A THERMODYNAMIC MODEL FOR LIQUID-LIQUID CHROMATOGRAPHY
WITH A BINARY MOBILE PHASE

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ABSTRACT

A simple model which previously led to successful predictive
equations for gas-liquid partition coefficients on mixed stationary
phases has been slightly modified to include liquid-liquid
partitioning. Predictive expressions are developed for dis-
tribution coefficients determined from liquid-liquid chromato-
graphic studies using a binary mobile phase. Limitations of the
method are briefly discussed.

INTRODUCTION

Liquid-Liquid Chromatography (LLC) is a very powerful
technique for chemical separations. This technique has not been
applied to analytical determinations as frequently as the more
modern method of gas-liquid chromatography. Recent improvements
in column technology and instrumental design have led to a renewed
interest in LLC. The desirable experimental features include;
small (μl) samples, relatively short analysis times, a large
selection of possible partitioning systems, and the ability to
use nonvolatile solutes. Theoretically, there exist numerous
combinations of binary immiscible phases which can be used in LLC.
The number grows even larger if one considers the ternary (or
higher order multicomponent) systems which can be mixed to form
two immiscible liquid phases.

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The ability to conveniently work at very low solute concen-
trations offers possibilities to determine thermodynamic properties
through equations developed by Locke and Matire[1-2]. In this paper,
we extend the considerations of Locke and Matire to include thermo-
dynamic studies using a binary solvent as the mobile phase. In
many instances the derived equations should provide an indication
of phase compositions needed to achieve desired elution character-
istics. Similar expressions developed specifically for gas-liquid
chromatography have been shown to be beneficial in the selection
of mixed stationary phases and in the study of associations com-
plexes between the solute and one of the solvent components[3,4].

Relationship Between Solute Retention and Thermodynamic Properties.

The partitioning of a solute between two immiscible liquid
phases provides the physical basis for liquid-liquid chromatography.
As such, it is often convenient to define an experimental distri-
bution coefficient as the ratio of solute concentration in each
phase:

$$K_R = \frac{\text{concentration of solute in stationary phase}}{\text{concentration of solute in mobile phase}} \tag{1}$$

For LLC it has been shown that solute retention volume (V_R) is
related to the distribution coefficient through

$$V_R = \nu_m + K_R \nu_S \tag{2}$$

where ν_S is the volume of the stationary liquid in the column and
ν_m is the interstitial volume occupied by the mobile phase. To
express retention measurements in a manner independent of experi-
mental parameters, Littlewood et al.[5], suggested specific retention
volume (V_g):

$$V_g = \frac{K_R}{\rho_S} \tag{3}$$

where ρ_S is the density of the stationary phase.

The mathematical derivation of equation (2) assumes normal
LLC operating conditions, and if one further requires liquid-

liquid partitioning to be the sole retention mechanism, then
retention measurements can be related to thermodynamic quantities.
The activity coefficient of a solute relative to Raoult's law,
$\gamma_3^{\ell}(T,P)$, in a binary solution is defined by:

$$RT \ln \gamma_3^{\ell}(T,P) = \mu_3^{\ell}(T,P) - \mu_3^{O,\ell}(T,P) - RT \ln X_3^{\ell} \quad (4)$$

where $\mu_3^{O,\ell}(T,P)$ is the chemical potential of pure liquid solute
at T and P, $\mu_3^{\ell}(T,P)$ is the solute chemical potential in the solu-
tion, and X_3^{ℓ} is the mole fraction of solute.

In liquid-liquid chromatography the condition for thermo-
dynamic equilibrium is

$$\mu_3^S(T,P) = \mu_3^m(T,P) \quad (5)$$

in which $\mu_3^S(T,P)$ and $\mu_3^m(T,P)$ are the solute chemical potentials in
the stationary and mobile phases respectively. Substitution of
equation (5) into equation (4) with rearrangement yields:

$$\mu_3^{O,m}(T,P) - \mu_3^{O,S}(T,P) = RT \ln \frac{\gamma_3^S \, X_3^S(T,P)}{\gamma_3^m \, X_3^m(T,P)} \quad (6)$$

since both $\mu_3^{O,m}(T,P)$ and $\mu_3^{O,S}(T,P)$ represent the chemical potential
of pure liquid solute at T and P, $(\lim_{X_3 \to 1} \gamma_3^i = 1)$, their difference is
zero. For simplicity we have elected to choose the column pres-
sure (P) as our reference and interested readers are referred to
an article by Locke and Matire if another reference state is pre-
ferred. In very dilute solutions the experimental distribution
coefficient is expressed more conveniently as:

$$K_R = \frac{X_3^S \bar{V}_m^O}{X_3^m \bar{V}_s^O} \quad (7)$$

where $\bar{V}_i^O$ is the molar volume of pure liquid phase i. Combination
of equations (6) and (7) give:

$$\ln K_R^O = \ln \frac{\gamma_3^{m,\infty}(T,P) \, \bar{V}_m^O}{\gamma_3^{S,\infty}(T,P) \, \bar{V}_s^O} \quad (8)$$

the superscript ∞ denoting values at infinite dilution. Expressed
in terms of specific retention volume, equation (8) becomes

$$\ln V_g = \ln \frac{\gamma_3^{m,\infty}(T,P) \ \bar{V}_m^o}{\gamma_3^{s,\infty}(T,P) \ M_s} \tag{9}$$

in which M_s is the molecular weight of the stationary phase. These simple mathematical relationships enable a priori predictions of distribution coefficients and retention volumes for any system in which the activity coefficients are known or can be estimated from solution theories.

The Nearly Ideal Binary Solvent (NIBS) Approach to Liquid-Liquid Partition Coefficients in Non-Complexing Systems.

The Nearly Ideal Binary Solvent (NIBS) approach developed by Bertrand and co-workers has been shown to be quite successful in predicting heats of solution[6], gas-liquid partition coefficients[3], and solubilities[7,8] in systems containing only nonspecific interactions. Using a simple mathematical model for the excess Gibbs free energy of a multicomponent system:

$$\Delta \bar{G}^{mix} = RT \sum_{i=1}^{N} (X_i \ln \phi_i) + \Delta \bar{G}^{fh} \tag{10}$$

$$\Delta \bar{G}^{fh} = (\sum_{i=1}^{N} X_i \bar{V}_i^o) \ _{all \ pairs} \sum \phi_i \phi_i A_{ij} \tag{11}$$

Acree and Bertrand developed a zero-parameter equation (Equation VV, reference 7) which predicts solubilities in 35 systems of non-specific interactions containing naphthalene, stannic iodide, iodine and benzil as solutes with an average deviation of 2.2% and a maximum deviation of 25%. This maximum deviation occurs in a system (Benzil-Benzene + Cyclohexane) in which complex formation has been suggested and if this system is excluded from calculations, the maximum deviation becomes 6%. The success of this model is even more remarkable if one realizes the mole fraction solubility of benzil changes by a factor of 14 in the carbon tetrachloride + n-hexane system[8].

Using the following thermodynamic definitions

$$\Delta \bar{G}^{fh} = RT \sum_{i=1}^{N} X_i \ln \gamma_i^{fh} \tag{12}$$

$$\ln\gamma_i^{fh} = \ln\ (a_i/\phi_i) - (1 - \frac{\bar{v}_i^o}{\bar{v}_M^o}) \tag{13}$$

$$(\gamma_i^{fh})^\infty = \lim_{X_i \to o} \gamma_i^{fh} \tag{14}$$

$$\gamma_3^\infty = (\gamma_3^{fh})^\infty \frac{\bar{v}_3^o}{\bar{v}_{solvent}^o} \exp\ (1 - \frac{\bar{v}_3^o}{\bar{v}_{solvent}^o}) \tag{15}$$

the activity coefficient for a solute (relative to Flory-Huggins entropy) at infinite dilution in binary solvent mixtures (components 1 and 2)

$$\ln(\gamma_3^{fh})^\infty = \phi_1^o\ \ln(\gamma_3^{fh})^\infty_{x_1=1} + \phi_2^o\ln(\gamma_3^{fh})^\infty_{x_2=1} \tag{16}$$

$$- \bar{v}_3^o\ (x_1^o\bar{v}_1^o + x_2^o\bar{v}_2^o)(RT)^{-1}\ \Delta\bar{G}_{12}^{fh}$$

where,

$$\phi_1^o = \frac{x_1^o\bar{v}_1^o}{x_1^o\bar{v}_1^o + x_2^o\bar{v}_2^o} \quad \text{and} \quad X_1^o = \frac{X_1}{X_1 + X_2} \tag{17}$$

is shown to depend on a weighted average of the solute activity coefficient in each of the pure solvents $(\gamma_3^{fh})^\infty_{x_1=1}$, $(\gamma_3^{fh})^\infty_{x_2=1}$ and a contribution due to the "unmixing" of the solvent pair by the presence of the solute. Enhancement of the unmixing term by a large solute molecule can lead to predictions of maxima or minima in the thermodynamic properties of the solute.

Although the NIBS approximations for solute activity coefficients in binary solvent mixtures cannot be rigorously extended to liquid-liquid partitioning in systems of practical importance, expressions developed for "model" systems may possess predictive applicability[9]. The simplest system to consider involves the partitioning of a solute between two "completely" immiscible liquid phases where only nonspecific interactions are permitted. The mobile phase consists of a binary mixture of inert solvent molecules (completely immiscible with the stationary phase at all

binary compositions) and the stationary phase is such that the solute activity coefficients at infinite dilution $\gamma_3^{s,\infty}$ remains constant. The combinations of equations (8), (15) and (16) then gives:

$$\ln K_R^o = \phi_1^o \ln \ (K_R^o)_{x_1^o=1} + \phi_2^o \ln \ (K_R^o)_{x_2^o=1} - \bar{V}_3^o (X_1^o \bar{V}_1^o + X_2^o \bar{V}_2^o)(RT)^{-1} \Delta \bar{G}^{fh}(T,P)$$

(18)

With this equation retention volumes in pure solvents can be used to calculate solute distribution coefficients at infinite dilution in the pure solvents. These values can be combined with the excess free energy of the binary solvent mobile phase to predict solute distribution coefficients. The predictive ability of this equation will depend to a large extent on the complexity of the system under investigation. It is anticipated that this approach will provide reasonably accurate approximations for simple systems containing only nonspecific interactions and will fail in systems having either specific solute-solvent or solvent-solvent interactions. The extension of equation (18) to systems involving complexation between the solute and one component of the binary mobile phase should be similar to methods employed in gas-liquid chromatography to study association complexes.

Experimental LLC partition coefficinets were unavailable for comparison, but similar expressions based on mole fractions have been applied by Buchowski and Teperek[10] to infinite dilution partition coefficients of benzoic acid and o-nitroaniline in systems benzene + cyclohexane--water and isooctane + bromoform--water. This general approach if proven successful, will offer new possibilities to study association phenomenon for nonvolatile solute molecules.

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