differences between pseudostationary phases in electrokinetic chromatography.[11]

We have developed a comparison scheme based on LSERs that ultimately generates the same type of relationships as those of Horvath et al. We do so because LSERs are available for a wide variety of separation systems across multiple chromatographic techniques.[12] We note, however, that this approach, like the ones cited above, is applicable to any multiple parameter model of retention.

THEORY AND METHODOLOGY

Unifying LSERs with the Energy Relationships of Horvath *et al.* Because LSERs reflect the energetics of intermolecular interactions and their influence on retention, it seems clear that, according to the scheme of Horvath et al., two systems with similar LSER coefficients will exhibit a homo- or homeoenergetic relationship, while two systems with very different LSER coefficients will exhibit a heteroenergetic relationship. Below, we unify LSERs and the $\kappa-\kappa$ plots of Horvath et al. To do so, it is necessary to consider the work of Zhao and Carr.[13] They state that if a system's retention energetics are described by two or more parameters (i.e., the lower case coefficients in the LSERs), then the comparison of two systems cannot be based on the magnitude of the individual coefficients but rather must be based on the ratio of those coefficients. This is explained in more detail in the original reference and in the Supporting Information.

We note that others had used system constant ratios to compare separation systems before Zhao and Carr. For example, Abraham et al. discussed the fact that even though several RPLC octadecylsilane columns had different magnitudes for their LSER coefficients, when the coefficients were normalized to the v-coefficient, the columns appeared to be much more similar.[14] In fact, Zhao and Carr in an earlier publication noted that the v-coefficient in RPLC systems vary considerably depending on mobile phase composition, and thus, they suggested normalizing all the other coefficients to it.[15] However, it was in a subsequent manuscript that they showed mathematically why it is necessary to do so (see the Supporting Information for details).[13]

We have recreated the algebraic method of Zhao and Carr with a complete LSER equation. If two different systems, 1 and 2, have been characterized by LSER equations, they can be represented as

$$\log k_1 = b_1B + a_1A + s_1S + e_1E + v_1V + c_1 \qquad (3)$$

$$\log k_2 = b_2B + a_2A + s_2S + e_2E + v_2V + c_2 \qquad (4)$$

(2) Abraham, M. H.; Ibrahim, A.; Zissimos, A. M. *J. Chromatogr., A* **2004**, *1037*, 29–47.
(3) Snyder, L. R.; Dolan, J. W.; Carr, P. W. *J. Chromatogr., A* **2004**, *1060*, 77–116.
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(14) Abraham, M. H.; Rosés, M.; Poole, C. F.; Poole, S. K. *J. Phys. Org. Chem.* **1997**, *10*, 358–368.
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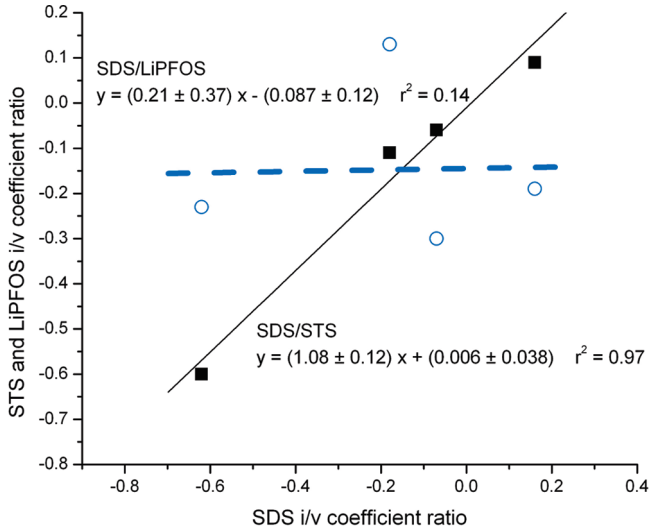

Figure 1. A plot of the correlation of STS and LiPFOS versus SDS. The axes are defined as the *i*/*v* LSER coefficient ratio, where *i* = *a*, *b*, *e*, or *s*. STS and SDS (■) are highly correlated with a slope statistically equal to 1.0 and an intercept statistically equal to 0.0, indicating a homo- or homeoenergetic relationship, depending on the volume coefficient ratio (which in this case is 1.05, essentially indicating a homoenergetic relationship). Conversely, the LiPFOS and SDS (○) ratios are poorly correlated, indicating a heteroenergetic relationship. These conclusions match chemical intuition as STS and SDS are structurally similar while LiPFOS and SDS are different.

Here, systems 1 and 2 could represent MEKC systems using, for example, lithium perfluorooctane sulfonate (LiPFOS) and sodium dodecyl sulfate (SDS), respectively. Combining these equations as shown in the Supporting Information yields

$$\frac{\log k_1}{v_1} = \frac{\log k_2}{v_2} + \left(\frac{b_1}{v_1} - \frac{b_2}{v_2}\right)B + \left(\frac{a_1}{v_1} - \frac{a_2}{v_2}\right)A + \left(\frac{s_1}{v_1} - \frac{s_2}{v_2}\right)S + \left(\frac{e_1}{v_1} - \frac{e_2}{v_2}\right)E + \left(\frac{c_1}{v_1} - \frac{c_2}{v_2}\right) \quad (5)$$

This general equation is used as a starting point to determine specific relationships of retention of two systems under different conditions. The volume system coefficient is chosen to be the denominator according to convention,[13−18] but the conclusions are the same if any system coefficient is chosen.

Next, consider the special case in which

$$\frac{b_1}{v_1} = \frac{b_2}{v_2} \quad \text{and} \quad \frac{a_1}{v_1} = \frac{a_2}{v_2} \quad \text{and} \quad \frac{s_1}{v_1} = \frac{s_2}{v_2} \quad \text{and} \quad \frac{e_1}{v_1} = \frac{e_2}{v_2} \quad (6)$$

In this case, eq 5 simplifies to

$$\log k_1 = \frac{v_1}{v_2}\log k_2 + \left(\frac{c_1}{v_1} - \frac{c_2}{v_2}\right) \quad (7)$$

Thus, if all the system coefficient ratios are equal, retention on one system is linearly related to retention on the other. The slope of this correlation is v_1/v_2.

(16) Fu, C.; Khaledi, M. *J. Chromatogr., A* **2009**, *1216*, 1891–1900.
(17) Fu, C.; Khaledi, M. *J. Chromatogr., A* **2009**, *1216*, 1901–1907.
(18) Zhang, Y.; Carr, P. W. *J. Chromatogr., A* **2009**, *1216*, 6685–6694.

Equations 5 and 7 can easily be related to the classification scheme of Horvath et al.: (1) Homoenergetic relationships occur when the above conditions are met and $v_1 = v_2$, such that the relationship of the two systems is given by eq 7 with a unity slope. (2) Homeoenergetic relationships occur when the condition of equal ratios exists but $v_1 \neq v_2$ such that a nonunity slope in eq 7 results. (3) Heteroenergetic relationships occur when the coefficient ratios are not equal and therefore eq 5 cannot be simplified to eq 7. In this case, retention on one phase is not related to retention on the second because the characteristics of the individual solutes (*B*, *A*, *S*, and *E*) still appear in the equation.

In the case where coefficient ratios are not equal but rather related by some scalar quantity, *m*, as shown in eq 8:

$$\frac{i_1}{v_1} = m\frac{i_2}{v_2} \quad (8)$$

where "*i*" represents the system coefficients *a*, *b*, *s*, and *e*, substituting the relationship shown in eq 8 into eq 5 yields

$$\log k_1 = \frac{v_1}{v_2}\log k_2 + v_1\left(\frac{c_1}{v_1} - \frac{c_2}{v_2}\right) + (1 - m)(b_1B + a_1A + s_1S + e_1E) \quad (9)$$

In contrast to eq 7, this relationship is characterized by the presence of solute parameters. The relationship is solute dependent, leading to scatter in a κ−κ plot and therefore a heteroenergetic relationship of the two systems.

When the coefficient ratios of two systems are related linearly with a nonzero intercept such that

$$\frac{i_1}{v_1} = \frac{i_2}{v_2} + X \quad (10)$$

Substitution of eq 10 into eq 5 yields

$$\log k_1 = \frac{v_1}{v_2}\log k_2 + v_1\left(\frac{c_1}{v_1} - \frac{c_2}{v_2}\right) + v_1X(B + A + S + E) \quad (11)$$

This equation again includes solute dependent parameters, which induces scatter in a κ−κ plot, indicating that a heteroenergetic relationship exists between systems 1 and 2.

Determining the Energetic Relationship between System Coefficients. Equations 6−11 make it clear that the relationship of the energetics of retention can be determined by correlating LSER coefficients for two different systems. Plotting the system coefficient ratios *a*/*v*, *b*/*v*, *e*/*v*, and *s*/*v* of one system against another, as in Figure 1, illustrates two of the types of relationships that can exist. In this plot, the ratio of LSER coefficients for MEKC systems using LiPFOS and sodium tetradecyl sulfate (STS) as the pseudostationary phase are both plotted against those for an SDS pseudostationary phase. The LSER coefficients were taken from a large literature compilation of MEKC LSERs.[16] LiPFOS was chosen as one of the systems because it is generally different than most other surfactants as demonstrated by Fuguet et al. using principle component analysis of LSER coefficients.[11]

Linear correlations such as those shown in Figure 1 result in statistical parameters that characterize the correlation, including the slope, intercept, and the square of the correlation coefficient (r^2). A correlation with a high r^2 value, a slope close to unity, and an intercept close to zero, like SDS and STS in Figure 1, represents a homeoenergetic relationship (homoenergetic if $v_{sts} = v_{sds}$). A poor correlation, as illustrated by the comparison of SDS and LiPFOS, indicates a heteroenergetic relationship of the two systems.

Thus, the energetics of retention for two systems can be compared using the slope, intercept, and correlation coefficient resulting from the correlation of LSER coefficient ratios. In this way, we have unified the LSER formalism for characterizing chromatographic systems with the $\kappa-\kappa$ plots of Horvath et al. for comparing the energetics of retention.

Ishihama and Asakawa indicated in their analysis of lipophilicity scales that correlations should exist between LSER coefficient ratios for "analogous" systems, but they did not relate their work to that of Horvath et al.[8] Poole and Poole applied Ishihama and Asakawa's approach as well as principle component analysis and the *d*-parameter of Lázaro et al. to compare the selectivity of GC phases using LSER coefficients.[19] These studies, and others like them aimed at comparing the selectivities of multiple systems simultaneously, are related in spirit, but not in methodology, to that presented here.

3D Visualization of Simultaneous System Comparisons. The form of direct comparison detailed above is still limited to considering just two systems at a time. In order to compare many systems simultaneously, we have created a three-dimensional plot that we call the system selectivity cube (SSC). The name is meant to recognize Snyder's valuable contributions to the study of chromatographic selectivity resulting from his solvent selectivity triangle (SST).[20] In the case of the SSC, a three-dimensional plot is created as shown in Figure 2. The axes of the plot are the slope, intercept, and r^2 value resulting from the correlation of LSER ratios of two systems. Each comparison of two systems is therefore represented by a single point in 3D space within the SSC. The point with a slope = 1.00, intercept = 0.00, and r^2 = 1.00 represents an ideal homeoenergetic relationship. Therefore, any spheres (i.e., glyphs) in close proximity to this point denote systems with at least a homeoenergetic relationship and possibly homoenergetic if $v_1 = v_2$. The farther a given glyph falls from this homeoenergetic region, the greater the difference in the energetics of retention for the two systems being compared and thus the greater the likelihood for differences in selectivity.

Because a homoenergetic relationship is a special case in which the same conditions as a homeoenergetic relationship exist *and* the volume coefficients of the two systems are equal, we developed a way to add this dimension of information to the SSC. The ratio of the volume coefficients is depicted by spikes attached to the glyphs with lengths reflecting their ratios, using the larger *v*-coefficient as the numerator so as to always have a ratio greater than or equal to 1.00. Shorter spikes (or essentially spherical glyphs) indicate a ratio closer to unity, while longer spikes indicate a larger ratio (see Figure S-1 in the Supporting Information). If a glyph is in close proximity to slope = 1.00, r^2 = 1.00, and intercept = 0.00 *and* exhibits very short spikes, indicating the volume coefficients of the two systems are close to equal, then the two systems have a homoenergetic relationship. The relationship of the energetics of retention for two systems based on the correlation of their LSER system coefficient ratios is summarized in Table 1.

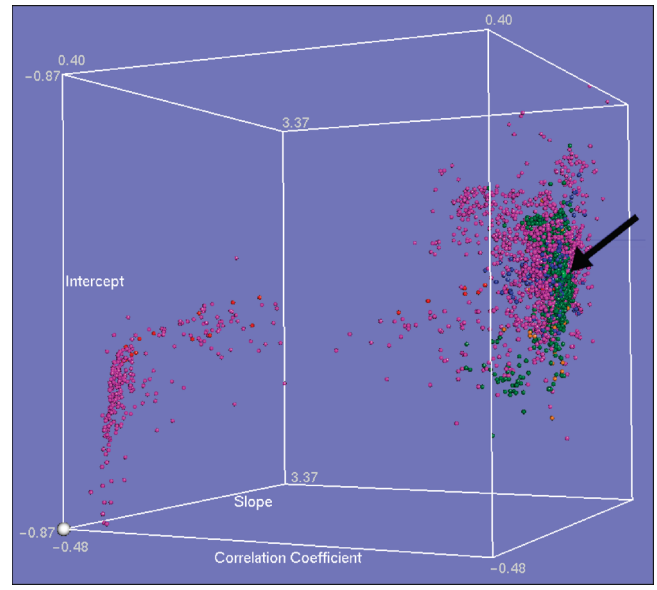

Figure 2. The SSC created from 74 MEKC systems[16] showing all glyphs. The point representing an ideal homeoenergetic relationship has an r^2 = 1.00, intercept = 0.00, and slope = 1.00. It is therefore on the rightmost face of the cube, roughly in the center and indicated with an arrow. As is evident from the figure, many system comparisons congregate around this point, indictating that many systems in MEKC, although subtly different, operate on similar energetics of retention. The correlation coefficient spans 0.00 to 1.00 from left to right and is not labeled for clarity. The spikes denoting the v_1/v_2 ratio are also omitted for clarity.

Effective Selectivity. As discussed in the introduction, the aim of the SSC is to aid in identifying chromatographic systems that may provide useful differences in selectivity. In order to more accurately define "useful differences in selectivity" we incorporate the concept of "effective" selectivity proposed by Zhao and Carr.[13] Building off the energetic relationships of Horvath et al., they classify system comparisons by whether or not they provide effective differences in selectivity. Homoenergetic systems will produce essentially identical separations. In a homeoenergetic relationship, the retention of solutes could change between systems but not differentially. This could produce a chromatogram that was compressed or expanded, but the elution order remains the same. Because large changes to selectivity are the most successful way to increase resolution, effective differences in separation more likely occur when switching to a heteroenergetic system.

Simulated chromatograms help to illustrate these relationships. On the basis of literature reports of MEKC LSERs[21,22] and solute

(19) Poole, C. F.; Poole, S. K. *J. Sep. Sci.* **2008**, *31*, 1118–1123.
(20) Snyder, L. R. *J. Chromatogr.* **1974**, *92*, 223–230.
(21) Trone, M. D.; Leonard, M. S.; Khaledi, M. G. *Anal. Chem.* **2000**, *72*, 1228–1235.
(22) Trone, M. D.; Khaledi, M. G. *J. Microcolumn Sep.* **2000**, *12*, 433–441.

Table 1. Summary of the LSER Coefficient Ratio Correlations and the Corresponding Relationship of the Energetics of Retention for Two Systems

results for correlation of s/v, a/v, b/v, and e/v for two systems					
r^2	slope	intercept	$v_1 = v_2$	interpretation	selectivity
high	= 1.00	= 0.00	yes	homoenergetic	ineffective
high	= 1.00	= 0.00	no	homeoenergetic	ineffective
high	≠ 1.00	= 0.00	yes or no	potentially heteroenergetic	potentially effective
high	= 1.00 or ≠ 1.00	≠ 0.00	yes or no	potentially heteroenergetic	potentially effective
low	= 1.00 or ≠ 1.00	= 0.00 or ≠ 0.00	yes or no	potentially heteroenergetic	potentially effective

parameters[23] shown in Table S-1 (see the Supporting Information), we created the simulated chromatograms shown in Figure 3. The correlation of SDS and STS indicates that the two systems have a homeoenergetic relationship (and very nearly homoenergetic), as discussed in relation to Figure 1. From Figure 3, it is clear that choosing homeoenergetic systems may change selectivity and resolution but not in the dramatic ways necessary to change elution order and thus resolve overlapping peaks in complex separations. The simulated chromatograms of SDS and LiPFOS, which exhibit a heteroenergetic relationship, show differences in elution order. In this way, they demonstrate the effective differences in selectivity suggested by Zhao and Carr. The SSC makes it easy to visually identify homo-, homeo-, and heteroenergetic systems and thus helps select different systems when trying to improve separations.

Methodology. Figure 2 shows the SSC created from Fu and Khaledi's tabulation of the LSER coefficients of 74 MEKC systems.[16] They use a selectivity triangle scheme akin to Synder's solvent selectivity triangle[20] to assign the 74 systems to one of four groups, denoted as A, B, C, and D. The groupings are based on where the systems fall within the micellar selectivity triangle (MST). The idea behind this approach is that pseudostationary phases within a particular group should all demonstrate similar retention characteristics.

To analyze the data using our SSC, the coefficient ratios of the first system in the list (SDS in this case) are correlated against systems 2−74 in their compilation. Then, the second system is correlated against systems 3−74, and so on. In this way, each comparison of two systems is plotted only once (e.g., 2 vs 3, but not 3 vs 2). If both comparisons of two systems were plotted, the SSC would display a secondary point for each comparison and would ultimately display twice the necessary number of points. For 74 systems, the SSC contains 2701 glyphs. We arbitrarily chose to display those glyphs which compare a lower numbered system to a higher numbered system. This should not play a role in the conclusions drawn from the SSC as the two comparisons are related. The slope of one is equal to the reciprocal slope of the other, and the intercept of one is equal to the negative slope multiplied by the intercept of the other. Regardless of the order of the correlation, highly correlated systems will have high r^2 values and dissimilar systems will have low r^2 values.

In order to produce a SSC from LSER system coefficients, the coefficients are exported from Microsoft Excel in a text format. Mathematica version 7 is used to perform a linear least-squares regression to produce a text spreadsheet of the pertinent regression results. The LINEST() function in Microsoft Excel is also capable of performing the regression. The regression results (slope and the uncertainty in the slope, intercept and the uncertainty in the intercept, and r^2), volume ratio, and the group to which each system was assigned by Fu and Khaledi are read into the SSC program for each comparison. The SSC program is written in C++ with OpenGL graphics libraries.[24] Color is used to indicate comparisons of systems within the same group, and the length of spikes denotes the volume ratios. The user has control of viewing the SSC from any angle as rotation, translation, and zoom are controlled with a mouse. A free version of the SSC analysis and visualization program is available at http://artsci.drake.edu/urness/download/ssc.html.

SSC Manipulation. While the SSC containing 2701 points is much easier to view than 2701 individual slopes, intercepts, and r^2 values in a spreadsheet, it does contain a lot of data, and the desired results could be difficult to discern. In addition to the zooming, rotating, and translating features mentioned previously, the range displayed on each axes (slope, intercept, and r^2 value) can be adjusted to reduce the number of glyphs shown and focus only on comparisons of interest. This is done using the SSC manipulation window shown in Figure 4. For example, to view only heteroenergetic relationships, the maximum r^2 value can be lowered so that only poorly correlated systems are displayed (see Figure S-2 in the Supporting Information). The points shown for any filtered views take into account the uncertainties in the slope and intercept. For example, if the program is manipulated to show only those points with a slope between 0.90 and 1.00, a point whose slope is 1.05 ± 0.10 will be shown on the SSC.

The SSC is also capable of only showing desired comparisons. For example, if the user wants to compare system 10 in this particular listing of LSER coefficients to systems 5, 20, 36, 52 and 74, this can be done using the individual systems comparison tool in the user interface box (see Figure 4). The result is shown in Figure S-3 in the Supporting Information.

The SSC also shows comparisons of systems that are within a specific group using the same color glyphs in the cube. The grouping feature can be used for a wide variety of applications. For example, as discussed above, Fu and Khaledi proposed that each of the 74 MEKC pseudophases could be sorted into four groups: A, B, C, and D. If only group A is selected in the user interface box, the SSC displays only those glyphs which compare one system in group A to another system in that group (see Figure 5a). These groupings are helpful for the comparison of the SSC to the MST. According to the theory underlying system selectivity

(23) Poole, C. F.; Poole, S. K.; Abraham, M. H. *J. Chromatogr., A* **1998**, *798*, 207–222.

(24) Shreiner, D.; Woo, M.; Neider, J.; Davis, T. *OpenGL Programming Guide: The Official Guide to Learning OpenGL, Version 2.1*, 6th ed.; Addison-Wesley Professional: New York, 2007.

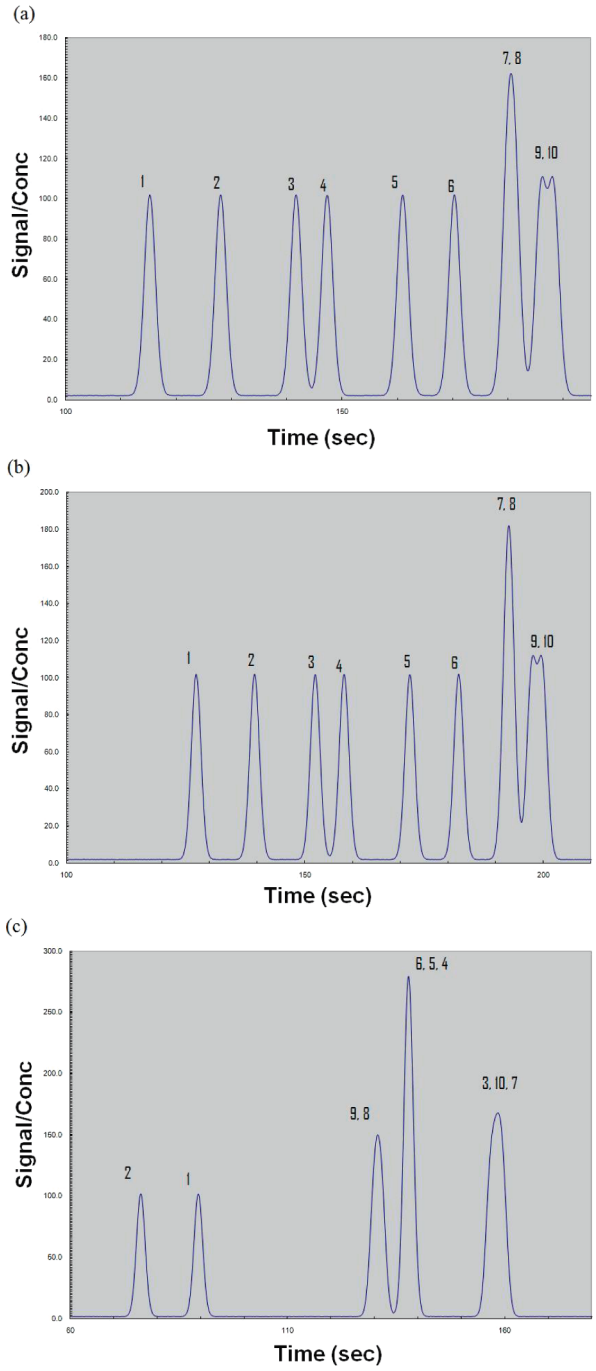

Figure 3. Simulated chromatograms of 10 solutes given in Table S-1 in the Supporting Information with (a) SDS, (b) STS, and (c) LiPFOS. Note the elution order is identical among parts a and b, two homoenergetic systems, but differs greatly among parts a and c, two heteroenergetic systems. To calculate retention times from predicted log k values, a dead time (t_m) of 74 s was arbitrarily chosen.

triangles like the MST, systems within the same group should produce similar selectivities. Therefore, points involving two systems from the same group should exhibit a homeoenergetic or homoenergetic relationship. In general, the groupings of Khaledi and Fu created points in the homeoenergetic region of the SSC. However, there are some cases in which systems within the same group are shown to have a heteroenergetic relationship according to their position on the SSC (See Figure 5b). This was particularly true of group B systems. Group B contains some SDS-

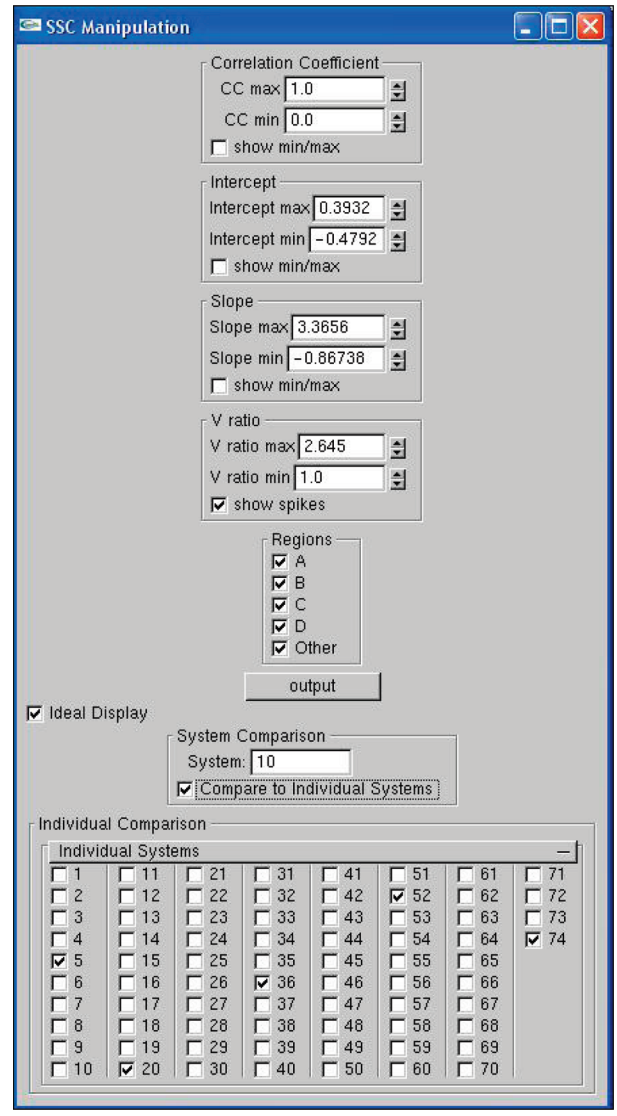

Figure 4. The user interface showing the options and features of the SSC described in the text.

containing pseudophases and some LiPFOS-containing pseudophases. The comparisons between SDS- and LiPFOS-containing system are generally plotted in the heteroenergetic region of the SSC. This suggests that perhaps systems in group B could be further divided into two subgroups. In addition, the SSC contains points involving systems that were classified as belonging to different groups that are shown to have a homeoenergetic relationship. For example, system 17 in ref 16 is classified in group D. However, comparisons of system 17 to the group C systems are plotted in the homeo- or homoenergetic region of the SSC.

While our interest in the groupings is to analyze the energetics of selectivity and thereby identify similar and dissimilar systems, we imagine that this grouping feature could also be used to categorize systems by cost, system type, or any other pertinent user-defined category.

DISCUSSION

The SSC, and any system classification scheme, can only predict general differences in selectivity. In order to effect a change in selectivity in two systems for a specific solute set, the

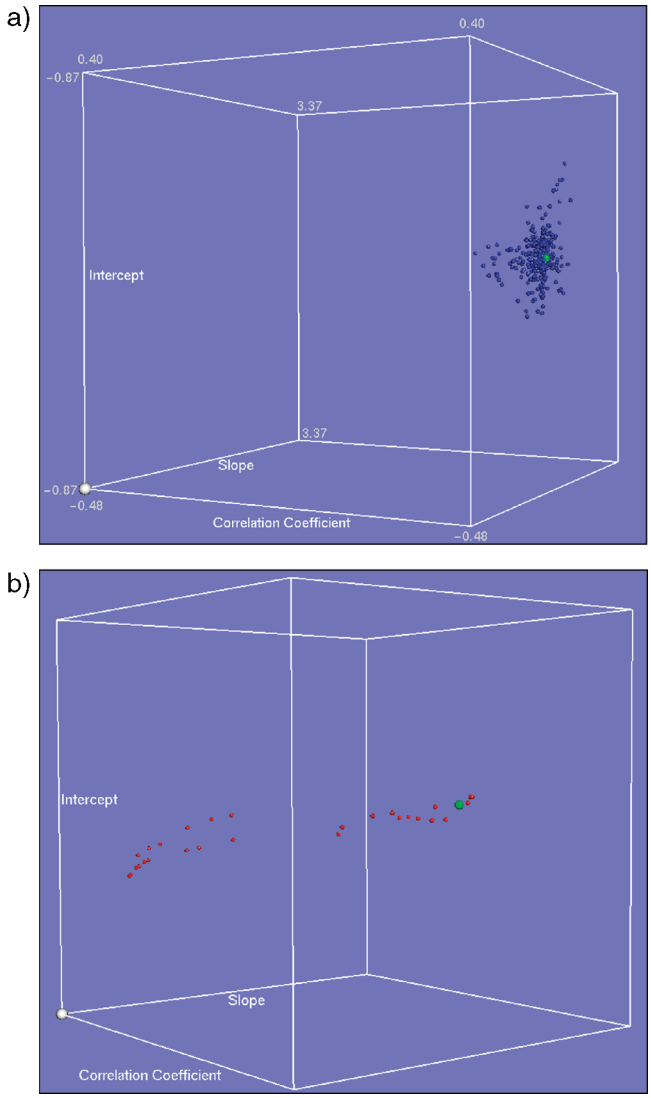

Figure 5. (a) The SSC created from 74 MEKC systems showing only those points which compare two systems in Group A of ref 16. Note that most of the systems are in the homeoenergetic region of the SSC, but some appear to be sufficiently far away to be considered heteroenergetic. (b) Comparisons of systems within Group B of ref 10 indicate that some systems within the group display heteroenergetic retention, suggesting that the MEKC systems within that group demonstrate different energetics of retention. The correlation coefficient axis spans 0.00 to 1.00 from left to right and is not labeled for clarity. The spikes denoting the v_1/v_2 ratio are also omitted for clarity.

solute set must take advantage of the corresponding system properties that make the two systems chemically distinct. This mirrors Giddings' concept of dimensionality[25] in both the system and sample set. Sample dimensionality is defined as the number of variables required to distinguish the components in a sample. The solute parameters may be thought of as the dimensions of a sample. Only when the solutes in the sample differ in at least one dimension and the two systems differ in the corresponding dimension(s) will there be a change in selectivity. For example, suppose two systems are found to exhibit a heteroenergetic relationship and that this relationship is due almost exclusively to a large difference in their b/v ratios (i.e., the other ratios are the same or strongly covary). In such a case, the retention of solutes with $B = 0$ will be similar even if the other solute parameters are different, despite the apparent heteroenergetic relationship of the systems. In order for the solutes to be retained in a differential manner, they must take advantage of the corresponding property (or properties) that make the two systems chemically different.

The interplay between the particular characteristics of the solute and the system will always have an impact on retention. Therefore schemes that classify systems, like the SSC, Khaledi and Fu's MST,[16,17] and Carr and Zhang's[18] selectivity triangle for over 300 RPLC systems based on the HSM,[3] can only predict potential differences in selectivity assuming that the solute set represents a broad range of interaction abilities. However, further work on the SSC will be aimed at allowing classification and comparison of systems tailored to more specific solute characteristics. For instance, if the solutes in a mixture differ primarily in their basicities (B), the LSER (or HSM) coefficients could be weighted prior to the correlations so that the position of comparisons within the SSC are dictated largely by system acidity (b).

Advantages of the SSC. Perhaps the most significant advantage of the SSC is that LSERs can be used as the basis for their construction. This is advantageous because a large number of systems have already been classified by LSERs.[12] Additionally, LSER equations are theoretically more universal than a small set of individual retention factors used to construct $\kappa-\kappa$ plots, and LSERs do not require identical solute solutes whereas $\kappa-\kappa$ plots do. LSERs also add reliability to the comparisons, as they are sometimes based on hundreds of different solutes. Therefore, they can be more broadly representative of the retention energetics of a system than those that classify systems with just a few solutes.

The SSC, furthermore, makes use of all five LSER system coefficients simultaneously in each comparison, while triangle methods are restricted to using four coefficients for one plot.[16−18] The fact that one coefficient has to be ignored to create triangle plots is often regarded as unimportant as most systems tend to be grouped similarly regardless of which three of the four ratios are used to create the triangle plot. However, it is possible that two systems may be similar except for the neglected coefficient, leading to an incorrect conclusion that the two systems will likely produce similar selectivities. With our approach, if one coefficient is different, the correlation may suffer and the comparison will show that the systems exhibit heteroenergetic retention.

Given that LSERs have been used to characterize GC, RPLC, SFC, and MEKC systems, our approach is also applicable to those modes. In some cases, it may even be possible to make selectivity comparisons between modes, such as comparing MEKC systems to RPLC systems. However, this can only be done if the same solute parameters are used to characterize the systems. For example, in GC LSERs, the V-parameter is often replaced with the solute gas-to-hexadecane partition coefficient (log L[16]). Thus, it is unlikely that GC systems could be compared to LC or MEKC systems.

While the SSC can be used to compare many systems simultaneously, it is based upon the same principles and theories of energetics underlying the $\kappa-\kappa$ plot of Horvath et al. Furthermore, the comparisons are visual, making it easy to identify homo-

(25) Giddings, J. C. *J. Chromatogr., A* **1995**, *703*, 3–15.

and heteroenergetic systems, even when there are hundreds or thousands of data points.

The SSC was developed for use with LSER equations, but it can be extended to any multiparameter system characterization scheme. We have already started work using the Snyder−Dolan HSM as the basis of an RPLC SSC.

Disadvantages of the SSC. LSERs reduce dozens, sometimes hundreds of retention factors to just five coefficients. As expected, there is some uncertainty inherent in the LSER coefficients. In fact, the r^2 values for LSERs are sometimes lower than 0.95.[26−29] This uncertainty means that while the model performs relatively well over a large diverse solute set, individual solute retention factors may be very different than the predicted values. Because the SSC is based on LSER equations, this uncertainty is also embedded in the SSC.

LSER coefficients represent the difference in the interaction strength of the mobile phase and stationary phase. Therefore, a change in mobile phase will change the LSER equation for a system. RPLC stationary phases thus cannot be categorized absolutely (i.e., in the absence of a mobile phase). So, while LSERs are available for many systems, the results are specific to the stationary phase and mobile phase studied.[30−32] Although this is a disadvantage at this stage, as stated before, the SSC is applicable to any multiparameter characterization scheme. So the SSC will likely be able to accommodate schemes that classify stationary phases independent of mobile phase or more likely ones that use an identical mobile phase with a variety of stationary phases such as the work currently being done by Snyder, Dolan, Carr and others to classify RPLC columns using the hydrophobic subtraction model (HSM).[3,18]

Another potential limitation is that the SSC reduces a significant amount of data down to a single point. As stated earlier, LSER equations reduce dozens or hundreds of retention factors down to the five LSER coefficients. The coefficients of two systems are then correlated with one another to produce the three parameters (slope, intercept, r^2) that create a single glyph, or sphere, in the SSC. Thus, all of the chemically relevant information embedded in the potentially hundreds of contributing retention factors is ultimately reduced to three parameters containing very little specific chemical information. The SSC only tells the user if two systems are similar or different in the blend of their overall retention characteristics. The LSER coefficients need to be examined to understand the chemical origin of their differences.

Because the coefficients of a comparison point on the SSC are based on correlations of all five LSER system coefficients, the model does not take into account the possibility that all but one coefficient are well correlated. For example, in the comparison of SDS and LiPFOS shown in Figure 1, the correlation would be good if the s/v ratio (the outlier in that figure) were excluded but that single ratio creates a remarkably poor correlation. This drawback is not unique to the SSC. Triangle schemes suffer from similar problems.

CONCLUSIONS

We have unified LSERs with Horvath's homo-, homeo-, and heteroenergetic classification scheme while incorporating Zhao and Carr's concept of effective selectivity. By correlation of the ratios of LSER coefficients for two different chromatographic systems and plotting the resulting slope, intercept, and the r^2 value, systems that have similar or different energetics of retention can be readily identified. This will aid in the selection of orthogonal phases for 2D GC and HPLC and in the identification of comparable systems when replacements need to be found. Plotting the results of the correlation leads to easy visualization of the data. Furthermore, the ability to rotate the SSC and make selections via the user interface allows for many degrees of freedom for viewing only desired data, thereby reducing the complexity of large data sets. While we have demonstrated the approach using a compilation of MEKC LSERs, the approach is also applicable to other chromatographic techniques (e.g., GC, SFC, and RPLC) and also to any multiparameter model of retention. We have started analyzing RPLC data based on the Snyder−Dolan hydrophobic subtraction model. We hope that this model proves useful in a range of applications for analyzing similarities and differences within a variety of chromatographic systems.

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SUPPORTING INFORMATION AVAILABLE

Additional information as noted in text. This material is available free of charge via the Internet at http://pubs.acs.org.

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