High Performance Displacement Chromatography: Calculation and Experimental Verification of Zone Development

Effluent concentration profiles from high performance displacement chromatography were calculated by using the theory of equilibrium chromatography of Helfferich and Klein (1970). The close agreement between predictions of the theory neglecting mass transfer resistances and experimental results demonstrates that conditions close to ideal chromatography are attainable in HPLC. Individual adsorption isotherms, as measured by frontal development, closely followed Langmuirian behavior.

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SCOPE

Over the last decade high performance liquid chromatography (HPLC) has grown into a paramount analytical method. The efficiency of state-of-the-art columns and the ubiquity of these instruments led us to extend their use to displacement chromatography. Recent results from our laboratory (Horváth et al., 1981; Horváth et al., 1983; Kalász and Horváth, 1981; Kalász and Horváth, 1982) have demonstrated the potential of displacement development for preparative scale separations with columns and equipment used in analytical HPLC. Due to the relatively large feed volume and high concentration of feed components, the displacement mode offers advantages on the preparative scale compared to the linear elution mode, which is generally used in chromatographic practice. Instead of eluting the feed components as distinct peaks moving through the column with different velocities, a front of a "displacer" solution moving behind the feed drives the separation of the individual components into adjacent isotachic zones. Basic principles of the method were put forward by Tiselius (1943), who recognized that the juxtaposed bands of the feed components travel with the velocity of the displacer front and related their concentrations in these zones to the pertinent isotherms. In order to facilitate the development and maintain the integrity of the pure zones as they travel down the column, high mass transfer efficiencies are required (Claesson, 1946). Therefore, due to a lack of efficient chromatographic systems, early attempts (Partridge and Brimley, 1952) to develop the displacement mode into a practical separation process for organic compounds were disappointing, although it has been successful in ion exchange separations of rare earths (Powell and Spedding, 1956). Recent advances in HPLC and the availability of sorbents exhibiting rapid kinetics and mass transfer, however, now allow the potential of displacement chromatography to be explored.

This report describes the application to the displacement process of the theory of multicomponent chromatography presented by Helfferich (1967) and described in detail by Helfferich and Klein (1970). An equivalent theory, developed from a different point of view, was given by Rhee et al. (1970). The theory assumes constant separation factors for all components of the system and local equilibrium between the stationary and mobile phases and neglects kinetic and mass transfer resistances. With these constraints it is possible to effect a nonlinear transformation of variables, the so-called h-transformation, through which the process can be described by a simple set of algebraic equations. The first application of the theory was by Helfferich and James (1970), who calculated the ion exchange displacement separation of a mixture of 15 rare earths, a problem whose solution is facilitated by the stoichiometric exchange unique to this type of chromatography. Recently, h-transformation predictions were compared with experimental measurements on a four-component ion exchange sorption system by Clifford (1982). A procedure for mimicking stoichiometric behavior in a system with Langmuir adsorption isotherms was given by Helfferich and Klein (1970) and applied by Tien et al. (1976) to the calculation of the breakthrough curve for the adsorption of a binary mixture onto a charcoal bed. A calculation procedure for displacement development in systems exhibiting Langmuirian behavior was presented by Rhee and Amundson (1982), using their approach to multicomponent chromatography.

By using the h-transformation the course of the separation is calculated by transforming the concentration variables via the h-transformation into a coordinate system where algebraic equations describe the process for any number of components. The solution of these equations is simple compared to the operose numerical techniques required when the calculation is made in terms of the concentration variables themselves.

The goal of this study is to compare the theoretically calculated and experimentally measured concentration profiles obtained in displacement chromatography under a variety of operating conditions. High efficiency columns and precision equipment developed for HPLC were employed in order to approach the equilibrium conditions on which the model is based. The use of this equipment with 5-μm particle diameter

and regular packing structure of the porous stationary phase results in highly efficient separations with little evidence of axial dispersion or nonequilibrium. Adsorption isotherms of the phenolic compounds employed in this study were also determined by using HPLC in the frontal chromatography mode. The isotherms and column hold-up volume (Melander et al., 1983) were the only physical property data necessary to calculate the effluent concentration profiles in displacement chromatography by this method.

CONCLUSIONS AND SIGNIFICANCE

In the past, poor column efficiency, crudeness of analytical methods for monitoring the column effluent, and the gap between the theory and practice of displacement development have hampered the expansion of the method in science and technology. The columns and equipment developed for HPLC make it feasible to obtain rapid, highly efficient separations of many kinds of substances by displacement chromatography. Therefore, prediction of the course of development and the effect of process variables has become of technical interest.

We have found that the model based on the h-transformation accurately described displacement development on reversed phase HPLC systems under conditions employed here. The theory quantitatively predicted the transient and ultimate patterns of binary separations carried out on analytical size equipment under a variety of conditions. The course of development calculated from the theory was confirmed by varying the column length as well as the feed conditions. The calculations involved in applying the theory to this system are straightforward and require no demanding numerical procedures.

A high efficiency HPLC apparatus was used to achieve conditions as near as possible to equilibrium in the chromatographic process. A similar unit was also employed to measure the isotherms of the feed and displacer substances. Equilibrium conditions are reached in this manner despite the poor wetting of the sorbent by the liquid phase, which prohibits measurement by a static method. Isotherms for all compounds investigated were found to be Langmuirian, or nearly Langmuirian, in shape.

The model provided an opportunity to investigate the relationship between various operating parameters and the stationary phase volume required to achieve separation. The mass of pure product recoverable per unit mass of stationary phase was the quantity used to represent the efficiency of the process. This measure, dubbed the "stationary phase effectiveness," was found to be essentially proportional to the amount of feed, almost independent of feed concentration, and moderately sensitive to the ratio of feed components for a given feed mass. Increasing the displacer concentration was found to enhance process efficiency and reduce the amount of displacer used per run.

QUALITATIVE DESCRIPTION OF DISPLACEMENT CHROMATOGRAPHY

Chromatography is widely practiced in the elution mode, under conditions where the sorption process is linear, i.e., the equilibrium constant for partitioning between the mobile and stationary phases is independent of solute concentration. Separation is based on the differences among mixture components in the equilibrium constant. In order to maintain linearity, elution chromatography is usually separated at low feed concentrations, where the adsorption of each component is independent of the local composition, i.e., interference among feed components is negligible. In most cases the elution mode is extended to preparative separations by enlarging the bed volume and using larger, more concentrated feeds. However, at a certain point the departure from linearity of the species isotherms makes the process strongly dependent on the amount and composition of the feed, with consequent loss of reproducibility and tailing of the peaks. The latter exacerbates dilution of the band, which intrinsically accompanies separation by elution chromatography and further reduces the efficiency of the process. For these reasons, elution chromatography in the preparative mode is also generally carried out at low concentrations, where the adsorption behavior is linear (de Jong et al., 1980).

For a given column size, displacement development permits loading of much greater amounts of feed than the elution mode and tackles the problems of reproducibility and tailing by following the feed slug with a solution of a substance called the "displacer" that is more strongly adsorbed than any of the feed components. This solution is continuously pumped into the column until all the separated products have emerged at the outlet in the carrier fluid. By contrast, in isocratic elution development the feed is loaded into the column and followed by a solvent that has the same composition as that present in the column ahead of the feed.

The use of a displacer solution distinguishes the operating procedure in this mode from elution chromatography. Starting from a column equilibrated with the carrier solvent, the inlet stream is switched to load the appropriate volume of feed solution. After completion of loading of the feed slug, the inlet is switched again to cause the displacer solution to be pumped into the column. After traveling a certain length down the column the feed components sort themselves out into adjacent bands of the individual components that form a displacement train that moves with the velocity of the displacer front. A third shift in the inlet stream occurs after completion of the separation and allows for regeneration of the column. Regeneration is an unavoidable step that warrants attention in optimizing the separation, and has been treated elsewhere (Frenz and Horváth, 1983). Here the separation of the feed components into pure bands is considered, and the regeneration process will be neglected.

The chromatogram in Figure 1 shows the result of the separation process by a plot of the component concentrations against the volume of effluent for a fully developed displacement train. When the isotachic condition is attained, the concentrations of the pure component zones are uniquely related to that of the displacer solution as first proposed by Tiselius (1943) and illustrated in Figure 2, where the individual isotherms of the feed components and displacer are shown together. The line drawn from the origin to the point on the displacer isotherm corresponding to the displacer concentration is called the operating line. The abscissa values of the intersections of the operating line with the isotherms are the isotachic concentrations of the components in the product stream. Thus from Figure 2 the final concentration attained by component 4 is c_4 and of component 3 is c_3, and so on. The product concentration in displacement development, unlike in elution chromatography, is independent of feed concentration, and the technique not only separates but may also concentrate the feed components.

A convenient way to represent the displacement process is by a development graph such as depicted in Figure 3. The horizontal

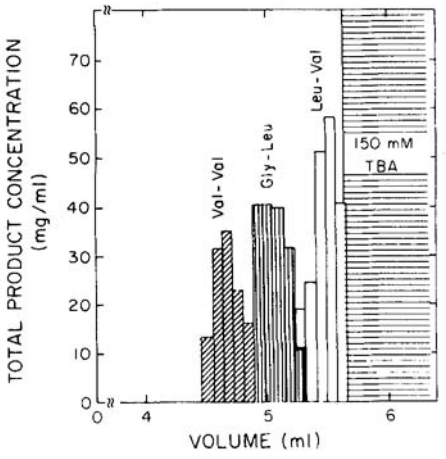

Figure 1. Separation by high performance displacement chromatography of a feed containing three dipeptides. Column, 25 × 0.46 cm, stationary phase B; carrier, 50 mol/m³ phosphate buffer, pH 2.0; displacer, 150 mol/m³ tetrabutylammonium bromide in the carrier; flow rate 14.3 mm³/s; fraction volume, 86 mm³; temperature, 60°C; feed, 10 × 10^{-6} kg valyl-valine, 15 × 10^{-6} kg glycyl-leucine, and 15 × 10^{-6} kg leucyl-valine in 0.5 cm³ of carrier.

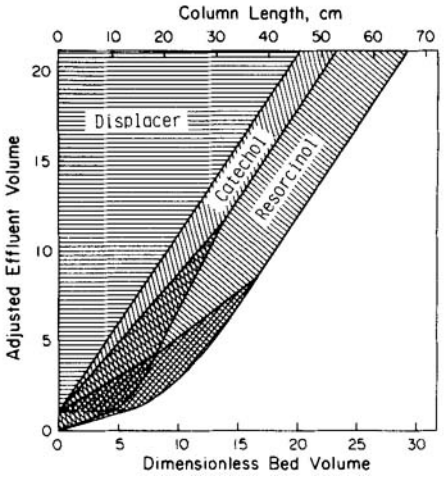

Figure 3. Displacement development graph for separation of a binary mixture. The cross-hatched areas represent mixed regions in the transient part of the development, and the line-shaded areas represent the pure component regions in the pattern. The darkly shaded region is the diffuse transition boundary. The concentrations of the feed components drop across the transition boundary from their value in the feed solution to that in later parts of the development. In calculating this graph, the feed contained 40 × 10^{-6} kg each of resorcinol and catechol in 0.4 cm³. Isotherm parameters from Figure 5b were used and phenol as the displacer at a concentration of 50 kg/m³.

axis of the diagram is the dimensionless volume into the column, V_z, given by

$$V_z = \frac{zA}{V_F} \tag{1}$$

V_z is therefore the distance coordinate while time is expressed on the ordinate by the adjusted volume of effluent, V^*, given as

$$V^* = \frac{F/V_F}{q/c}\left[t - \frac{V_z}{F}\right] \tag{2}$$

where

$$q/c = \frac{q_1}{c_1} \tag{3}$$

is the slope of the operating line (see Figure 2), the parameter that characterizes the system.

The thick solid lines on the development graph are the trajectories of boundaries between zones of constant composition. The area of the development graph labeled "displacer" shows the advance, at a constant velocity, of the displacer front into the column. The line-shaded regions represent zones of pure components within the column and the area where the shadings overlap is the unseparated band containing both components. As seen in Figure 3, separation proceeds through the widening of the pure zones in the column with concomitant shrinking of the mixed band. Upon attainment of the final isotachic pattern, only zones containing pure components remain, and the boundaries between them follow parallel paths in the development graph.

A diffuse boundary is a gradual, rather than abrupt, change in concentration between zones of constant composition and may arise at the end of the feed step when the concentrations in the feed decrease in reaching isotachic conditions. Such a diffuse boundary is shown by the darkly shaded region of the development graph depicted in Figure 3. A diffuse boundary arises in practice when the volume occupied by the feed components in the fully developed train is larger than the feed volume, so that the feed zone "stretches out" into a larger ultimate volume. Since the appearance of a diffuse boundary is a common occurrence, analysis of the displacement process must take into account both self-sharpening and diffuse boundaries.

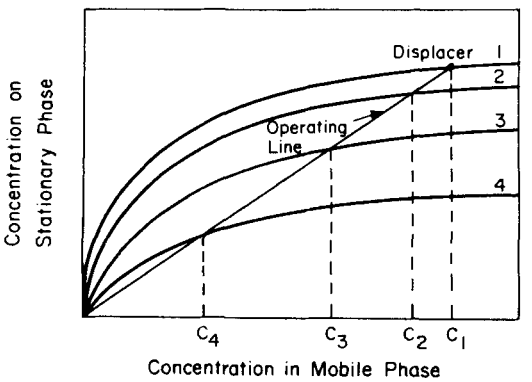

Figure 2. Schematic of displacer and feed component adsorption isotherms, showing their points of intersection with the operating line. The isotachic concentrations of the feed components are C_2, C_3, and C_4, respectively, when the displacer concentration is C_1.

THEORY

A material balance argument shows (DeVault, 1943) that as a concentration gradient of a pure substance travels through the column, the speed at which any given concentration c in the mobile phase moves is given by

$$u_c = \left(\frac{dz}{dt}\right)_c = \frac{u_o}{1 + \phi(dq/dc)} \tag{4}$$

The mobile phase velocity, u_o, is assumed to be fixed for the chromatographic system in question.

It has been found (de Jong et al., 1980) that the function $q(c)$ is well approximated by a Langmuir adsorption isotherm in liquid chromatography under conditions similar to those used in this study. For a single component, it is given by (Langmuir, 1916)

$$q = \frac{ac}{1 + bc} \tag{5}$$

Combining this relation with Eq. 3 gives

$$u_c = \frac{u_o}{1 + a\phi/(1 + bc)^2} \tag{6}$$

from which it is evident that the concentration velocity increases with an increase in concentration. The behavior gives rise to a self-sharpening boundary upon an increase in the concentration of a substance at the column inlet and a diffuse boundary upon a similar decrease in concentration. The concentration velocities in

the diffuse boundary is given for Langmuirian behavior by Eq. 6.

The derivative in Eq. 4 is undefined for the discontinuity in concentration that occurs when the boundary is self-sharpening, but a material balance argument (DeVault, 1943) gives the velocity of such a boundary for a single component as

$$u_S = \frac{u_o}{1 + \phi(\Delta q/\Delta c)} \tag{7}$$

Displacement development involves a step change in mobile phase concentration at the column inlet upon introduction of the feed and a second step increase in concentration when the displacer solution enters the column. Both step changes give rise to self-sharpening boundaries, between which lie the feed components. As long as the displacing agent has higher affinity for the stationary phase than any of the feed components, the rear boundary of the feed slug remains sharp because the displacer suppresses adsorption of the component immediately ahead of itself.

The expressions given in Eqs. 6 and 7 are written for a pure substance in the carrier. In a multicomponent system, similar equations hold, but q_i for each compound depends on the concentrations of all the other substances present. The extension of the Langmuir isotherm, Eq. 5, to a multicomponent system is given by the relationship

$$q_i = \frac{a_i c_i}{1 + \sum_j b_j c_j} \qquad j = 1,2,\ldots N \tag{8}$$

The derivative in Eq. 4 is replaced by a partial derivative when evaluating the velocity of a concentration for a given species in a multicomponent system. Therefore several equations must be solved simultaneously in order to calculate the trajectories of boundaries that involve changes in all the feed component concentrations. The complexity of these expressions when all concentrations change with both distance and time renders the calculation of concentration profiles very difficult in these terms.

The calculation of boundary velocities in multicomponent chromatography under certain conditions is greatly simplified by an appropriate transformation of variables, the h-transformation, introduced for this purpose by Helfferich (1967). An equivalent transformation to the "characteristic parameters" was given by Rhee et al. (1970). The power of this transformation rests with the fact that only one of the new dependent variables—h_1, h_2, . . . , h_i, . . . , h_N for a mixture containing N components—changes from one side of a boundary to the other in contrast to the possible change of N concentration variables. Thus the expression for the velocity of a boundary has only one variable when written in these terms, whereas an expression such as Eq. 4 depends in general on all N variables c_i. If we identify the variable that changes across a boundary as h_i and give it the value $h_{i,a}$ ahead (i.e., downstream) of the boundary and $h_{i,b}$ behind (upstream) of the boundary, then Helfferich and Klein (1970) show that if $h_{i,a} < h_{i,b}$ the boundary is self-sharpening. The adjusted velocity of the boundary is given in view of Eq. 2 by

$$v_{S_i} = \frac{dV_z}{dV^*} = \frac{u(q/c)}{u_o - u} = h_{i,a} h_{i,b} P_i \tag{9}$$

where

$$P_i = \frac{\prod_{j=1}^{i-1} h_{j,a} \prod_{j=i+1}^{N} h_{j,b}}{\prod_{j+1}^{N+1} \alpha_{1,j}} \tag{10}$$

is constant across this boundary, since the h_j with $j \neq i$ do not change from a to b. The adjusted volume of column effluent, V^*, is defined in Eq. 2 so that the adjusted velocity, v, is unity for the displacer front, as will be shown below. If $h_{i,a} > h_{i,b}$, the boundary is diffuse and, just as there is a continuous change in the c_i, there is a continuous change in h_i from $h_{i,a}$ to $h_{i,b}$. The velocity of any value of h_i in this range is

$$v_{h_i} = h_i^2 P_i \tag{11}$$

TABLE 1. CONCENTRATIONS AND H-FUNCTION ROOTS IN DISPLACEMENT DEVELOPMENT

	$c_i = 0$		$c_i > 0$	
	i	$h_i^{(a)}$	i	$h_i^{(b)}$
Carrier	$1, \ldots, N$	$\alpha_{1,1}, \ldots, \alpha_{1,N}$	—	—
Feed	1	$\alpha_{1,1}$	$2, \ldots, N$	$h_{2,F}, \ldots, h_{N,F}$
Displacer	$2, \ldots, N$	$\alpha_{1,2}, \ldots, \alpha_{1,N}$	1	$\alpha_{1,N+1}$

[a] Trivial roots.
[b] Roots of Eq. 9.

The simplification in calculating boundary velocities by Eqs. 9 and 10 as opposed to the concentration velocities is due to transformation from the variables c_i to the h_i, which represent the "natural" (Helfferich and Klein, 1970) or "characteristic" (Rhee et al., 1970) coordinates for the system.

The transformation from c_i to h_i is applicable to systems that satisfy the condition that the separation factors, $\alpha_{i,j}$, are invariant. For Langmuirian behavior this condition is met since

$$\alpha_{ij} = \frac{q_i/c_i}{q_j/c_j} = \frac{a_i}{a_j} \tag{12}$$

If the components of the system are ranked according to affinity for the stationary phase and indexed from 1 to N, with component 1 being the displacer, i.e., the most strongly retained, the new variables h_i are obtained as the roots in h of the H-function, defined as

$$\sum_{i=1}^{N} \frac{b_i c_i}{h(a_i/a_1) - 1} = 1 \tag{13}$$

Equation 13 is a polynomial that cannot be solved explicitly but is readily evaluated by a numerical technique such as Newton's method. The "characteristic parameters," ω_i, employed by Rhee and Amundson (1982) are analogous to reciprocal h_i values.

In displacement chromatography, as described earlier, three different solutions—carrier, feed, and displacer—alternately enter the column. If the solutions contain altogether N sorbable components, then N values of c_i are associated with each solution: for the carrier $c_1 = c_2 = \ldots = c_N = 0$; for the feed $c_1 = 0$ and $c_2 > 0$, $c_3 > 0, \ldots, c_N > 0$; and for the displacer solution $c_1 > 0$ and $c_2 = c_3 = \ldots = c_N = 0$. Table 1 summarizes the compositions of the three solutions pertinent to displacement development.

Equations 13 alone is not sufficient to transform from concentration variables c_i to the new variables h_i for mixtures that lack one or more components, which is the case for all three considered here. The feed, for instance, does not contain the displacer substance, so $c_1 = 0$ and the first term of Eq. 13 vanishes. Thus the polynomial has only $N - 1$ terms and only $N - 1$ roots, which we call $h_{2,F}, h_{3,F}, \ldots, h_{N,F}$. In order to complete the set of h_i, Helfferich and Klein (1970) show that there is another root given by $h_1 = \alpha_{1,1} = a_1/a_1 = 1$. More generally, when $c_i = 0$, the corresponding "trivial" root that cannot be found from Eq. 13 is equal to the separation factor $\alpha_{1,i} = a_1/a_i$. Equation 13, along with the simple rule for evaluating trivial roots, then allows us to write down the values for the h_i of all three solutions involved in displacement development, and they are also given in Table 1. As shown above, the carrier is assumed to contain no sorbable components of interest, so none of its roots can be evaluated by Eq. 13. Instead, they are all given as the trivial roots $h_1 = \alpha_{1,1}(= 1), h_2 = \alpha_{1,2}, \ldots h_N = \alpha_{1,N}$. The displacer solution lacks components 2 through N, so only one of its roots is found by Eq. 13 as

$$h_N = 1 + b_1 c_1 = \frac{a_1}{q/c} = \alpha_{1,N+1} \tag{14}$$

and the first through $(N - 1)$th roots are $h_1 = \alpha_{1,2}, h_2 = \alpha_{1,3}, \ldots, h_{N-1} = \alpha_{1,N}$ corresponding to the separation factors of the missing components. Note that in the carrier and feed solutions the trivial root corresponding to $c_i = 0$ is h_i, while in the displacer the trivial root for $c_i = 0$ is h_{i-1}.

In accord with the rules given above, and as illustrated in Figure 3 for $N = 3$, the switch from carrier to feed changes $N - 1$ of the

h_i (h_1 is constant), and so gives rise to $N-1$ boundaries traveling through the column. All of these boundaries are self-sharpening, and their velocities are ordered as $v_{h_2} < v_{h_3} < \ldots < v_{h_N}$. The switch from feed to displacer solution changes all N values of h_i, thus giving rise to N boundaries. The boundary associated with h_N is the transition boundary and represents the change of h_N from $h_{N,F}$ to $\alpha_{1,N+1}$. This boundary alone may be self-sharpening or diffuse depending on the relative magnitudes of $h_{N,F}$ and $\alpha_{1,N+1}$, as noted earlier.

In the final pattern the feed components have separated into single-component zones. In each of these zones $h_N = \alpha_{1,N+1}$, and the other h_i are given by the trivial roots $\alpha_{1,i}$, for the components not present within the zone. For example, in the zone containing only component 2 the roots are $h_1 = \alpha_{1,1}$, $h_2 = \alpha_{1,3}$, $h_3 = \alpha_{1,4}, \ldots$, $h_N = \alpha_{1,N+1}$. The velocity of the boundary between the zones of the displacer and component 2, i.e., the velocity of the displacer front, is given by Eq. 9 as

$$v_{h_1} = h_{1,a}h_{1,b}P_1 = \alpha_{11}\alpha_{12}\left[\frac{\alpha_{13}\alpha_{14}\ldots\alpha_{1,N+1}}{\alpha_{11}\alpha_{12}\ldots\alpha_{1,N+1}}\right] = 1 \quad (15)$$

Thus, according to the coordinate frame used here, the velocity of the displacer front is by definition unity. By a similar calculation the isotachic velocities of all boundaries can be shown to be equal to that of the displacer front, the characteristic velocity of the system as determined by the operating or "speed" line, in accord with Tiselius's (1943) finding.

The inclusion of q/c in Eq. 2 yields units of v such that the final velocities of all components are unity. In this work the constant q/c implicitly fixes the value of the adjustable parameter R introduced by Helfferich and Klein (1970) in order to solve problems involving nonstoichiometric adsorption, such as that considered here, in exactly the same way as the simpler case of stoichiometric exchange. According to these authors the parameter R is adjustable anywhere in the range

$$0 < R < a_N \quad (16)$$

and the results of the calculations are not affected by the choice of R. In this work, q/c, the slope of the operating line, is used as the value of R and is always positive. Further, according to this choice the condition that $R < a_N$ yields

$$c_1 > \frac{1}{b_1}\left[\frac{a_1}{a_N} - 1\right] \quad (17)$$

which is Glueckauf's (1946) condition for achievement of displacement. We have found that using q/c as the parameter simplifies the calculations of the displacement process. This choice is for convenience only, and avoids the complications that may arise from use of an "arbitrary" parameter (Tien et al., 1976; Helfferich and Klein, 1977; Tien and Turian, 1977). The definition of $\alpha_{1,N+1}$ in Eq. 14 is a vestige of the formalism employed to convert to the method used for stoichiometric systems, but is retained in order to simplify the equations that follow.

Since the movements of the concentration boundaries are easily calculated with the transformed variables, a development graph such as in Figure 3 is readily constructed, given only knowledge of the isotherms of the components, the column hold-up volume, the feed volume and composition, and the displacer concentration. The starting points of the boundary trajectories are simply the beginning or end of the feed introduction step, i.e., the two times at which a change in the column influent occurs. The other points of interest in the diagram are those at which the boundaries originating from the beginning of the feed introduction intersect those arising from the end of the feed. At these points of intersection a change in the boundary velocity occurs that is predictable from knowledge of the H-function roots that change across each of the two intersecting boundaries. When the two boundaries are associated with a change in the same root, they combine into a single boundary after the intersection, with a velocity given by Eq. 9 or 11 that is intermediate in value between the preintersection boundary velocities. If the two boundaries do not represent changes in the same H-function root, then they both continue beyond the point of intersection with velocities that change due to a change in the value of the P_i terms in Eqs. 9 and 11. The displacer boundary, which is associated with a change in the value of h_1, is the only one that does not intersect another boundary and does not change velocity as it moves through the column.

After constructing the paths of the boundaries, the only remaining information we need in order to construct the displacement chromatogram are the concentrations of the components in each part of the development graph. Since the values of the h_i are known in each part of the graph, this is accomplished by reversing the transformation of Eq. 13. The reverse transformation, to calculate the concentrations from known values of h_i, is

$$c_j = \frac{\prod_{i=1}^{N}\frac{h_i a_j}{a_1} - 1}{b_j \prod_{\substack{i=1 \\ i\neq j}}^{N}\frac{a_j}{a_i} - 1} \quad (18)$$

EXPERIMENTAL

Materials

Two different batches, A and B, of a silica-bound hydrocarbonaceous stationary phase were used. The column packing materials were prepared by stirring Spherisorb (Phase Sep, Hauppage, NY) 5-μm spherical silica gel particles with octadecyldimethylchlorosilane from Petrarch Systems (Levittown, PA) in refluxing toluene (Fisher Scientific, Fair Lawn, NJ) for more than 96 hr. The packing materials were subsequently treated with trimethylchlorosilane (Petrarch Systems), washed, and slurry-packed (Manius and Tscherne, 1981) at 70 MPa into stainless steel columns having internal dimensions of 25 × 0.46 cm or 15 × 0.46 cm. The carbon content of these materials was determined by Barron Consulting Co. (Orange, CT) to be 7.16% (w/w) carbon for A and 7.97% for B. After packing, the columns were tested for efficiency by elution chromatography and yielded at least 60,000 theoretical plates/m (Karger et al., 1973). Resorcinol was obtained from J. T. Baker Chemicals (Phillipsburg, NJ), catechol from Matheson, Coleman and Bell (Norwood, OH), n-propanol from Mallinkrodt Chemical Works (St. Louis, MO), and phenol, HPLC-grade methanol, triethylamine, and phosphoric acid were from Fisher Scientific. Distilled water was prepared by a Barnstead unit.

Column Hold-up Volume

The hold-up, or "dead," volumes of the columns were measured by a gravimetric technique (Riedo and Kováts, 1982). The mass of the column when filled with methanol was subtracted from its mass when filled with carbon tetrachloride (Fisher Scientific), and this mass was divided by the difference in density of the two liquids to give the column hold-up volume. Since the carrier was pure water this method was appropriate (Melander et al., 1983).

Isotherm Measurement

Isotherms were measured for resorcinol and catechol on the two stationary phases and for phenol on the B material. No determination of the complete isotherm for n-propanol was made, but the appropriate value of q/c for each displacement run was calculated from the breakthrough volume of the displacer front. The isotherms were determined chromatographically by frontal analysis (Conder and Young, 1979) using a Model 100 (Altex, Berkeley, CA) solvent metering pump connected to the column via a Model 7010 (Rheodyne, Berkeley, CA) valve. The valve was configured to allow precise switching between solutions by the stop-flow technique. The effluent from the column was monitored by a Model 65-T (Perkin-Elmer, Norwalk, CT) UV detector/oven at a suitable wavelength. The detector signal was recorded by a Model Electronik 195 (Honeywell, Ft. Washington, PA) strip chart recorder. The isotherm data were fit to Eq. 5 by the nonlinear regression routine NLIN in the SAS statistics package (Helwig and Council, 1979). Single component data thus obtained were used in Eq. 8 for describing competitive multicomponent absorption equilibrium.

Displacement Development

Figure 4 schematically depicts the displacement chromatograph used for separations. The Model 601 (Perkin-Elmer) dual pump system was

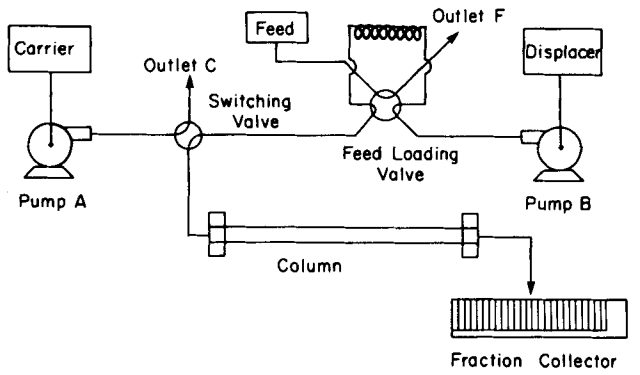

Figure 4. Schematic of displacement chromatograph. The carrier and displacer solutions are delivered by pumps A and B, respectively. The switching valve controls which solution is led to the column, while the feed valve permits pulseless introduction of the feed solution ahead of the displacer.

replumbed to bypass the mixing chamber and connected to a Model 7030 (Rheodyne) switching valve to permit pulseless switching between carrier and displacer solution flows to the column. The feed valve Model 7010 (Rheodyne) was fitted with a 1.0 cm^3 loop. The effluent from the column was collected by a Model 7000 (LKB, Rockville, MD) fraction collector. In all separations the carrier was distilled water and the column and mobile phase were at room temperature.

Displacement development runs began with the switching valve turned to the position that delivered the carrier through pump A to the column. In this position the value blocked flow from pump B. The feed loading valve was rotated into the position for filling the loop with the feed solution. After filling, the feed valve was rotated into the position shown in Figure 4 and pump B was started in order to pressurize the feed. When the pressure in pump B equaled that in pump A, the switching valve was turned to the position shown in Figure 4. This allowed the displacer solution to push the feed into the column. After the desired volume of feed flowed into the column the feed valve was returned to its former position, and flow of the displacer to the column commenced. The column effluent was directed into the fraction collector to obtain 100 mm^3 fractions. When breakthrough of the displacer front occurred, the operation was halted, and the column was regenerated by washing with 20 column volumes of methanol and reequilibrated with the carrier.

Analysis of Fractions

Aliquots of the fractions of the column effluent were diluted 25-fold and analyzed using an analytical HPLC unit consisting of a Model 100 (Altex) solvent metering pump, a Model 725 (Micromeritics, Norcross, GA) automatic injector, a Model 65-T detector/oven, and a Model SDR 306 (Kratos, Ramsey, NJ) chart recorder. The sample size was 10 mm^3 and the analytical column was operated at 50°C with an eluent consisting of 10% (v/v) methanol, 0.5% phosphoric acid, and 0.5% triethylamine in distilled water.

Numerical Computations

A FORTRAN IV program was written to calculate the points of intersection of the boundary trajectories in an N-component displacement separation. The main program calculated the zone compositions via Eq. 18 and trajectories of self-sharpening boundaries and drove subroutines for solving Eq. 13 for the h_i and for calculating the diffuse transition boundary. Additional subroutines set up input data files for plotting of development graphs and displacement chromatograms by the TELLAGRAF (ISSCO, 1981) system.

RESULTS AND DISCUSSION

The goal of this study was to compare experimental results of the displacement process with those calculated from the model described above. The experimental system was operated under conditions expected to satisfy the assumptions underlying the theory as closely as possible. This was facilitated by the use of high performance liquid chromatographic columns packed with 5 μm particles and equipment designed to minimize mass transfer resistances and flow maldistribution. The model neglects axial dispersion, which is a consequence of such nonideal effects. It is believed that the flow rates used in the experiments were low enough to obviate the effect of slow displacement kinetics (Horváth et al., 1982) as well. A mixture of resorcinol and catechol was chosen as the feed. These phenolic compounds adhere closely to Langmuir adsorption behavior, and their concentration is conveniently measured spectrophotometrically. Our previous experience guided the choice of displacers, especially with regard to their solubility in the carrier and strong affinity for the stationary phase used. The system and conditions employed here typify the practice of displacement chromatography and are expected to lie within the scope of the theory outlined above. The surface of the stationary phase employed here is rather homogeneous in comparison to that of conventional sorbents because the octadecyl moieties covalently bound to it form a uniform molecular "fur." Such hydrocarbonaceous bonded phases that have a hydrophobic surface are used with polar mobile phases in reversed phase chromatography (Melander and Horváth, 1980).

TABLE 2. RETENTION FACTORS IN ELUTION CHROMATOGRAPHY WITH THE CARRIER AS MOBILE PASE

Component	Stationary Phase	Retention Factor, k'
Resorcinol	A	5.03
	B	6.62
Catechol	A	7.57
	B	7.94
Phenol	B	15.04

The elution mode of HPLC provides a rapid means of measuring the relative retentions of the compounds of interest, at least in the linear range of their isotherms. It is thus an easy means for preliminary investigation of the chromatographic conditions for displacement development. The dimensionless parameter used in elution chromatography to measure solute retention is the retention factor, defined as

$$k' = \frac{t_R - t_o}{t_o} = \phi K \tag{19}$$

Table 2 shows the retention factors measured in this manner for phenol, resorcinol, and catechol on the two stationary phases with plain water as the eluent. The retention factors of resorcinol and catechol are greater on phase B, as expected from the higher carbon content of this material. The retention factors of the feed components are significantly different, indicating that this combination of mobile and stationary phases is a suitable choice for this feed mixture. The k' of phenol further qualifies it as a suitable displacer candidate since it is more strongly retained than either feed component.

For analysis of displacement chromatography, however, the isotherms of feed components have to be known over a wide concentration range. This measurement was made by frontal analysis on HPLC equipment. Points on the isotherm were calculated by Eq. 7 from the velocities of self-sharpening boundaries measured by this technique. Figure 5 shows the isotherms measured by this method on the two stationary phases. The solid lines represent the regression curve fitted to Eq. 5 for each substance, and the regression parameters a and b are given in the inset. The Langmuir equation fits the isotherm data well throughout the range of concentrations measured, though it slightly underestimates at low concentrations, where the k' is measured. The Henry's law constant was evaluated from retention factors by Eq. 19 and was found to match the measured isotherm points better than the a parameter in the Langmuir model, Eq. 5, at low concentrations. Thus it appears that the adsorption behavior of these compounds is more complex than predicted by the Langmuir model. Still the higher concentrations are of greater concern in displacement chromatography, and in this region Eq. 5 represents the data well.

The isotherm of n-propanol was not determined, owing to the difficulty in detecting aliphatic compounds with the available equipment. However, inspection of Eqs. 18–24 reveals that for description of the process only the parameter q/c is pertinent, not

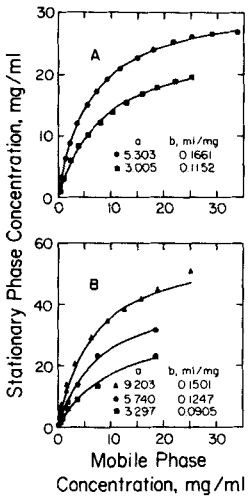

Figure 5. Isotherms of resorcinol (■), catechol (●), and phenol (▲) measured on the two stationary phases: A, with a carbon load of 7.16%, and B, with 7.97% carbon. The solid lines are the curves fitted to Eq. 5.

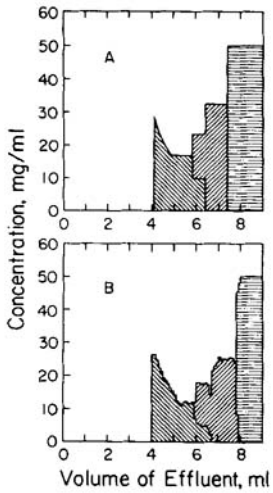

Figure 7. Calculated (*A*) and experimental (*B*) chromatograms for conditions identical to Figure 6, but a column length of 25 cm.

the entire isotherm of the displacer. Physically this means that the slope of the operating line is the important quantity, not the entire displacer isotherm. The quantity q/c is readily determined from the displacement chromatogram since the rear boundary of the catechol zone can be detected spectrophotometrically and coincides with the front of the displacer zone. Thus the velocity of the displacer front can be determined from the displacement experiment, and using Eq. 7 gives the value for the q/c ratio. Therefore, the model can be used even in the absence of complete isotherm data for the displacer.

Our interest was focused on predicting the results of displacement development under a variety of conditions. In particular we performed experiments with columns shorter than required for attainment of the isotachic pattern since this allowed examination of the transient part of the process, the analytical description of which is much more involved than that of the final pattern. Along these lines the success of the model in predicting the shape of the diffuse transition boundary was also an object of study. The initial test of the model was the displacement development of a feed containing 40×10^{-6} kg each of resorcinol and catechol in 0.4 cm^3 with phenol as the displacer on stationary phase B. Figure 3 shows the development graph for this system. From the graph it is apparent that a 15 cm column will yield a chromatogram with a large diffuse boundary that encompasses all the pure resorcinol zone as well as part of the mixed zone. Figure 6 shows the calculated and experimentally determined chromatograms for the 15 cm column. The diffuse boundary is indeed found to extend into the mixed zone, and has the shape of a spike at the front of this zone in both the calculated and experimental profiles. The same displacement development with a 25 cm column yielded the calculated and experimental chromatograms shown in Figure 7. As a result of the larger column volume, the diffuse boundary has shrunk and is confined to a portion of the resorcinol zone. The mixed zone has also shrunk in size. Finally with a 40 cm column the isotachic pattern is attained as shown in Figure 8, and the two product zones overlap to only a small extent in the experiment, indicating that the magnitude of axial dispersion is very low in HPLC columns under such conditions.

The only significant discrepancy between the theoretical and experimental results is that the measured resorcinol concentration in the mixed zone is lower than predicted. This effect is likely due to an insufficiency of the compound Langmuir isotherm used in the model to represent the competitive sorption behavior of the substances. The applicability of such a model for competitive adsorption is probably somewhat narrow. However its use in this work greatly simplifies the analysis of the process compared to the numerical calculation that would be demanded by the use of more realistic, and more complex, representations of competitive isotherms. The small error in the model predictions introduced by this

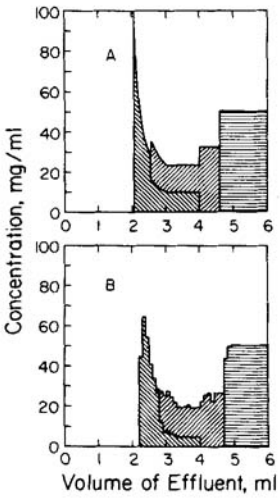

Figure 6. *A*. Effluent concentration profile for a 15 cm column calculated from Figure 3. *B*. Displacement development of a binary mixture. Column, 15 × 0.46 cm, stationary phase B; carrier, water; displacer, 50 kg/m^3 phenol in water; flow rate, 3.33 mm^3/s; fraction volume, 100 mm^3, temperature, 25°C; feed, 40×10^{-6} kg each or resorcinol and catechol in 0.4 cm^3 water.

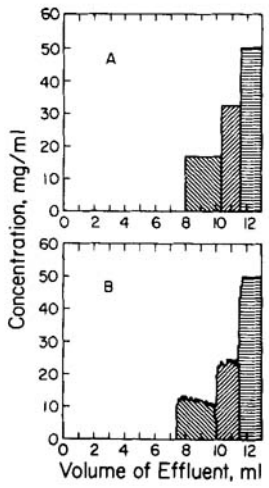

Figure 8. Calculated (*A*) and experimental (*B*) chromatograms for conditions identical to Figure 6, but a column length of 40 cm.

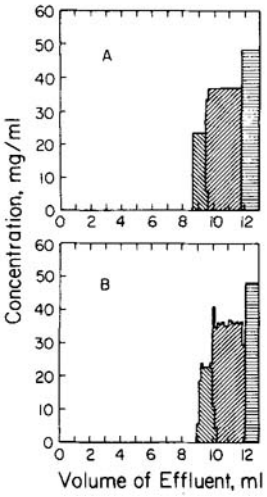

Figure 9. Calculated (*A*) and experimental (*B*) chromatograms for displacement development of 0.7 cm³ of a solution containing 21 × 10^{-6} kg resorcinol and 84 × 10^{-6} kg catechol in water. The displacer *n*-propanol at a concentration of 48 kg/m³, q/c = 1.14, and isotherm parameters from Figure 5a were used. Column, 50 × 0.46 cm, stationary phase A; flow rate, 3.33 mm³/s; carrier, water; fraction volume, 100 mm³; temperature, 25°C.

approximation does not warrant recourse to a more elaborate approach under the conditions used here.

Further investigation of the applicability of the model involved calculation of the chromatogram for a separation under widely differing conditions. The development graph for a run with a feed containing 21 × 10^{-6} kg of resorcinol and 84 × 10^{-6} kg catechol and *n*-propanol as the displacer at a concentration of 48 kg/m³ was calculated and used to construct the chromatogram shown in Figure 9a. The adsorbent in this case was stationary phase A and the chromatogram was calculated for a column length of 50 cm and a q/c value of 1.14. The experimental result under these conditions is shown in Figure 9b. The 50 cm column falls short of the predicted minimum length required for complete separation by several centimeters, so both results show a similar slight intermixing of the product zones.

The results of all tests of the model showed good agreement between theoretical predictions and experiments on displacement development in the nonstoichiometric system employed here. The *h*-transformation procedure assumes equilibrium conditions, which are approximated quite closely with the microparticulate stationary phases employed in high performance liquid chromatography. The very slight overlap between adjacent zones in, for example, Figure 8b indicates that mass transfer and kinetic limitations have only a small effect on the process under the operating conditions employed here.

The model provides an opportunity to investigate the requirements for separation of a given mixture and thus optimize the

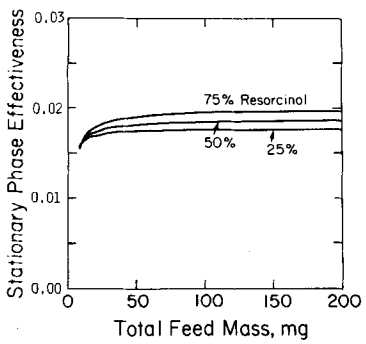

Figure 10. Dependence of stationary phase effectiveness on mass of feed loaded to column. The volume of feed was fixed at 0.7 cm³ and calculations used the isotherm parameters from Figure 5b. The feed in calculations comprising the top curve was 75% resorcinol, the middle curve 50% and the lower 25%.

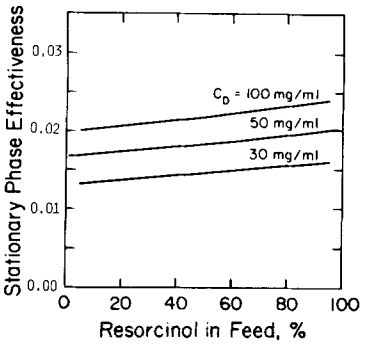

Figure 11. Variation of stationary phase effectiveness with composition of feed. The calculations were performed using the conditions of Figure 3 but varying the feed composition and displacer concentration. The latter was 100, 50, and 30 kg/m³ in the upper, middle, and lower curves, respectively.

operating conditions with respect to a specific goal. In separation processes involving adsorption the column capacity is frequently the dominant factor that determines equipment and materials costs. A quantity that represents the efficiency of utilization of the stationary phase in displacement chromatography under isotachic conditions is the mass of product recovered in pure form per unit mass of column packing, designated the "stationary phase effectiveness," η_{SP}. It is found by dividing the mass of product obtained per run by the stationary phase mass required to achieve complete separation. The effect of the feed size on this parameter is shown in Figure 10, which illustrates the stationary phase effectiveness for separation of mixtures of resorcinol and catechol as a function of the total mass of feed loaded onto the column. The volume of feed solution was constant in these calculations. Three feeds were used containing 25, 50, and 75% (w/w) resorcinol, and the results are given in Figure 10 by the upper, middle, and lower curves, respectively. In each case η_{SP} is independent of the total mass of feed except at low loadings. This relationship can be helpful in scaling up the process from a particular set of operating conditions, because it shows that under most practical operating conditions the bed volume required for separation is essentially proportional to the mass of feed to be separated. The result in Figure 10 further shows that the process is not sensitive to variations in feed concentration, since the volume of feed was constant and its concentration increases along the abscissa.

The sensitivity to feed composition was also calculated and the results are illustrated in Figure 11, where η_{SP} is plotted as a function of the weight fraction of resorcinol in the feed. The dependence is almost linear and shows an increase in the parameter of less than 18% when the fraction of resorcinol in the feed increases from 2% up to 98%. Here the total mass of feed was constant and the result shows that under such conditions the effect of changing feed composition on the efficiency of displacement development is only moderate.

Besides the stationary phase, the displacer is another material cost of the displacement process and is an important operating parameter that can be adjusted to optimize the process. For this reason we introduce the "displacer effectiveness," η_D, defined as the mass of product divided by the amount of displacer taken up by the column to reach isotachic conditions. Figure 12 shows both the stationary phase effectiveness and displacer effectiveness as functions of the displacer concentration used in the development. As seen, both effectiveness parameters initially increase sharply with the displacer concentration, then begin to level off and increase more slowly. The apparent result is that a higher displacer concentration always yields more efficient use of the stationary phase and also requires less displacer overall. It should be noted that at some concentration each component reaches its solubility limit and therefore in practice the maximum displacer concentration is determined by the solubilities of the components. In Figure 12 the dashed portions of the curves represent the region beyond the saturation concentration of phenol. The solubilities of the feed components are important since they often become more con-

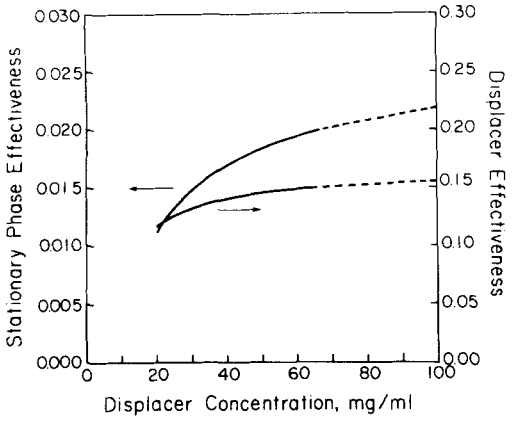

Figure 12. Effect of displacer concentration on stationary and displacer effectiveness. Conditions of Figure 3 were used in the calculations, but with varying phenol concentration.

centrated in the course of displacement development and may precipitate in the column (Horváth et al., 1982).

Scale-up of the separation in chromatography is most easily done by enlarging the column volume and feed size, maintaining the linear velocity of the mobile phase, and using the same sorbent and carrier solutions. High performance columns with inner diameters up to 2.5 cm are available with equipment that obviates the problems arising from nonuniform inlet conditions or bed structure. A 2.5 cm dia. column with a length of 50 cm would contain about 0.22 kg of packing material and under conditions similar to those described above would be able to purify 5×10^{-3} kg of material in a single pass. The specific permeability of such a column would be about the same as an analytical column—approximately 20×10^{-12} m^2—so at a flow rate of 0.11 dm^3/s, the pressure drop across it would be about 4.5 MPa, if packed with 5-μm dia. particles. The relatively high cost of achieving the level of efficiency described here makes this technique most attractive for expensive, difficult to purify products, such as those of the pharmaceutical industry.

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NOTATION

a_i = Langmuir parameter for component i
A = cross-sectional area of the empty column tube
b_i = Langmuir parameter for component i
c_i = mobile phase concentration of solute i per unit volume of bed
Δc_i = increase in c_i across a concentration front
C_i = concentration of solute i per unit volume of mobile phase
F = flow rate
h_i = ith root of H-function
$h_{i,F}$ = value of h_i in feed solution
$h_{i,a}$ = value of h_i ahead of a concentration front
$h_{i,b}$ = value of h_i behind a concentration front
k' = retention factor $= (t_R - t_o)/t_o$
K = Henry law constant
N = number of components in system (excluding carrier, including displacer)
P_i = constant in adjusted velocity equations
q/c = slope of operating line
q_i = stationary phase concentration of solute i per unit volume of bed
Δq_i = increase in q_i across a concentration step
R = adjustable parameter of Helfferich and Klein (1970)
t = time
t_o = mobile phase holdup time in column
t_R = retention time of peak in elution chromatography
u_c = concentration velocity
u_o = mobile phase velocity
u_S = velocity of a concentration step
v_S = adjusted front velocity
v_k = adjusted velocity of h_k
V_F = volume of feed
V^* = adjusted volume of effluent
V_z = dimensionless column volume
z = axial position in column

Greek Letters

$\alpha_{i,j}$ = separation factor between components i and j
$\alpha_{1,N+1}$ = value of h_N in displacer solution
ϵ = total bed porosity
ϕ = phase ratio
ω_i = characteristic parameter of Rhee and Amundson (1982)

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