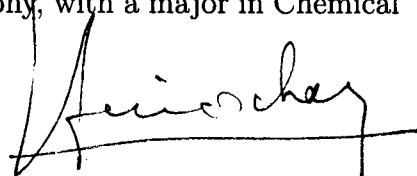


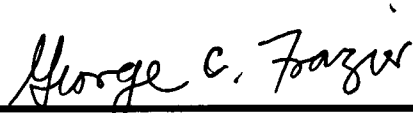
To the Graduate Council:

I am submitting herewith a dissertation written by Igor Quiñones-García entitled "Application of multisolute adsorption equilibrium to the simulation of nonlinear chromatographic band profiles". I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemical Engineering.



Georges A. Guiochon, Major Professor

We have read this dissertation
and recommend its acceptance:



Accepted for the Council:



Associate Vice Chancellor and
Dean of the Graduate School

**Application of
multisolute adsorption equilibrium
to the simulation of
nonlinear chromatographic band profiles**

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Igor Quiñones-García
August 1999

This dissertation is dedicated to ALL my family,
especially to José and Lucía and
to Marlene, Arlene and Alina,
for their love, support and understanding.
God bless all of them.

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Abstract

In this study, multisolute adsorption equilibrium data were determined experimentally for three systems which are relevant to the area of preparative liquid chromatography. The first system refers to the multisolute adsorption of three light aromatic alcohols on a reversed phase column from a mobile phase composed of a mixture of water and methanol. The second system corresponds to the adsorption of three basic drugs on a C_{18} column from a buffered mixture of water and acetonitrile. The third system refers to the adsorption of a racemic pharmaceutical intermediate on a chiral column from acetonitrile.

A nonideal, adsorbed solution theory model was developed in order to better understand the distribution of the phenylalcohols between the adsorbed and the bulk phases. The model is able to accurately predict the competitive data based on the single solute adsorption data. It was found that the activity coefficients of the solutes in both phases at equilibrium are roughly constant. In our opinion, this fact explains why the competitive adsorption data presented in this and previous studies can be successfully predicted using simple models like the Langmuir, bi-Langmuir or the ideal adsorbed solution theory models.

Finally, high-concentration band profiles and system peaks were also measured for the aforementioned experimental systems. Theoretical band profiles were calculated using the relevant adsorption isotherms and the equilibrium-dispersive model of nonlinear chromatography. Very good agreement was found between the experimental and the calculated band profiles. This fact provides additional evidence about the usefulness of the equilibrium-dispersive model for the method development, scale-up and optimization of preparative separations when using highly efficient columns.

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Notation

a_i = adsorbate-adsorbent interaction constant of the i -th component (l/g)

A = specific surface area of the adsorbent (cm²/g)

$A_{i,j}$ = configuration integral of components i and j

A_i^b = activity of the i -th solute in the bulk liquid

Bi = Biot number

C_i^f = nonequilibrium concentration of the i -th component in the mobile phase (g/l)

C_1^F = frontal analysis concentration of benzyl alcohol in the feed (g/l)

C_2^F = frontal analysis concentration of 2-phenyl ethanol in the feed (g/l)

C_3^F = frontal analysis concentration of 2-methyl benzyl alcohol in the feed (g/l)

C_1^1 = frontal analysis concentration of benzyl alcohol in the first subplateau (g/l)

C_1^2 = frontal analysis concentration of benzyl alcohol in the second subplateau (g/l)

C_2^2 = frontal analysis concentration of 2-phenyl ethanol in the second subplateau (g/l)

C_i = equilibrium concentration of the i -th component in the bulk liquid phase (g/l)

C_i^{sp} = equilibrium concentration of the i -th component in the model stationary phase (g/l)

C_i^s = equilibrium concentration of the i-th component on the surface of the particle (g/l)

$C_{i,o}$ = equilibrium concentration of the i-th single solute in the bulk liquid phase (g/l)

C_i^o = proportionality factor of the i-th solute in eq. (2.22a) (g/l)

D_L = axial dispersion coefficient in the chromatographic column (cm²/sec)

D_d = axial dispersion coefficient in the dispersion column (cm²/sec)

D_{eff} = effective, intraparticle diffusion coefficient (cm²/sec)

D_i^x = distribution coefficient of the i-th component based on the ratio of mole fractions

D_i^c = distribution coefficient of the i-th component based on the ratio of molar concentrations

$D_i^{c,\infty}$ = infinite dilution distribution coefficient of the i-th component based on the ratio of molar concentrations

F = Fisher parameter

$F(\epsilon)$ = adsorption energy distribution

ΔG_i^o = standard molar Gibbs free energy of adsorption of the i-th component (kJ/mol)

ΔH_i^o = standard molar enthalpy of adsorption of the i-th component (kJ/mol)

I_{norm} = normalized absorbance

I = absorbance (mAU)

I_{max} = maximum value of the absorbance (mAU)

K_{a1} = association constant of component 1 in the Kiselev model

K_{a2} = association constant of component 2 in the Kiselev model

k'_i = retention factor of the i -th solute

K_m = mixed association constant in Kiselev model

K_i = Langmuir or Jovanovic equilibrium constant of the i -th component (l/g)

K_i^L = Langmuir equilibrium constant of the i -th solute (l/g)

K_i^{app} = apparent Langmuir equilibrium constant of the i -th solute (l/g)

k_f = film mass transfer coefficient (cm/sec)

K_i^{exp} = experimental Henry constant of the i -th component

K_i^x = Henry constant of the i -th component defined in terms of mole fractions

K_i^c = Henry constant of the i -th component defined in terms of molar concentrations

l = number of adjusted parameters in the model, eq. (3.41) or axial coordinate in the dispersion column (cm), eq. (5.4)

L = length of the chromatographic column (cm)

L_d = length of the dispersion column (cm)

n = number of molecules present in the biggest cluster, eq. (2.9) or total number of experimental points, eq. (3.41)

n_i^∞ = capacity of the adsorbed layer for the i -th component (g/l)

n^∞ = capacity of the adsorbed layer or lattice (g/l)

N = number of components in the system or column plate number

N_s = number of solutes in the system

Pe = Peclet number in the chromatographic column

Pe_{app} = apparent Peclet number in the chromatographic column

Pe_d = Peclet number in the dispersion column

q_{exp} = experimental value of the equilibrium concentration in the adsorbed phase
(g/l)

q_i = equilibrium concentration of i-th component in the adsorbed phase (g/l)

$q_{i,o}$ = equilibrium concentration of the single i-th solute in the adsorbed phase
(g/l)

q_t = theoretical value of the equilibrium concentration in the adsorbed phase
(g/l)

Q_i^{iso} = isosteric heat of adsorption of the i-th component (kJ/mol)

Q_i = nonequilibrium concentration of the i-th component in the stationary phase
(g/l)

r = radial position in the particle (cm)

r_i = number of lattice sites occupied by the i-th adsorbate

R = universal gas constant (kJ/mol K) or particle radius (cm)

$S_{1,2}$ = selectivity between solute 1 and 2

ΔS_i^o = standard molar entropy of adsorption of the i-th component (kJ/mol K)

t = time (sec)

$t_{R,i}$ = retention time of the i-th solute (sec)

t_o = column dead time (sec)

T = absolute temperature (K)

u = interstitial velocity in the chromatographic column (cm/sec)

u_d = superficial velocity in the dispersion column (cm/sec)

v = volume of the cage in the Ruthven model (cm³)

V_i = breakthrough volume of the i-th solute (ml)

V_o = system hold-up volume (ml)

V_{sp} = volume of the stationary phase (ml)

x_i = solvent-free mole fraction of the i-th solute in the adsorbed phase

x_i^a = mole fraction of the i-th component in the adsorbed phase

x_i^{sp} = mole fraction of the i-th component in the model stationary phase

x = axial coordinate in the chromatographic column (cm)

x_i^b = mole fraction of the i-th component in the bulk liquid phase

y = nondimensional position in the dispersion column

z = nondimensional position in the chromatographic column

Greek Letters

α_i = constant of the i-th component in the Flory-Huggins model

α = starting point of integration in the binary solute domain

β = volume of the molecule (cm³) or final point of integration in the binary

solute domain

Γ_i = excess concentration of the i-th component in the adsorbed phase (g/l)

γ_i^{sp} = activity coefficient of the i-th component in the model stationary phase

γ_i^b = activity coefficient of the i-th component in the bulk liquid phase

γ_i^a = activity coefficient of the i-th component in the adsorbed phase

$\gamma_i^{b,\infty}$ = infinite dilution activity coefficient of the i-th component in the bulk liquid phase

$\gamma_i^{a,\infty}$ = infinite dilution activity coefficient of the i-th component in the adsorbed phase

Δ = error in eq. (3.49)

δ = relative error calculated in the consistency test

ϵ = adsorbate-adsorbent energy (kJ/mol), column void fraction or error in eq. (3.9)

θ = nondimensional time in the chromatographic column

θ_i = surface or fractional coverage of the adsorbed phase by the i-th component

θ_A = surface coverage of nonassociated molecules of component A in the Kiselev model

θ_B = surface coverage of nonassociated molecules of component B in the Kiselev model

θ_t = overall surface coverage on an heterogeneous adsorbent

κ_i = equilibrium constant of the i-th component on the first site of the bi-

Langmuir model (l/g)

λ_i = equilibrium constant of the i-th component on the second site of the bi-

Langmuir model (l/g)

$\Lambda_{i,j}$ = adsorbate-adsorbate interaction constant of components i and j in the

Wilson model

μ_i^b = chemical potential of the i-th component in the bulk liquid (kJ/mol)

$\bar{\nu}$ = Average heterogeneity parameter

ν_i = Heterogeneity parameter of the i-th component

$\Xi(\rho)$ = initial profile of concentrations in the particle

π = spreading pressure of the adsorbed layer (dyne/cm)

π_i^o = spreading pressure at the interface between the adsorbent and pure i-th liquid (dyne/cm)

Π = value of the integral along the path in the binary solute domain

Π_{max} = largest sum of the integrals of the same sign, see eq. (3.10)

ρ = nondimensional position in the particle or molar density of the bulk liquid phase (mol/cm³)

ρ_{sp} = molar density of the model stationary phase (mol/cm³)

τ = residence time (sec)

Φ = function defined by eq. (2.17) or monolayer capacity of the first site in the bi-Langmuir model (g/l)

Φ_i^o = integral for the spreading pressure of the single i-th solute (g/l)

$\Phi(z)$ = initial profile of concentrations in the column

$\chi_{i,j}$ = adsorbate-adsorbate interaction parameter between components i and j

Ψ = function defined by eq. (2.7) or monolayer capacity of the second site in the bi-Langmuir model (g/l)

$\Psi(\tau)$ = boundary condition at the column inlet

ω = nondimensional time in the dispersion column

Subscripts and superscripts

A, B, C, D = different integration paths, see eq. (3.9)

a = adsorbed phase

b = bulk liquid phase

c = molar concentration

d = dispersion column

f = mobile (fluid) phase

F = feed

i = index

j = index

k = index

o = single solute

s = solvent or surface

sp = stationary phase

x = mole fraction

1 = component 1 or benzyl alcohol

2 = component 2 or 2-phenyl ethanol

3 = 2-methyl benzyl alcohol

4 = buspirone

5 = doxepin

6 = diltiazem

7 = first enantiomer

8 = second enantiomer

Abbreviations

ACN = acetonitrile

BA = benzyl alcohol

BU = buspirone

DI = diltiazem

DO = doxepin

E1 = first enantiomer

E2 = second enantiomer

ECP = elution by characteristic point

FA = frontal analysis

FACP = frontal analysis by characteristic point

FG = Fowler-Guggenheim

FH = Flory-Huggins

HIAS = heterogeneous ideal adsorbed solution

HPLC = high performance liquid chromatography

IAS = ideal adsorbed solution

LC = liquid chromatography

L-L = liquid-liquid

MBA = 2-methyl benzyl alcohol

PE = 2-phenyl ethanol

RAS = real adsorbed solution

RHS = right hand side

RPI = racemic pharmaceutical intermediate

RPLC = reversed-phase liquid chromatography

RSS = residual sum of squares

SPD = spreading pressure dependent

UV = ultraviolet

VLE = vapor liquid equilibrium

VSM = vacancy solution model

Chapter 1

Introduction

High-efficiency adsorption-based separation processes like batch elution chromatography and continuous, simulated moving bed chromatography have now become important purification techniques, widely used for large-scale separations in the pharmaceutical industry [Stinson, 1995]. The time required by the method development, scale-up and optimization of these preparative techniques is relatively long and contributes significantly to the cost of the process [Bidlemeier, 1987]. Conventional trial-and-error methods could be improved by the application of appropriate models of the process [Guiochon et al., 1994]. One of the major difficulties encountered is the selection of the most suitable model of nonlinear chromatography to account for the behavior of the individual band profiles and the acquisition of the experimental data required for the calculation of accurate solutions of this model. If the calculated profiles can be validated by their agreement with experimental profiles, a rapid optimization of the experimental conditions for maximum production rate, minimum production cost, or extremum of any other objective function can be achieved [Felsing and Guiochon, 1994, 1998]. This optimization is rapid, inexpensive compared to the conventional empirical approaches and avoids the wasting of chemicals.

Detailed models based on mass balance equations have been developed in order to describe the separation process on a chromatographic column [Rhee et al., 1986]. They include the different contributions to the mass transfer in the column like the axial dispersion, the liquid film resistance and the diffusion in the packing [Suwondo et al., 1991]. However, the effective use of these models requires that some important physical characteristics of the system be modeled accurately. First among our needs is the attainment of an accurate quantitative description of the multicomponent equilibrium for the particular system under consideration. For obvious economic reasons, preparative chromatography must be carried out at high concentrations, in which case a nonlinear equilibrium takes place. Under these circumstances, the thermodynamic factors play an important role in the outcome of the separations. Second is the modeling of the mass transfer processes. For the highly efficient chromatographic columns widely used today, the influence of the mass transfer resistance on band profiles is small compared to that of thermodynamics. In this particular case, the mass transfer effects can be accounted for by an overall, apparent dispersion coefficient and the process can be accurately modeled by the equilibrium-dispersive model, which has been quite successful [Guiochon et al., 1994]. So, the the determination of the multisolute adsorption equilibrium remains of paramount importance for most of the practical applications of nonlinear chromatography.

Molecular dynamics simulations have been performed for simplified, yet rel-

evant systems like reversed phase chromatography [Klatte and Beck, 1996]. In principle, the calculation of solute adsorption equilibria in such systems is possible via molecular simulation. Since these are quite complex molecular systems, the initial work is being directed towards the calculation of solute distribution constants at infinite dilution [Schure, 1998]. From the experimental point of view, it is worth noting that reliable, multisolute adsorption data are scarce even for important systems like reversed phases and chiral separations [Guiochon et al., 1994]. The determination of competitive isotherms is long, costly and time-consuming [Jacobson et al., 1987]. There are models available which allow the derivation of reasonable approximations of the competitive isotherms from single solute isotherms, which are much easier to measure [Ruthven, 1984; Valenzuela and Myers, 1989]. These methods allow a considerable reduction in the time and cost required by the acquisition of the multicomponent data. However, these models have been applied mainly to the description of multicomponent gas adsorption equilibria. Accordingly, the identification of simplified models able to predict multisolute equilibrium data based on the analysis of a limited number of experimental measurements is another important task.

One important goal of this dissertation is to obtain reliable, multisolute adsorption equilibrium data for several experimental systems relevant to preparative chromatography like reversed and chiral stationary phases. Such data could be crucial in the future in order to better understand the behavior of these

systems when comparing the experimental results with the results of molecular simulations or other advanced models of phase equilibria.

Another goal is to analyze the experimental adsorption data in terms of different models of adsorption equilibria. It is important to evaluate our present ability to predict multisolute adsorption data based on the parameters derived from the correlation of single solute data. In the particular case of the racemic mixture analyzed here, another important problem was evaluated; namely the prediction of the single and binary solute adsorption data based on the parameters derived from the analysis of the racemate adsorption data.

The final goal of this work was to obtain experimental, high concentration band profiles and system peaks in the aforementioned experimental systems. The knowledge of the adsorption equilibria in such systems and the ability to calculate band profiles from the solution of mass balance equations permitted us to compare experimental and theoretical results.

The work is presented in four parts:

1. A review of the literature regarding the experimental determination of multisolute adsorption equilibrium and the isotherm models currently employed in the analysis of such data.
2. The first case study refers to the comprehensive analysis of a ternary solute system corresponding to the adsorption of light aromatic alcohols on a reversed packing from a mixture of methanol and water. For this system; composed of

rather simple, nonionic organic molecules we were able to check the adsorption data for thermodynamic consistency. Also, from the single solute adsorption data measured at different temperatures, we derived relevant thermodynamic functions which proved to be useful for the assessment of important issues like the heterogeneity of the surface. We also analyzed the data in terms of different equilibrium models that include the nonideality of both the adsorbed and liquid bulk phases.

3. The second case study refers to a more complicated system corresponding to the adsorption of three basic drugs on a reversed phase packing from a buffered mobile phase composed of a mixture of acetonitrile, water and significant amounts of inorganic ions. The drugs studied are the corresponding hydrochlorides of buspirone (N-[4-(4-[2-Pyrimidinyl]-1-piperazinyl)butyl]-8-azaspiro[4,5]-decane-7,9-dione), doxepin (11[16H]-[3-(Dimethylamino)-propylidene]dibenz[b,e]oxepine) and diltiazem (*cis*-(+)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one).

4. The last case study corresponds to the adsorption of a racemic pharmaceutical intermediate on a chiral stationary phase from acetonitrile as the mobile phase.

Chapter 2

Review of the Literature

2.1 Adsorption Equilibrium.

Single solute or multisolute adsorption equilibria can be measured by different techniques. Among them, the more important ones are frontal analysis (FA), frontal analysis by characteristic point (FACP), elution by characteristic point (ECP), perturbation method, hodograph transform method, numerical solution of the inverse problem, adsorption-desorption method and static method. There are several excellent references with detailed explanations of these methods [Guiochon et al., 1994; Dose et al., 1991; Nicoud and Seidel-Morgenstern, 1996; Tondeur et al., 1996]

In the domain of liquid chromatography (LC), the number of reports regarding experimental single solute adsorption data is quite large [Guiochon et al., 1994]. On the other hand, there are just a few studies concerning multisolute adsorption data because of the sheer volume of the experimental effort required. Most, if not all, studies on multisolute adsorption refer to binary solute systems [Jacobson et al., 1987; Huang and Guiochon, 1989; Ma et al., 1990; Katti et al., 1990; Zhu et al., 1991; Bellot and Condoret, 1993; Nicoud et al., 1993; Charton et al., 1993, 1994; Jandera and Komers, 1997; Heuer et al., 1998; Pais et al., 1998]. It seems

that there are no reports on ternary solute systems. The binary solute adsorption data have been measured either by FA [Huang and Guiochon, 1989; Ma et al., 1990; Zhu et al., 1991; Bellot and Condoret, 1993; Charton et al., 1993, 1994; Jandera and Komers, 1997], hodograph transform [Ma et al., 1990; Katti et al., 1990], adsorption-desorption method [Nicoud et al., 1993; Pais et al., 1998] and perturbation technique [Heuer et al., 1998]. It is clear that FA is the method of choice in most situations.

Different isotherm models have been used to correlate single solute adsorption data and to predict multicomponent equilibria in the domain of LC. Some of these models consider an ideal behavior of the system, without taking into account the possible sources of non-ideal behavior, like the adsorbate-adsorbate interactions in the adsorbed phase, the heterogeneity of the adsorbent surface, the actual differences in the molecular size of the adsorbates, the interactions among the components of the bulk liquid phase leading in some cases to the formation of associates, the limited solubility of the components in the bulk liquid phase, or even the existence of synergistic effects [Valenzuela et al., 1989; Ruthven, 1984; Jaroniec and Madey, 1988; Prausnitz et al., 1986; Jandera and Guiochon, 1992; Poppe, 1993]. Because of the complexity of the systems under consideration, different simplifications have been done in order to make the problem tractable.

2.1.1 Models for homogeneous surfaces without lateral interactions.

These models are the simplest ones. Within this group, the Langmuir model considers that the adsorption process takes place on a surface which can be represented by a lattice composed of a fixed number of adsorption sites of equal energy, one molecule being adsorbed per adsorption site until monolayer coverage is achieved [Langmuir, 1916]. See figure 2.1 for details. No other nonideal effects are included in this model. In addition, the multicomponent Langmuir model [Schwab, 1928] assumes equal adsorption capacities for all the components in the mixture (and equal to the capacity of the lattice), in order to satisfy the requirement of thermodynamic consistency [LeVan and Vermeulen, 1981]. For practical purposes, however, it is possible to allow the values of the monolayer capacity to be different for different species as long as the model, used only as a mean of empirical correlation, provides a good representation of the whole set of multisolute adsorption data.

Adsorption isotherm equations relate the equilibrium concentrations of the studied components in the bulk liquid phase, C_i , and in the adsorbed phase, q_i . The equilibrium concentration in the adsorbed phase is usually expressed through the surface coverage $\theta_i = q_i/q_s$, where q_s is the adsorption capacity of

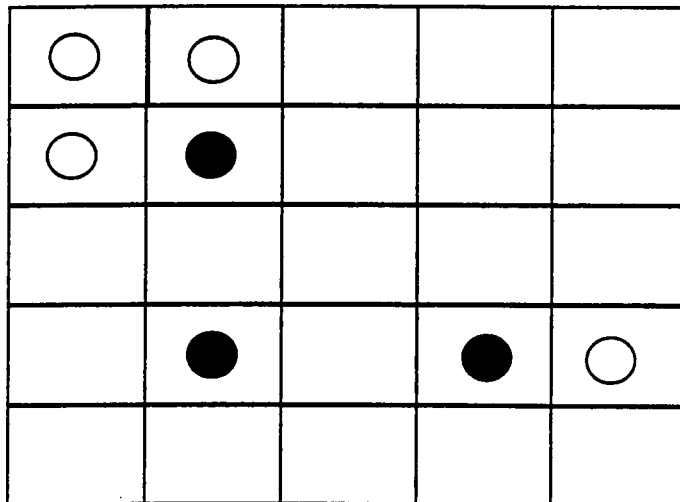


Figure 2.1 Schematic representation of the Langmuir model.

the lattice. The Langmuir model for a binary mixture is defined by

$$\theta_1 = \frac{K_1 C_1}{1 + K_1 C_1 + K_2 C_2} \quad (2.1a)$$

$$\theta_2 = \frac{K_2 C_2}{1 + K_1 C_1 + K_2 C_2} \quad (2.1b)$$

where K_i is the adsorbate-adsorbent or Langmuir equilibrium constant for the i -th component. Note, that all the parameters of the competitive isotherm can be derived from measurements made with the single solutes, which is very convenient from the experimental point of view.

The Langmuir model gives a good correlation of single solute LC data in most situations [Guiochon et al., 1994]. The competitive Langmuir model has been often applied to LC adsorption data. In some cases, this model gives a good prediction of the binary adsorption data or binary band profiles based on the single solute isotherm parameters [Frenz and Horvath, 1985; Jacobson et al., 1987; Ma et al., 1990; Katti et al., 1990; Katti and Guiochon, 1990; Katti et al., 1991]. In other cases, similar calculations have not been satisfactory [Huang and Guiochon, 1989; El Fallah and Guiochon, 1990; Zhu et al., 1991; Bellot and Condoret, 1993].

The Jovanovic model is the second important model classified within this group [Jovanovic, 1969]. The Jovanovic model keeps the same assumptions contained in the Langmuir model, only considering in addition the possibility of some mechanical contact between the adsorbing and desorbing molecules. The

model is defined as

$$\theta = 1 - e^{-KC} \quad (2.2)$$

Later, the Jovanovic model was extended to mixtures of compounds having different distribution functions governing the settling times of the adsorbed molecules on the surface [Vlad and Segal, 1979]. The main drawback of the competitive equations proposed by Vlad and Segal resides in the fact that binary solute data are required in order to estimate the cross-interactions parameters present. A simpler model was derived later for the multicomponent Jovanovic model [Sircar, 1991]. For a binary mixture it is defined as

$$\theta_1 = \frac{K_1 C_1}{K_1 C_1 + K_2 C_2} [1 - e^{-(K_1 C_1 + K_2 C_2)}] \quad (2.2a)$$

$$\theta_2 = \frac{K_2 C_2}{K_1 C_1 + K_2 C_2} [1 - e^{-(K_1 C_1 + K_2 C_2)}] \quad (2.2b)$$

Note that all the parameters can be derived from single solute measurements. The Jovanovic model has been applied to the description of single solute [Huang and Horvath, 1987] and binary solute data [Quiñones and Guiochon, 1996a, 1998; Jandera and Komers, 1997]

2.1.2 Models for homogeneous surfaces with lateral interactions.

These models attempt to account for one additional non ideal effect, the possible lateral interactions in the adsorbed layer. Several derivations employing a statistical thermodynamics approach show that the adsorption of a binary mix-

ture on an homogeneous surface can be represented by the following adsorption isotherm model [Martire, 1992; Martinez and Basmadjian, 1996; Russell and LeVan, 1996]

$$K_1 C_1 = \frac{\theta_1}{(1 - \theta_1 - \theta_2)^{r_1}} e^{-r_1(\chi_{11}\theta_1 + \chi_{12}\theta_2)} \quad (2.3a)$$

$$K_2 C_2 = \frac{\theta_2}{(1 - \theta_1 - \theta_2)^{r_2}} e^{-r_2(\chi_{21}\theta_1 + \chi_{22}\theta_2)} \quad (2.3b)$$

In these equations, the fractional coverage of the *i*-component is $\theta_i = r_i q_i / q_s$, where r_i is the number of lattice sites occupied by one molecule of the *i*-component. So, r_i is a measure of the adsorbate size in the monolayer and the model given by Eqs 2.3a and 2.3b makes possible to account for the differences in the monolayer capacities of the adsorbates. The parameters χ_1 and χ_2 in Eqs. 2.3a and 2.3b account for the energy of interaction between molecules of the first and the second component, respectively. The parameters χ_{12} and χ_{21} (which have, in principle, the same value) account for the cross interactions between molecules of component 1 and of component 2. If there are no great differences in size or polarity between the molecules of the two components undergoing interactions, the value of the cross parameter can be estimated using the geometric mean of the single component parameters [Prausnitz et al., 1986], i.e.

$$\chi_{12} = \chi_{21} = (\chi_1 \chi_2)^{1/2} \quad (2.4)$$

For compounds of similar size and polarity, this classical combining rule often gives a good approximation. This could be the case for closely eluted compounds

in chromatography. However, for molecules of widely different size and polarity, the proper interaction parameters should be obtained from binary data. Once these values are known, the behavior of ternary or more complex mixtures could be predicted.

In the particular case in which the molecules of each component occupy only one adsorption site in the lattice (see figure 2.2), $r_1 = r_2 = 1$, this model reduces to the well known multicomponent Fowler-Guggenheim (FG) model, when derived using the Bragg-Williams approximation [Fowler and Guggenheim, 1960].

$$K_1 C_1 = \frac{\theta_1}{1 - \theta_1 - \theta_2} e^{-(\chi_{11}\theta_1 + \chi_{12}\theta_2)} \quad (2.5a)$$

$$K_2 C_2 = \frac{\theta_2}{1 - \theta_1 - \theta_2} e^{-(\chi_{21}\theta_1 + \chi_{22}\theta_2)} \quad (2.5b)$$

The above equations reduce to the competitive Langmuir model when lateral interactions are neglected (i.e., if $\chi_1 = \chi_2 = \chi_{21} = \chi_{12} = 0$). The Jovanovic model was extended to account for lateral interactions in the monolayer [Quiñones and Guiochon, 1998]. The model is described by the following equations

$$\theta_1 = \Psi_1 \{1 - e^{-(K_1 C_1 e^{\chi_{11}\theta_1 + \chi_{12}\theta_2} + K_2 C_2 e^{\chi_{21}\theta_1 + \chi_{22}\theta_2})}\} \quad (2.6a)$$

$$\theta_2 = \Psi_2 \{1 - e^{-(K_1 C_1 e^{\chi_{11}\theta_1 + \chi_{12}\theta_2} + K_2 C_2 e^{\chi_{21}\theta_1 + \chi_{22}\theta_2})}\} \quad (2.6b)$$

where

$$\Psi_1 = \frac{K_1 C_1 e^{\chi_{11}\theta_1 + \chi_{12}\theta_2}}{[K_1 C_1 e^{\chi_{11}\theta_1 + \chi_{12}\theta_2} + K_2 C_2 e^{\chi_{21}\theta_1 + \chi_{22}\theta_2}]} \quad (2.7a)$$

$$\Psi_2 = \frac{K_2 C_2 e^{\chi_{21}\theta_1 + \chi_{22}\theta_2}}{[K_1 C_1 e^{\chi_{11}\theta_1 + \chi_{12}\theta_2} + K_2 C_2 e^{\chi_{21}\theta_1 + \chi_{22}\theta_2}]} \quad (2.7b)$$

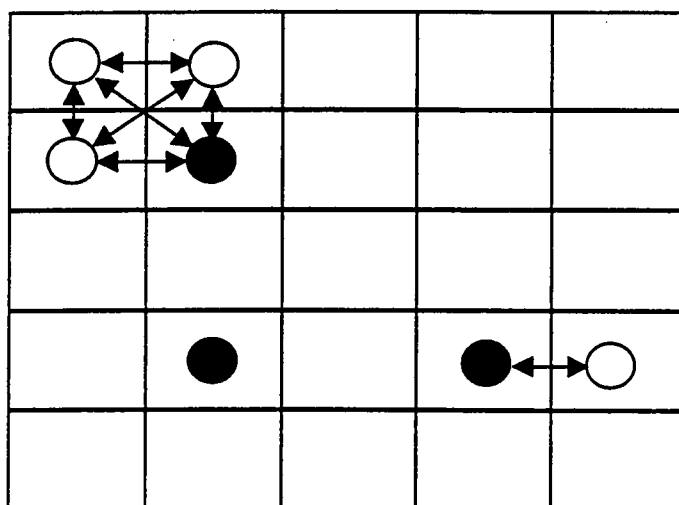


Figure 2.2 Schematic representation of the Fowler model.

In turn, Eqs. 2.6a and 2.6b reduce to the competitive Jovanovic model given by Eqs 2.2a and 2.2b if the lateral interactions are neglected .

The aforementioned models are implicit with respect to the solid phase concentrations, so their implementation in the simulation of multicomponent band profiles is time-consuming. Another group of models, also derived using a statistical thermodynamic approach, provide the adsorbed phase concentrations as explicit functions of the concentrations in the bulk fluid phase.

In one of these models [Ruthven, 1984], the molecules are localized at different surface sites or cages, with little interchange between cages (see figure 2.3). Each cage is considered to be a separate subsystem containing a finite number of adsorbate molecules. As a first approximation, interactions between molecules belonging to neighbor cages are neglected. The model has been applied successfully to account for adsorption in zeolites, where the structure consists of subsystems interconnected through small windows. For a binary mixture the model gives

$$\theta_1 = \frac{K_1 C_1 + \sum_j \sum_i [(K_1 C_1)^i (K_2 C_2)^j / (i-1)! j!] A_{ij}}{1 + K_1 C_1 + K_2 C_2 \sum_j \sum_i [(K_1 C_1)^i (K_2 C_2)^j / i! j!] A_{ij}} \quad (2.8a)$$

$$\theta_2 = \frac{K_2 C_2 + \sum_j \sum_i [(K_2 C_2)^i (K_1 C_1)^j / (i-1)! j!] A_{ij}}{1 + K_2 C_2 + K_1 C_1 \sum_j \sum_i [(K_2 C_2)^i (K_1 C_1)^j / i! j!] A_{ij}} \quad (2.8b)$$

The summation is carried out over all cages satisfying the requirement that $i\beta_1 + j\beta_2 \leq v$ where β_1 , β_2 and v are the volumes of the first molecule, second molecule and cage, respectively. The parameters A_{ij} are configuration integrals which

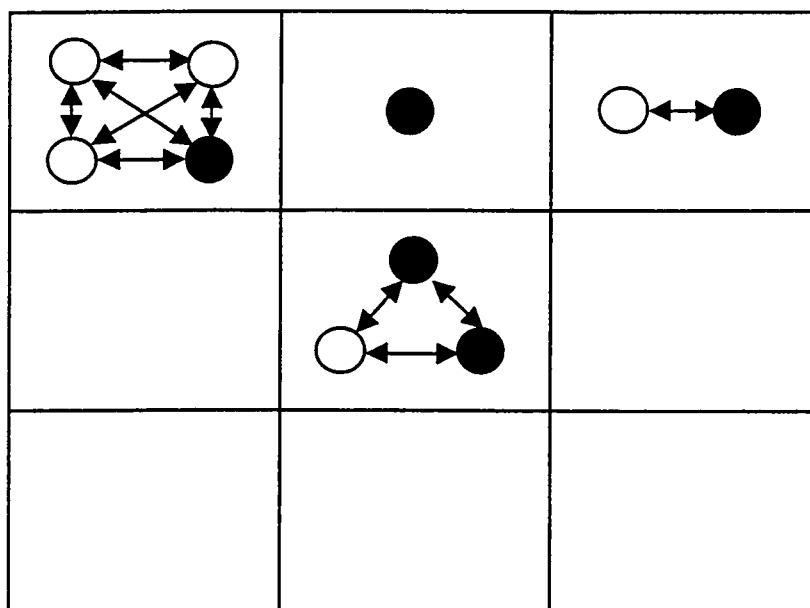


Figure 2.3 Schematic representation of the Ruthven model.

account for the adsorbate-adsorbate interactions. Some of these integrals can be estimated from the correlation of single component data. The configuration integrals corresponding to the interaction of different species could be estimated, as a first approximation, using the geometric mean expression stated above. Other models have been developed following a similar approach [Moreau et al., 1991].

A third group of models account for the interactions between the adsorbed molecules via a set of quasichemical reversible reactions [Berezin and Kiselev, 1972]. The adsorption isotherm is obtained by combining the association constants for all the reactions in an overall constant that describes the annexation of an adsorbed molecule to the given associated group. See figure 2.4 for details. In principle, the value of this constant is independent of the dimension of the molecular cluster. The model was extended to the case of a binary mixture [Quiñones and Guiochon, 1996c] and is defined by the equations

$$\theta_1 = \theta_A + \sum_{i=2}^n i K_{a1}^{i-1} \theta_A^i + \sum_{j=2}^n \sum_{k=1}^{j-1} k K_m^{j-1} \theta_A^k \theta_B^{j-k} \quad (2.9a)$$

$$\theta_2 = \theta_B + \sum_{i=2}^n i K_{a2}^{i-1} \theta_B^i + \sum_{j=2}^n \sum_{k=1}^{j-1} k K_m^{j-1} \theta_B^k \theta_A^{j-k} \quad (2.9b)$$

In the previous equations, n is the number of molecules present in the biggest cluster. K_{a1} , K_{a2} and K_m are the association constants characterizing the formation of clusters of the first component, second component and mixed components, respectively. Finally θ_A and θ_B are the surface coverages of the single, nonasso-

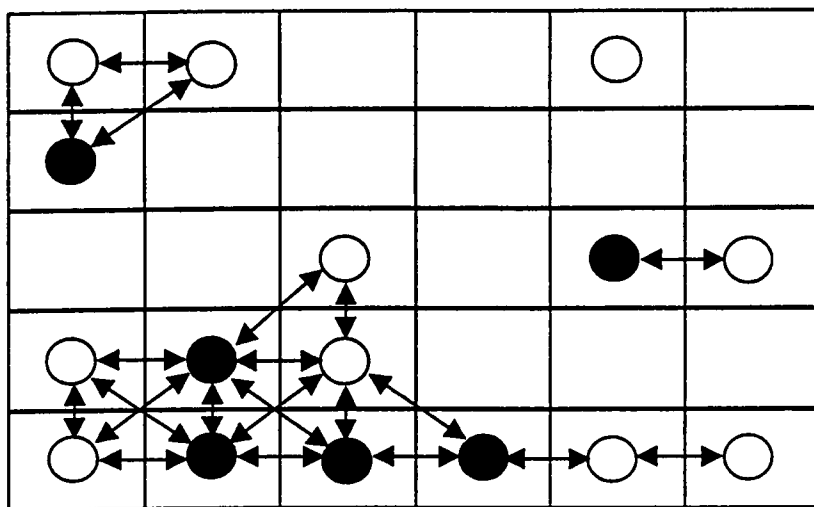


Figure 2.4 Schematic representation of the Kiselev model.

ciated molecules of the two components of the mixture. They can be estimated from the competitive Langmuir model,

$$\theta_A = K_1(1 - \theta_1 - \theta_2)C_1 \quad (2.10a)$$

$$\theta_B = K_2(1 - \theta_1 - \theta_2)C_2 \quad (2.10b)$$

If associations of any dimension may be formed, the following expressions for the competitive binary isotherm are valid

$$\theta_1 = \frac{\theta_A}{(1 - K_{a1}\theta_A)^2} + \frac{K_m\theta_A\theta_B}{(1 - K_m\theta_B)(1 - K_m\theta_A)^2} \quad (2.11a)$$

$$\theta_2 = \frac{\theta_B}{(1 - K_{a2}\theta_B)^2} + \frac{K_m\theta_A\theta_B}{(1 - K_m\theta_A)(1 - K_m\theta_B)^2} \quad (2.11b)$$

Several isotherm models for homogeneous surfaces with lateral interactions described in this section have been applied to the interpretation of single solute and multisolute LC adsorption data [Lin et al., 1989; Zhu et al., 1991; Bellot and Condoret, 1993; Quiñones and Guiochon, 1996a, 1996c, 1998; Jandera and Komers, 1997]

2.1.3 Models for heterogeneous surfaces without lateral interactions.

The models of this group share the same assumptions already contained in the simple models for homogeneous surfaces, such as the Langmuir and Jovanovic models. The only nonideal effect they try to account for is the heterogeneity of the adsorbent surface. Most of the adsorbents used in current practice, such

as activated carbons, silica gels, alumina, and even zeolites exhibit surface and structural heterogeneities [Jaroniec and Madey, 1988].

Silica is the most widely used material in liquid chromatography. In the specific case of silica packings employed in liquid chromatography, there exist both experimental and theoretical evidence of the heterogeneity of these adsorbents, as suggested in several reviews [Unger, 1979; Nawrocki, 1991a, 1991b, 1997]. In the preparation of reversed-phase packings derivatization of bare silica is rarely complete. As a result, all reversed-phase silicas possess unreacted silanols which constitute high energy adsorption sites, especially for basic compounds. On the other hand, the bonded alkyl chains constitute low energy sites. So, qualitatively, there exist at least two main groups of sites. Moreover, different types of silanols exist, they could be either isolated, geminal or vicinal. Each type of site provides a different value of the adsorbate-adsorbent interaction energy, thus originating a continuous energy distribution. Accordingly, the chromatography of organic bases is difficult due to several mechanisms governing their retention. Among these mechanisms, ion-exchange, hydrogen bonding, salting-out and hydrophobic interactions are the most important [Nawrocki, 1997].

An heterogeneous surface is characterized by an energy distribution function. For sites with equal values of the adsorbate-adsorbent interaction energy, a model valid for an homogeneous surface is applied, known as the local isotherm. The global or overall surface coverage on the heterogeneous surface for the single

component adsorption case, θ_t , is obtained from the integral equation [Jaroniec and Madey, 1988]

$$\theta_t = \int_0^\infty \theta(C, \epsilon) F(\epsilon) d\epsilon \quad (2.12)$$

where $\theta(C, \epsilon)$ is the local adsorption isotherm for the sites with an adsorption energy ϵ , and $F(\epsilon)$ is the adsorption energy distribution. As local isotherms for heterogeneous adsorption, the Langmuir, Fowler-Guggenheim, or Jovanovic models may be employed. The former two local isotherms are those most applied in practice for systems without or with lateral interactions, respectively [Jaroniec and Madey, 1988].

Equation (2.12) is the fundamental equation in the theory of adsorption on heterogeneous surfaces. Because this Fredholm integral equation is ill-posed, it does not have a unique solution. Attempts at the derivation of the adsorption energy distribution from the experimental isotherm, using numerical solutions and an assumed local isotherm have not led to convincing results but have demonstrated the difficulties, usually underestimated, of collecting proper experimental data [Stanley and Guiochon, 1994; 1995]. Another approach consists in deriving closed-form integrals of Eq. (2.12), assuming simple functional dependences for $\theta(C, \epsilon)$ and $F(\epsilon)$ and fitting experimental results to these equations in an effort to identify the relevant parameters. One model obtained in such a fashion is the UNILAN model [Valenzuela and Myers, 1989].

A significant number of other overall isotherms of adsorption on heterogeneous

surfaces were originally proposed for empirical or semiempirical reasons, with the sole aim of describing accurately and as simply as possible the adsorption behavior of real systems. Examples of these models are the Freundlich, Langmuir-Freundlich, Tóth, Dubinin-Astakhov, Dubinin-Radushkevich, Temkin-Pyzhev, Generalized Freundlich and Marckzewsky-Jaroniec models. A detailed analysis of all these models has been presented elsewhere [Jaroniec and Madey, 1988]. Many of these empirical equations for the overall isotherm can be obtained with local Langmuir behavior if an appropriate choice is made for the adsorption energy distribution.

For multicomponent adsorption, an expression analogous to Eq. (2.12) is applied, where the single component overall and local isotherms are replaced by the competitive overall and local isotherm models, with corresponding integration regions for each component and the multidimensional energy distribution function.

We note that Langmuir [Langmuir, 1918] proposed to describe the adsorption on an heterogeneous surface as the sum of a finite number of Langmuir isotherms, each of them characterizing adsorption on an homogeneous patch of the surface. This, in effect, introduces a discrete energy distribution. When only two types of sites are considered, the model is known as the dual site Langmuir or bi-Langmuir

model. See figure 2.5 for details. For a binary mixture, the model is defined as,

$$q_1 = \frac{\Phi \kappa_1 C_1}{1 + \kappa_1 C_1 + \kappa_2 C_2} + \frac{\Psi \lambda_1 C_1}{1 + \lambda_1 C_1 + \lambda_2 C_2} \quad (2.13a)$$

$$q_2 = \frac{\Phi \kappa_2 C_2}{1 + \kappa_1 C_1 + \kappa_2 C_2} + \frac{\Psi \lambda_2 C_2}{1 + \lambda_1 C_1 + \lambda_2 C_2} \quad (2.13b)$$

In the above equations, Φ and Ψ are the monolayer capacities on the first and second type of sites, respectively; κ_i and λ_i are the adsorbate-adsorbent equilibrium constants on the first and second type of sites, respectively.

The bi-Langmuir model has proven to be extremely successful in the description of the adsorption data of enantiomers on chiral phases or for the calculation of their band profiles [Charton et al., 1993, 1994; Jacobson et al., 1990b, 1991]. It is assumed that both enantiomers undergo the same non-selective interactions with most patches of surface, i.e $\lambda_1 = \lambda_2$, while enantio-selective interactions are highly selective, but take place in well-defined sites which are localized and relatively far from each other, ensuring the lack of adsorbate-adsorbate interactions on the enantio-selective sites. Furthermore, the adsorption energies on these sites are high and saturation is achieved at low values of the concentration in the mobile phase.

The bi-Langmuir model was also applied to the correlation of protein adsorption equilibria on reversed phases [El Fallah and Guiochon, 1992]. In this case a crude picture can be assumed, according to which two types of sites exist for the adsorption of the protein. The hydrophobic and hydrophilic patches or pock-

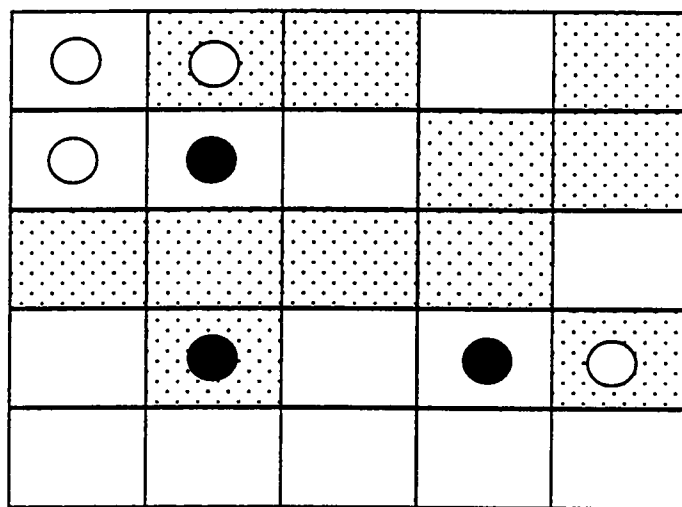


Figure 2.5 Schematic representation of the bi-Langmuir model.

ets of the protein adsorb on the alkyl chains and the silanols, respectively. The identification of the actual nature of the interactions involved in this case is of course beyond the simplification, but it is possible that the model captures the essential feature.

Other isotherm data exhibiting inflection points were accounted by the sum of a Langmuir and a Quadratic term [Diack and Guiochon, 1991]. These data refer to the adsorption of phenyldodecane from acetonitrile onto porous carbon. In this case, the Langmuir term accounts for adsorption on one type of site at very low surface coverages and could be explained by selective adsorption of the alkyl chains on surface defects (micropores). On the other hand the quadratic term accounts for adsorption on a second type of site (the flat 001 graphite planes) on which adsorbate-adsorbate interactions involving the alkyl groups take place at moderate degrees of surface coverage.

Other adsorption data on reversed phase packings have been fitted using the sum of a linear and a Langmuir terms. This model has been justified (i) in terms of the limited solubility of the adsorbates in the liquid phase and the possible association phenomena taking place in the adsorbed layer [Jandera and Guiochon, 1992; El Fallah and Guiochon, 1991] or (ii) in terms of the existence of two kind of adsorption sites responsible for the adsorption of enantiomers [Nicoud et al., 1993; Heuer et al., 1998; Pais et al., 1998].

The majority of these multiterm isotherms assume the existence of a discrete

number of different types of adsorption sites on the surface, each of them with a different value of the adsorbate-adsorbent interaction energy, thus assuming a discrete energy distribution [Jaroniec and Madey, 1988].

Theoretically, as stated before, a continuous distribution of such adsorption energies is more probable. The Freundlich model was applied to the correlation of single component adsorption data of Angiotensin II as an alternative to the correlation using the bilangmuir model [Eble et al., 1987]. In both cases, a fair correlation is obtained despite the fact that the Freundlich model uses two parameters instead of the four parameters contained in the bilangmuir model. The result can be explained by the fact that the Freundlich model is a generalization of the Langmuir model for an heterogeneous surface with a distribution function corresponding to an exponential decay [Jaroniec and Madey, 1988]. It is probable, of course, that the actual interaction of the peptide with the surface is much more complex than the simple picture provided by the Freundlich model.

The Langmuir-Freundlich model (see figure 2.6) has been applied successfully to the description of multisolute adsorption data on heterogeneous adsorbents [Jaroniec and Madey, 1988]. Its energy distribution function corresponds to a symmetrical quasi-Gaussian function. The model reduces to the monolayer but does not obey the Henry law. At low concentrations, the model reduces to the Freundlich model. The Langmuir-Freundlich model reduces to the Langmuir model for the case of an homogeneous surface. For a binary mixture, the model

is represented by the equations [Jaroniec and Madey, 1988]

$$\theta_{t1} = \frac{a_1 C_1}{a_1 C_1 + a_2 C_2} \frac{(a_1 C_1 + a_2 C_2)^{\bar{\nu}}}{[1 + (a_1 C_1 + a_2 C_2)^{\bar{\nu}}]} \quad (2.14a)$$

$$\theta_{t2} = \frac{a_2 C_2}{a_1 C_1 + a_2 C_2} \frac{(a_1 C_1 + a_2 C_2)^{\bar{\nu}}}{[1 + (a_1 C_1 + a_2 C_2)^{\bar{\nu}}]} \quad (2.14b)$$

where a_1 and a_2 are parameters which characterize the magnitude of the adsorbate-adsorbent interactions. On the other hand, $\bar{\nu}$ is the average heterogeneity parameter for the binary, which accounts for the dispersion of the energy distribution. It can be calculated via the arithmetic mean of the individual parameters [Kapoor et al., 1990]. Note that all the parameters in the previous equations can be estimated from the correlation of single solute isotherms. Another form of the competitive Langmuir-Freundlich model is also applied [Ruthven, 1984].

$$\theta_{t1} = \frac{(a_1 C_1)^{\nu_1}}{1 + (a_1 C_1)^{\nu_1} + (a_2 C_2)^{\nu_2}} \quad (2.15a)$$

$$\theta_{t2} = \frac{(a_2 C_2)^{\nu_2}}{1 + (a_1 C_1)^{\nu_1} + (a_2 C_2)^{\nu_2}} \quad (2.15b)$$

Another model belonging to this group was recently derived from a differential relationship relating the surface coverage and the bulk concentration of the adsorbate [Quiñones and Guiochon, 1996b]. The model reduces to the Jovanovic model when the surface is homogeneous. The energy distribution corresponding to this model for Jovanovic local behavior is a quasigaussian function skewed in the direction of high adsorption energies [Quiñones and Guiochon, 1999]. The model was extended to the case of a binary mixture [Quiñones and Guiochon,

1998]. It is represented by the following set of equations

$$\theta_{t1} = \frac{a_1 C_1}{a_1 C_1 + a_2 C_2} [1 - e^{-(a_1 C_1 + a_2 C_2)^{\bar{\nu}}}] \quad (2.16a)$$

$$\theta_{t2} = \frac{a_2 C_2}{a_1 C_1 + a_2 C_2} [1 - e^{-(a_1 C_1 + a_2 C_2)^{\bar{\nu}}}] \quad (2.16b)$$

For an homogeneous surface $\bar{\nu} = 1$, the above model reduces to the competitive Jovanovic model given by eqs (2.2a) and (2.2b).

2.1.4 Models for heterogeneous surfaces with lateral interactions.

The Temkin model for heterogeneous surfaces has been extended to take into account lateral interactions in the case of protein adsorption [Johnson et al., 1996]. Several models which consider a uniform distribution of the adsorption energy were also extended to account for adsorbate-adsorbate interactions in the monolayer [Ritter et al., 1990; Yang, 1993]. The Langmuir-Freundlich model was extended to account for lateral interactions in the monolayer using the Fowler-Guggenheim model to account for the local adsorption isotherm [Jaroniec and Madey, 1988]. See figure 2.7 for details. In order to simplify the writing of the multicomponent isotherm equations, let us define the following functions,

$$\Phi_1 = \frac{a_1 C_1 e^{\chi_{11}\theta_{t1} + \chi_{12}\theta_{t2}}}{[a_1 C_1 e^{\chi_{11}\theta_{t1} + \chi_{12}\theta_{t2}} + a_2 C_2 e^{\chi_{21}\theta_{t1} + \chi_{22}\theta_{t2}}]} \quad (2.17a)$$

$$\Phi_2 = \frac{a_2 C_2 e^{\chi_{21}\theta_{t1} + \chi_{22}\theta_{t2}}}{[a_1 C_1 e^{\chi_{11}\theta_{t1} + \chi_{12}\theta_{t2}} + a_2 C_2 e^{\chi_{21}\theta_{t1} + \chi_{22}\theta_{t2}}]} \quad (2.17b)$$

The Langmuir-Freundlich model with lateral interactions can then be represented

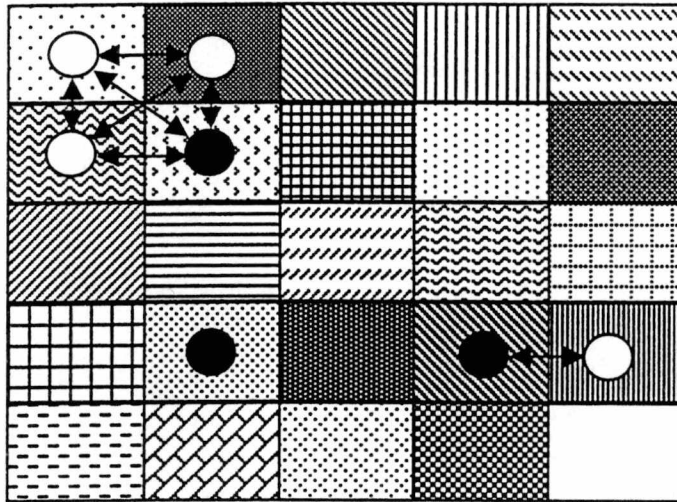


Figure 2.7 Schematic representation of the Langmuir-Freundlich-Fowler model.

by the following set of equations

$$\theta_{t1} = \Phi_1 \frac{[a_1 C_1 e^{\chi_{11}\theta_{t1} + \chi_{12}\theta_{t2}} + a_2 C_2 e^{\chi_{21}\theta_{t1} + \chi_{22}\theta_{t2}}]^{\bar{\nu}}}{\{1 + [a_1 C_1 e^{\chi_{11}\theta_{t1} + \chi_{12}\theta_{t2}} + a_2 C_2 e^{\chi_{21}\theta_{t1} + \chi_{22}\theta_{t2}}]^{\bar{\nu}}\}} \quad (2.18a)$$

$$\theta_{t2} = \Phi_2 \frac{[a_1 C_1 e^{\chi_{11}\theta_{t1} + \chi_{12}\theta_{t2}} + a_2 C_2 e^{\chi_{21}\theta_{t1} + \chi_{22}\theta_{t2}}]^{\bar{\nu}}}{\{1 + [a_1 C_1 e^{\chi_{11}\theta_{t1} + \chi_{12}\theta_{t2}} + a_2 C_2 e^{\chi_{21}\theta_{t1} + \chi_{22}\theta_{t2}}]^{\bar{\nu}}\}} \quad (2.18b)$$

Although the previous set of equations includes nonlinear functions of the adsorbed phase concentrations, the model is purely predictive, based solely on single component parameters. Note that for $\bar{\nu} = 1$, Eqs. (2.18a) and (2.18b) reduce to the competitive FG model represented by Eqs. (2.3a) and (2.3b).

In a similar fashion, the Jovanovic-Freundlich model was extended to account for lateral interactions in the monolayer [Quiñones and Guiochon, 1998]. The competitive model, is represented by the following set of the equations

$$\theta_{t1} = \Phi_1 \{1 - e^{-[a_1 C_1 e^{\chi_{11}\theta_{t1} + \chi_{12}\theta_{t2}} + a_2 C_2 e^{\chi_{21}\theta_{t1} + \chi_{22}\theta_{t2}}]^{\bar{\nu}}}\} \quad (2.19a)$$

$$\theta_{t2} = \Phi_2 \{1 - e^{-[a_1 C_1 e^{\chi_{11}\theta_{t1} + \chi_{12}\theta_{t2}} + a_2 C_2 e^{\chi_{21}\theta_{t1} + \chi_{22}\theta_{t2}}]^{\bar{\nu}}}\} \quad (2.19b)$$

In the special case of an homogeneous surface ($\bar{\nu} = 1$), the above equations reduce to the competitive model given by Eqs (2.6a) and (2.6b).

2.1.5 Solution Thermodynamics Models.

The framework of solution thermodynamics has been applied in the development of models for the prediction and correlation of multicomponent adsorption equilibria [Ruthven, 1984; Yang, 1987; Valenzuela and Myers, 1989; Talu and Myers, 1988]. Gas adsorption data has been the main subject of analysis.

The simplest among these models, known as the ideal adsorbed solution (IAS) model assumes ideality in both phases at equilibrium, viz the adsorbed phase and the bulk fluid phase [Myers and Prausnitz, 1965]. See figure 2.8 for details. The IAS model allows the prediction of multicomponent behavior based on the analysis of single component data. This model, originally developed for gas adsorption was later extended to the adsorption from dilute liquid systems [Radke and Prausnitz, 1972]. Within the framework of the model, a solvent-free mole fraction of the i -th solute in the adsorbed phase (x_i) is defined as

$$x_i = \frac{q_i}{\sum_{i=1}^{N_s} q_i} \quad (2.20)$$

where N_s is the number of solutes in the system. In addition, the single solute adsorption equilibrium is defined by the relationship

$$q_{i,o} = f(C_{i,o}) \quad (2.21)$$

where the subscript o emphasizes the fact that the correlation refers only to the single solute adsorption data. No assumptions have to be made regarding the nature of these data and any model could be used for the correlation provided that a good fit is obtained, especially at low concentrations.

The IAS model is defined by the following set of equations which are solved simultaneously in order to calculate all the values of the mole fractions x_i and

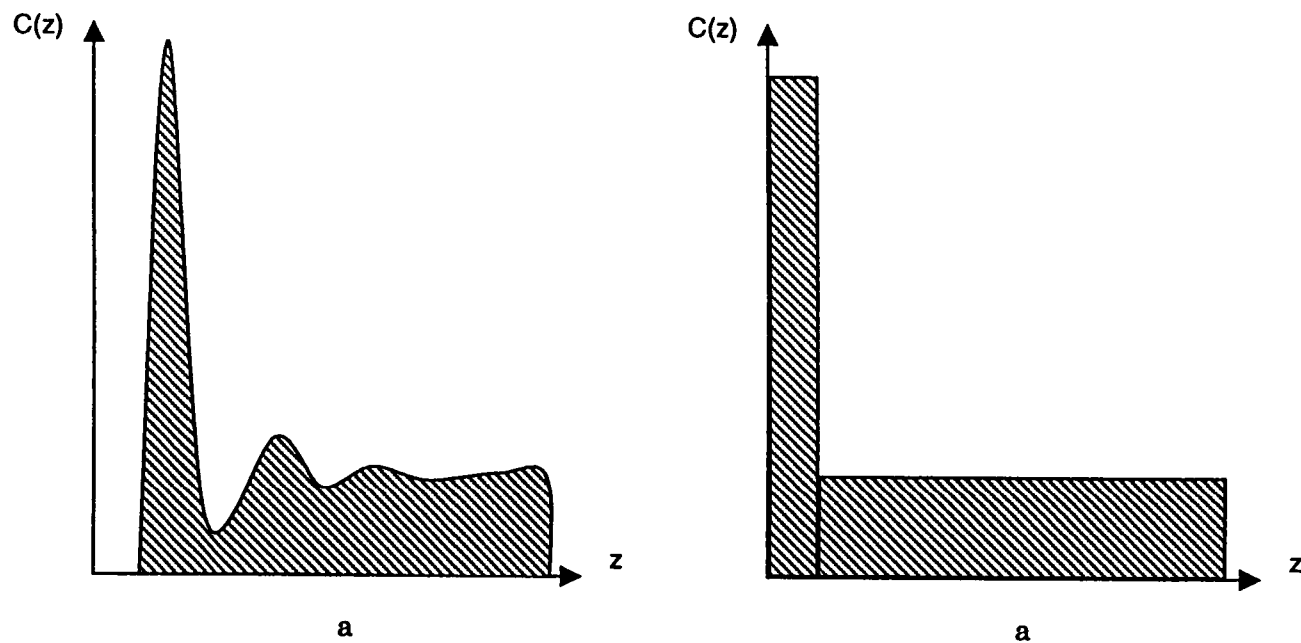


Figure 2.8 Schematic representation of the solid-liquid interface according to the Gibbsian model
a. Real distribution of the solute concentration with respect to the surface
b. Assumed distribution in the case of the adsorbed solution theory models

the corresponding proportionality factors C_i^o

$$C_i = C_i^o x_i \quad (2.22a)$$

$$\Phi_1^o = \Phi_2^o = \dots = \Phi_i^o = \dots = \Phi_{N_s}^o \quad (2.22b)$$

$$\sum_{i=1}^{N_s} x_i = 1 \quad (2.22c)$$

In eq. (2.22b) the integral for the spreading pressure of the single i -th solute (Φ_i^o) is defined by

$$\Phi_i^o = \frac{\pi A}{RT} = \int_0^{C_i^o} \frac{f(C_{i,o})}{C_{i,o}} dC_{i,o} \quad (2.23)$$

where π is the spreading pressure, A is the specific surface area of the adsorbent, R is the gas constant and T is the absolute temperature.

Finally, the adsorbed amount of each solute is given by

$$q_i = \frac{x_i}{\sum_{i=1}^N \frac{x_i}{f(C_i^o)}} \quad (2.24)$$

The IAS model has been applied to liquid chromatography adsorption data [Golshan-Shirazi et al., 1991; Zhu et al., 1991; Seidel-Morgenstern and Guiochon, 1993a; Bellot and Condoret, 1993; Charton et al., 1993], mainly via the LeVan-Vermeulen model [LeVan and Vermeulen, 1981]. The LeVan-Vermeulen model constitutes the IAS-based extension of the single component Langmuir model. For the particular case of equal saturation capacity for all the components in a mixture the LeVan-Vermeulen model reduces to the competitive Langmuir model.

In several studies, the IAS model has been able to correctly predict binary adsorption data or band profiles based on the fit of the single solute data [Golshan-Shirazi et al., 1991; Seidel-Morgenstern and Guiochon, 1993a; Bellot and Condoret, 1993; Charton et al., 1993]. The IAS model was extended to account for the adsorbent heterogeneity (HIAS) [Valenzuela et al., 1988]. For the particular case of a bimodal adsorption energy distribution with equal saturation capacities on each kind of site, the HIAS model reduces to the competitive bilangmuir model [Mathias et al., 1996]. Accordingly, it turns out that most of the experimental multisolute adsorption data or band profiles measured in the domain of liquid chromatography follow the IAS or HIAS formalism. The IAS and HIAS models applied to the dilute solute systems commonly employed in the domain of liquid chromatography tacitly assume the unsymmetric convention for normalization of activity coefficients [Prausnitz et al., 1986]. Accordingly, with the increase of the adsorbate concentration in the bulk liquid, the system deviates increasingly from ideality.

Other models within this group try to account for the nonideality of the adsorbed phase using excess Gibbs free energy models. The Flory-Huggins [Flory, 1953], Wilson [Wilson, 1964] and UNIQUAC [Abrams and Prausnitz, 1975] models have been employed in the correlation of pure and multicomponent equilibrium data [Suwanayuen and Danner, 1980; Costa et al., 1981, Cochran et al., 1985]. Since spreading-pressure effects are important in the adsorbed phase, spe-

cific models which account for these effects have been applied to the correlation of multicomponent adsorption equilibria [Talu and Zwiebel, 1986].

Among these models, the most popular are the real adsorbed solution model (RAS) [Costa et al., 1981], the vacancy solution model (VSM) [Suwanayuen and Danner, 1980; Cochran et al., 1985] and the spreading-pressure dependent model (SPD) [Talu and Zwiebel, 1986]. Other, more comprehensive models try to account simultaneously for the molecular interactions in the adsorbed phase and the heterogeneity of the surface [Karavias and Myers, 1992]. The majority of these nonideal models have been tested mainly with gas adsorption data. It is worth noting that the VSM model was also extended to the case of adsorption from dilute liquid solutions [Fukuchi et al., 1982].

A thermodynamic consistency test was developed to check adsorption data obtained from binary liquid mixtures [Sircar and Myers, 1971]. However, the concentration of the components of these binary mixtures is usually much higher than the solute concentrations commonly encountered in preparative chromatography separations. Adsorbed solution theory models were also developed and tested for these type of data [Larionov and Myers, 1971; Sircar et al., 1972; Minka and Myers, 1973]. The nonideality of the bulk liquid was accounted for in all cases via activity coefficients derived from corresponding VLE data. In one particular case, the nonideality of the adsorbed phase was correlated by the Redlich-Kister equation for the excess Gibbs free energy [Minka and Myers, 1973].

When ideality is assumed in both phases, a poor correlation of the experimental data has been observed [Liu and Pinto, 1997].

Liquid-liquid partition has been suggested as a possible model to describe the distribution of solutes in reversed-phase chromatography systems (Dorsey and Cooper, 1994). Within the framework of a liquid-liquid (*i.e.*, partition) model, the stationary phase is visualized as a bulk liquid instead of a most irregular silica surface covered with randomly bonded alkyl groups. Several liquids have been used to model the conventional reversed-phase packing materials. Most popular among these liquids are 1-octanol [Dasko, 1991] and *n*-hexadecane [Park et al., 1993]. The UNIFAC model [Hansen et al., 1991] has been applied to account for the nonidealities in both the stationary and the mobile bulk liquids in order to calculate distribution coefficients [Dasko, 1991; Park et al., 1993]

2.2 Thermodynamic Functions of Adsorption.

At low concentrations, the distribution of the *i*-th solute between the stationary phase and the mobile phase is characterized by the experimental Henry constant (K_i^{exp}) which is related to the retention time measured in HPLC [Guiochon et al., 1994]

$$K_i^{exp} = \frac{t_{R,i} - t_o}{t_o} \frac{\epsilon}{1 - \epsilon} \quad (2.25)$$

where $t_{R,i}$ is the retention time of the *i*-th solute, t_o is the column dead time and ϵ is the column porosity. All these parameters are determined from an analytical

chromatogram (recorded with a highly dilute sample) of a mixture of the solutes studied and a non-retained compound. Note that the above expression of the Henry constant is based on a ratio of molar concentrations. At equilibrium, the thermodynamic functions characterizing the distribution of the solutes among the two phases can be derived from well known relationships [Smith et al., 1996]. The standard molar Gibbs free energy of adsorption at temperature $T(K)$, ΔG_i° can be expressed as

$$\Delta G_i^\circ = -RT \ln K_i^{exp} \quad (2.26)$$

where R is the universal gas constant.

From the temperature dependence of the equilibrium constants we can derive the standard molar enthalpy of adsorption, ΔH_i° , via a Van't Hoff plot

$$\frac{\partial \ln K_i^{exp}}{\partial (1/T)} = -\frac{\Delta H_i^\circ}{R} \quad (2.27)$$

The adsorption entropy, ΔS_i° , is obtained from the fundamental equation

$$\Delta S_i^\circ = -\frac{\Delta G_i^\circ - \Delta H_i^\circ}{T} \quad (2.28)$$

The isosteric heats of adsorption, Q_i^{iso} , can be obtained for constant adsorbed phase concentrations from the isotherm data obtained at different temperatures, by using the Clausius-Clapeyron equation [Jacobson et al., 1990a]

$$\frac{\partial \ln A_i^b}{\partial (1/T)} = \frac{Q_i^{iso}}{R} \quad (2.29)$$

where A_i^b is the activity of the i -th solute in the bulk liquid phase.

The values of the thermodynamic functions described above have been evaluated from liquid chromatography adsorption data in both reversed-phase and chiral systems [Jacobson et al., 1990a; Miyabe and Suzuki, 1992; Seidel-Morgenstern and Guiochon, 1993b; Fornstedt et al., 1997]

2.3 Multisolute Band Profiles.

Multisolute band profiles originated as a result of the separation in a fixed bed chromatographic column can be calculated using models based on mass balance equations [Guiochon et al., 1994]. Among these models, a rate model [Suwondo et al., 1991] takes into account the different resistances to the mass transfer imposed by the axial convection, the diffusion in the film surrounding the particles and the intraparticle diffusion. Within the framework of this model, the column is assumed to be radially homogeneous, i.e. the concentration of the solutes and the parameters of the process (porosity, fluid velocity, temperature) are the same over the column cross section. Also, it is assumed that the mobile phase is incompressible; the process is isothermal and the plug flow pattern is valid. These assumptions render the problem one-dimensional in terms of space coordinates and no equations related to momentum or heat balances are needed. Finally, it is also assumed that equilibrium exists at the particle's interface. An schematic diagram which represents the physical picture and assumptions

involved is depicted in figure 2.9. Under the above conditions, the nondimensional mass balance in a column slice gives the concentration in the fluid stream as a function of both position and time, $C_i^f(z, \theta)$ as

$$\frac{\partial C_i^f}{\partial \theta} + \frac{\partial C_i^f}{\partial z} + \frac{(1 - \epsilon)}{\epsilon} \frac{\partial Q_i}{\partial \theta} = \frac{1}{Pe} \frac{\partial^2 C_i^f}{\partial z^2} \quad (2.30)$$

In the above equation the nondimensional position (z) is defined as ($z = x/L$) where x is the actual position in the direction of the flow and L is the column length. On the other hand, the nondimensional time (θ) is defined by ($\theta = t/\tau$) where t is the actual time and τ is the residence or dead time as defined by $\tau = L/u$ where u is the interstitial velocity in the packed bed. The Pe number is defined as $Pe = uL/D_L$ where D_L is the axial dispersion coefficient.

In eq (2.30) ϵ is the porosity of the packed bed and Q_i is the solute concentration in the particle. The increase over time of the solute concentration in the adsorbent should be balanced by the mass transfer across the film

$$\frac{\partial Q_i}{\partial \theta} = \frac{3k_f\tau}{R} (C_i^f - C_i^s) \quad (2.31)$$

where k_f is the film mass transfer coefficient and C_i^s is the concentration of the solute in the fluid at the surface of the particle.

The initial condition corresponding to eq. (2.30) is given by the profile of solute concentration along the column, $\Phi(z)$. It is usually equal to zero (empty column). The initial condition is defined by

$$C_i^f(z, 0) = \Phi(z) \quad (2.32)$$

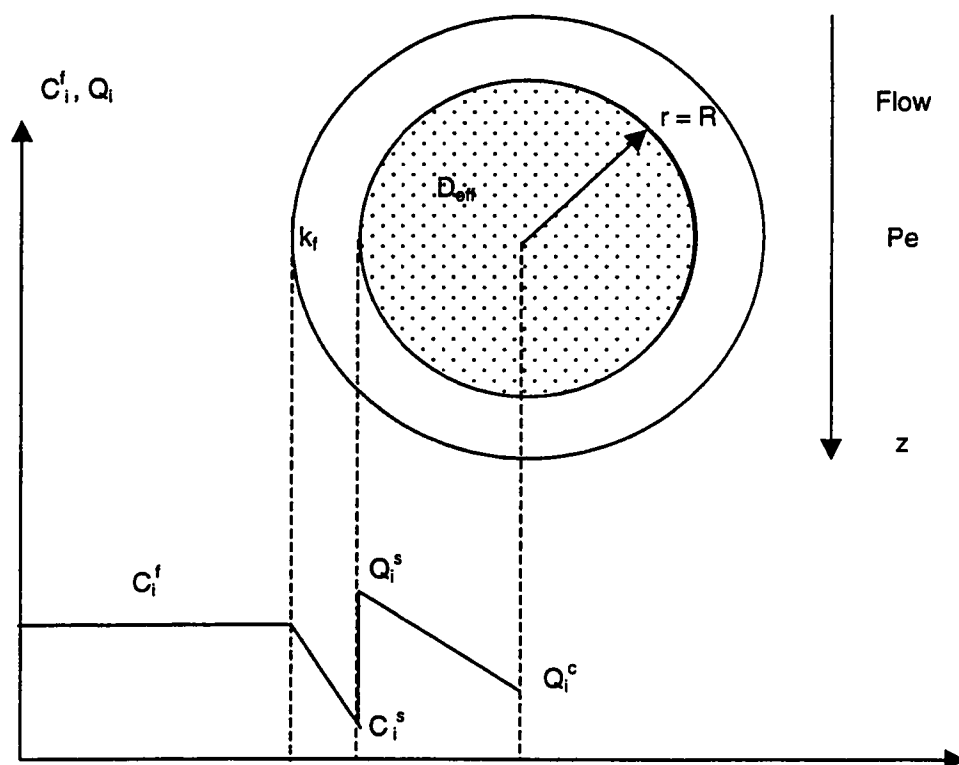


Figure 2.9 Schematic diagram employed in the derivation of the general rate model

The boundary conditions are defined by the shape of the injection profile at the column inlet, $\Psi(\theta)$;

$$C_i^f(0^-, \theta) = \Psi(\theta) \quad (2.33)$$

and the "close-close" Danckwerts conditions at the inlet

$$\left\{ \frac{\partial C_i^f}{\partial z} \right\}_{(0^+, \theta)} = -Pe[C_i^f(0^-, \theta) - C_i^f(0^+, \theta)] \quad (2.34)$$

and at the column outlet

$$\left\{ \frac{\partial C_i^f}{\partial z} \right\}_{(1, \theta)} = 0 \quad (2.35)$$

The mass balance over the spherical section of the particle gives $Q_i(\rho, \theta)$, also a function of time and position.

$$\frac{\partial Q_i}{\partial \theta} = \frac{\tau D_{eff}}{R^2} \left\{ \frac{\partial^2 Q_i}{\partial \rho^2} + \frac{2}{\rho} \frac{\partial Q_i}{\partial \rho} \right\} \quad (2.36)$$

Note the ρ is the nondimensional position in the particle defined as $\rho = r/R$, where r is the actual radial position and R is the radius of the particle. The initial condition corresponding to eq. (2.36) is given by the radial profile of solute concentration inside the particle, $\Xi(\rho)$. It is also usually equal to zero.

The initial condition is then defined by

$$Q_i(\rho, 0) = \Xi(\rho) \quad (2.37)$$

The boundary conditions are defined by the existence of equilibrium at the surface of the particle,

$$Q_i(1, \theta) = f(C_1^s, \dots, C_i^s, \dots, C_N^s) \quad (2.38)$$

by the balance of solute flux across the film,

$$\left\{ \frac{\partial Q_i}{\partial \rho} \right\}_{(1,\theta)} = Bi(C_i^f - C_i^s) \quad (2.39)$$

where the Biot number is defined as

$$Bi = \frac{3Rk_f}{D_{eff}} \quad (2.40)$$

and finally by the fact that there is no transfer at the particle's center

$$\left\{ \frac{\partial Q_i}{\partial \rho} \right\}_{(0,\theta)} = 0 \quad (2.41)$$

For HPLC columns, which usually possess a high efficiency, the equilibrium-dispersive model is a good approximation to the solution of the system of mass balance equations that governs the separation process in the column. In this case, because of the small particle diameter, the overall rate of mass transfer in the column is relatively fast and the effects produced by the different resistances to mass transfer are lumped into an apparent axial dispersion coefficient (D_{app}). See figure 2.10 for details. Note that the equilibrium-dispersive model assumes that q_i and C_i are the equilibrium values related by the multicomponent adsorption isotherm. For each component i in the column, the equilibrium-dispersive model is represented by the equation [Rhee *et al.*, 1971]

$$\frac{\partial C_i}{\partial \theta} + \frac{\partial C_i}{\partial z} + \frac{(1-\varepsilon)}{\varepsilon} \frac{\partial q_i}{\partial \theta} = \frac{1}{Pe_{app}} \frac{\partial^2 C_i}{\partial z^2} \quad (2.42)$$

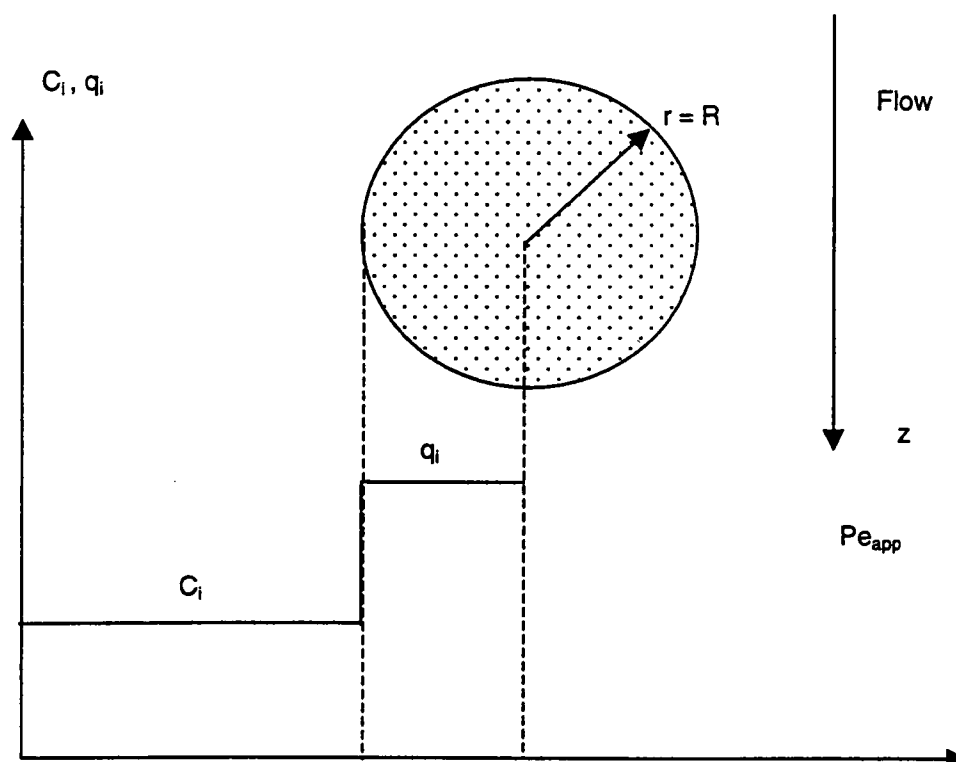


Figure 2.10 Schematic diagram employed in the derivation of the equilibrium-dispersive model

where $\frac{\partial q_i}{\partial \theta}$ is estimated from the adsorption isotherm

$$q_i = f(C_1, \dots, C_i, \dots, C_N) \quad (2.43)$$

we also need equations (2.32) and (2.33), which define the initial and boundary conditions. In eq. (2.42) the apparent Peclet number is defined by $Pe_{app} = 2N$, where N is the column plate number, an experimental parameter. The value of N is estimated from the chromatogram of an analytical injection (under linear conditions) of the solute of interest.

Suitable boundary conditions are needed to solve Eq. 2.42. The column is assumed to be empty of the solutes at the beginning of the process ($C_i(z, 0) = 0$) and the experimental injection profile at the column inlet is introduced in the calculations. The set of Eqs. 2.42 for different components is solved numerically using a finite-differences algorithm. In this study, we apply a forward-backward finite differences procedure based on the Godunov scheme [Rouchon *et al.*, 1987]. The equilibrium-dispersive model has been applied succesfully to the description of single solute and multisolute band profiles, provided there exist an accurate description of the associated adsorption equilibrium [Guiochon *et al.*, 1994]

Chapter 3

The Separation of Phenylalcohols

In this chapter, we describe the results of the experimental determination of multi-solute adsorption equilibria carried out on a system of three solutes, namely benzyl alcohol (BA), 2-phenyl ethanol (PE) and 2-methyl benzyl alcohol (MBA) in solution in a 1:1 (v/v) mixture of methanol and water. The adsorbent was a C₁₈ bonded porous silica for reversed phase chromatography.

The measured data includes the three single component isotherms, the three binary competitive isotherms, and the ternary competitive isotherm. The experimental data showed good thermodynamic consistency. Single solute adsorption data were determined at different temperatures by both FA and FACP. From these data, the free energies, enthalpies, entropies, and the isosteric heats of adsorption were evaluated in order to assess important features of the process like the heterogeneity of the surface.

In this chapter, the experimental data were fitted to an equilibrium model based on the concept of the adsorbed solution [Myers and Prausnitz, 1965]. This model is particularly suited for multisolute adsorption from dilute liquid solutions, which is the case usually encountered in preparative liquid chromatography. It accounts for the nonideal behavior of the adsorbed and bulk phases as

a result of molecular interactions. The nonidealities in the bulk mobile phase were estimated using the UNIFAC model [Hansen *et al.*, 1991] while the nonidealities in the adsorbed phase were accounted for using both the Wilson and the Flory-Huggins models [Wilson, 1964; Flory, 1953]. Under certain circumstances, the model applied here reduces to the multicomponent Langmuir model [Schwab, 1928].

As stated before, liquid-liquid partition was suggested as a possible model to describe the distribution of solutes in reversed-phase systems [Dorsey and Cooper, 1994]. A model of this type was also employed in this study to account for the experimental data. The nonidealities in both phases were accounted using the UNIFAC model. It was found that, although n-decanol as a model stationary phase fairly represented the multisolute behavior at low concentrations, it failed completely to describe the trend of the experimental data at higher concentrations and the influence of temperature.

Both analytical and preparative liquid chromatography separations are often carried out employing multicomponent mixtures of solvents. The multicomponent mobile phase usually contains a weak solvent and a strong additive that actively competes with the solutes for the adsorption sites in the stationary phase. The presence of the additive in the mobile phase is essential in order to control the retention of the separated solutes and to achieve proper resolution [Schoenmakers, 1986]. As a result of the strong interference between the solutes

and the additive, extremely unusual band profiles or system peaks are obtained in both analytical and preparative applications [Guiochon *et al.*, 1994]. Thus, the understanding of the underlying phenomena producing the system peaks is important for method development.

Under properly selected values of the process parameters, one specific component of the separated mixture can concentrate in a narrow zone of the chromatogram at high purity. Exploited properly, the phenomenon could be extremely useful for the isolation of minor components in mixtures of pharmaceutical relevance. For these reasons, system peaks have received much attention from the perspective of both analytical [Fornstedt, 1992; Golshan-Shirazi and Guiochon, 1990] and preparative chromatography [Guiochon *et al.*, 1994].

Previous theoretical studies have shown how system peaks arise as a result of the competitive interactions between the separated solutes and the strong additive of the mobile phase. Theoretical results were presented for one [Golshan-Shirazi and Guiochon, 1989a] and two solutes [Golshan-Shirazi and Guiochon, 1989c] eluted by a binary mobile phase containing a strong additive. In these studies, the competitive interactions among the components of the system were accounted for by a multicomponent Langmuir model. The band profiles were calculated using the equilibrium-dispersive model. Experimental studies [Golshan-Shirazi and Guiochon, 1989c; 1989d] show good qualitative agreement with the previous theoretical predictions. A quantitative comparison between experimen-

tal and theoretical results was not possible because of the lack of the experimental adsorption equilibria in the systems under consideration.

In a later theoretical study, a set of rules was proposed in an attempt to rationalize the conditions under which system peaks originate [Fornsted and Guiochon, 1994a]. Afterwards, the elution of a single solute band by a binary eluent in a reversed-phase, ion-pair system was studied [Fornsted and Guiochon, 1994b]. In this latter work, the single solute isotherm data were correlated by the bi-Langmuir model. The competitive isotherm was assumed to be described also by the bi-Langmuir model. Competitive adsorption data were not measured for mixtures of the solute and the additive. Accordingly, the parameters in the competitive model were estimated only from the single solute adsorption data and from additive data at low concentrations. Nevertheless, good quantitative agreement was obtained between the experimental and the calculated system peaks profiles.

Recently, large concentration system peaks were obtained when using the same species, 3-phenyl-1-propanol, both as the solute and the strong additive of the mobile phase [Sajonz *et al.*, 1996]. In this case, only the single solute adsorption isotherm of 3-phenyl-1-propanol was needed to perform the necessary calculations. Very good agreement was obtained between the experimental and calculated band profiles.

So far, the quantitative description of the system peaks arising during the

elution of a binary solute mixture by a binary eluent containing a strong additive has not been possible. This is a natural result of the lack of available ternary solute adsorption data in a system of chromatographic interest.

Another goal of this chapter is to compare experimental profiles of system peaks at high concentrations and those derived from the theory of nonlinear chromatography. The calculation of the latter requires a model accounting properly for the adsorption data of single-, binary-, and ternary-mixtures of three compounds. We will use the data in the ternary system of BA, PE and MBA for this purpose.

3.1 Experimental.

3.1.1 Equipment.

Chromatographic data, including analytical chromatograms, overloaded band profiles, system peaks and breakthrough curves were acquired using a HP 1100 series modular liquid chromatograph (Hewlett-Packard, Palo Alto, CA, USA). This instrument is composed of an isocratic pump, a vacuum degasser for the mobile phase, a variable wavelength detector, and a thermostated column compartment. A PC-based software was used to control these modules and to acquire and process the UV signal. The system was complemented by a Rheodyne 7725i injector (Cotati, CA, USA) and a Gilson (Middletown, WI, USA) Model 203 frac-

tion collector. The collected fractions were further analyzed using an HP 1090 series liquid chromatograph (Hewlett-Packard, Palo Alto, CA, USA) equipped with a ternary solvent delivery system, an automatic sample injector with a 25 μ l loop, a diode-array UV detector, and a PC-based data acquisition/processing system.

The experimental setup is depicted in figure 3.0. The isocratic pump (IP) draws the mobile phase from the solvent reservoir (SR). Afterwards, the fluid is pumped through the vacuum degasser (VD), through the injection valve (IV), through the chromatographic column (C) which is placed in a column compartment (CC) whose function is to keep the temperature constant, through the detector (D) and finally the effluent goes either to waste or to the fraction collector (FC).

The equilibration of the system is performed with the IV placed in the load position (dashed line flow path). Also in this position, the injection loop (IL) is loaded with sample using the syringe (S). Any excess of sample in the loop goes to waste through the port W. The run begins after switching the IV into the inject position (solid line flow path) which directs the sample into the column and simultaneously starts the data acquisition. When needed, the collected samples are diluted and placed in the Analytical HPLC which performs their quantitation. A personal computer (PC) controls the functions of the entire setup.

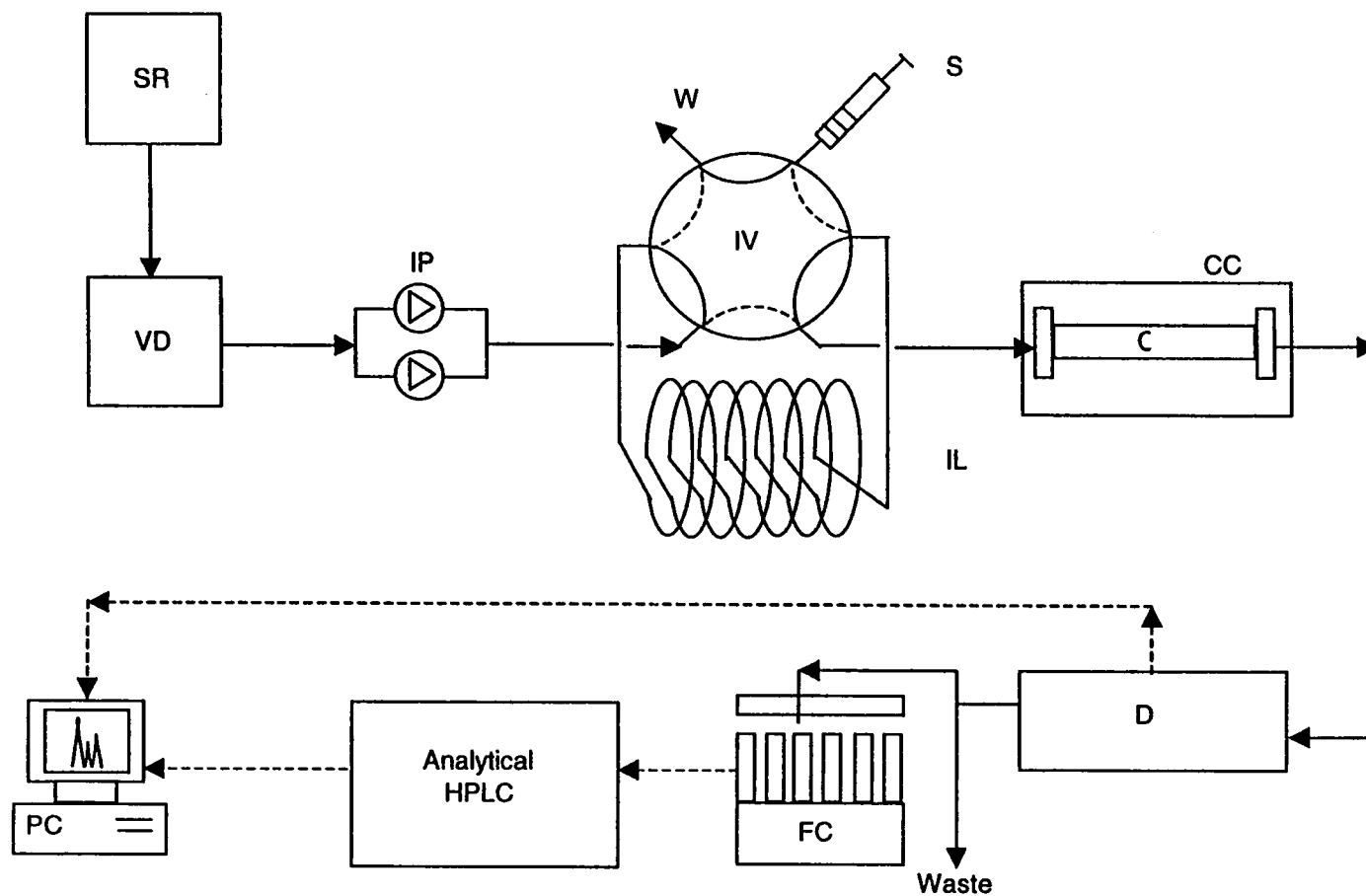


Figure 3.0 Schematic diagram of the experimental setup employed at the analytical scale.
See section 3.1.1 for details of the operation

3.1.2 Materials.

A 150 mm $\times$ 3.9 mm i.d. Symmetry C18 column (Waters, Mildford, MA) was used to measure the adsorption data. The particle size was 5 μ m and the void fraction of the column was 0.59. Using a dilute mixture of the three studied solutes, this column was characterized by elution chromatography before, during, and after the measurements of the adsorption data. It was found essentially unchanged (data not shown). In all the experiments the mobile phase was methanol-water (50:50, v/v). Both solvents were HPLC grade, purchased from Fisher Scientific (Pittsburgh, PA, USA). The solutes employed were benzyl alcohol (99+ %, ACS reagent Aldrich, Milwaukee, WI, USA), 2-phenylethanol (99+ % Fluka, Ronkonkoma, NY, USA) and 2-methylbenzylalcohol (99+ % Fluka, Ronkonkoma, NY, USA). A similar ODS column and the same mobile phase were used to analyze the collected fractions. In this study, we will use the indices 1, 2 and 3 when referring to BA, PE and MBA, respectively.

3.1.3 Procedures.

Adsorption data were measured by pumping solutions of the single, binary, or ternary solutes solutions in the mobile phase. After a breakthrough curve was recorded, the solution was replaced with one of higher concentration. For single and binary solute data, three replicas were measured at each mobile phase com-

position, via FA. For ternary solute data, because of the time and amount of work involved, only one measurement was made for each mobile phase composition.

The solutions were prepared and used on the same day. The column was held at 30°C. The signal was recorded at 275 nm. The flow rate was 1 ml/min. Figure 3.1 shows the different mixtures of solutes analyzed in the present study, in a ternary diagram. The single solute systems are represented by the vertices of the triangle, the binaries are represented by the sides of the triangle and the ternaries are represented by the points inside the composition triangle. For each pair of solutes, three different binary solute mixtures were employed, with mass ratios of the two solutes equal to 1:3, 1:1 and 3:1. Four different ternary solute mixtures were employed, with mass ratios of BA:PE:MBA equal to 1:1:1, 3:1:1, 1:3:1 and 1:1:3. Ten different levels of total solute concentration were employed, the first level at 5 g/l and the last one at 50 g/l, with increments of 5 g/l. The triangle in Figure 3.1 represents one level with the same total solute concentration, say 5 g/l.

3.1.3.1 Single solute isotherm data.

In the case of single solute adsorption, the isotherm data were derived from the chromatograms recorded by FA and FACP. Adsorption data determined via FA for the different solutes at 30°C are presented in Table 3.1. In this table the concentration in the mobile phase is represented by C and the concentration

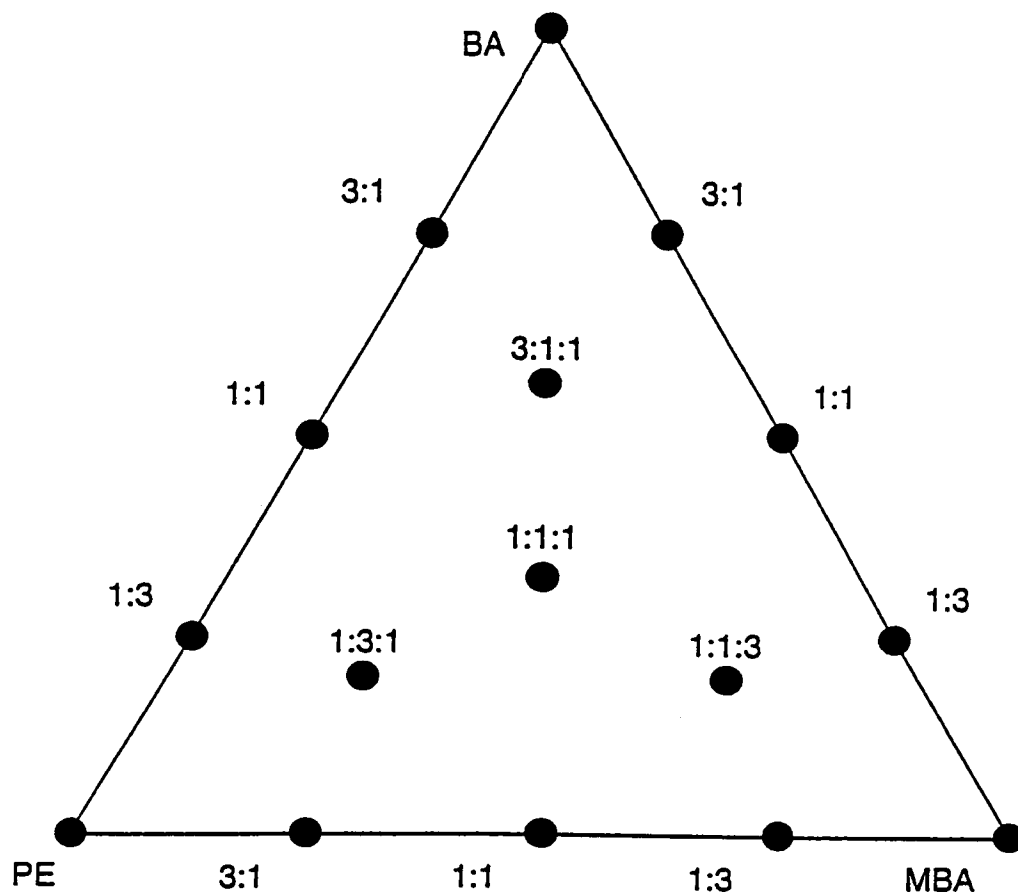


Figure 3.1 Composition diagram of the studied single, binary and ternary solute mixtures

Table 3.1. Single-solute equilibrium data measured by FA at 30 °C

C_1	Γ_1	C_2	Γ_2	C_3	Γ_3
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
5.00	9.18	5.00	15.00	5.00	16.51
10.00	16.85	10.00	27.26	10.00	29.59
15.00	24.04	15.00	36.99	15.00	40.68
20.00	30.41	20.00	45.48	20.00	49.86
25.00	35.96	25.00	52.74	25.00	57.88
30.00	40.68	30.00	58.77	30.00	64.93
35.00	45.07	35.00	63.77	35.00	71.44
40.00	49.32	40.00	68.49	40.00	77.26
45.00	53.01	45.00	72.74	45.00	82.60
50.00	56.16	50.00	76.71	50.00	86.99

in the stationary phase is represented by Γ . It was possible to apply FACP in this study because of the high efficiency of the column employed, in the order of 7000 to 8000 theoretical plates for the solutes of interest [Guan *et al.*, 1994]. The absorbance at the FA plateaus was correlated with concentrations using a fourth-order polynomial. This polynomial was employed to convert the rear profile signal obtained from the FACP experiments into concentrations. Five different temperatures were employed in the FACP experiments : 20°C, 30°C, 40°C, 50°C, and 60°C. Reported expressions [Jacobson *et al.*, 1984] were used in order to calculate the adsorbed amounts from FA and FACP results. Adsorption data determined via FACP at different temperatures are presented for benzyl alcohol, 2-phenyl ethanol and 2-methyl benzylalcohol in Tables 3.2, 3.3 and 3.4, respectively.

3.1.3.2 Binary solute isotherm data.

In all the experiments, the initial concentration of the components was zero in the column. Thus, the concentration of the more retained component in the intermediate plateau was zero. Accordingly, there was no need to analyze the eluate composition at this plateau. The concentration of the least retained solute in the intermediate plateau was derived from the same calibration polynomial used to deconvolute the rear FACP profiles. The retention times of both shocks, the hold-up time, and the proper concentrations were inserted into the reported

Table 3.2. Single-solute equilibrium data of benzyl alcohol

measured by FACP at different temperatures.

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
1.02	2.51	1.01	2.42	1.03	2.19	1.08	1.80	1.01	1.72
2.04	4.65	2.02	4.29	2.02	3.79	2.08	3.23	2.16	3.16
3.07	6.76	3.00	6.05	3.06	5.43	3.16	4.72	3.01	4.19
4.08	8.74	4.09	7.94	4.07	6.97	4.19	6.11	4.26	5.68
5.02	10.54	5.10	9.65	5.15	8.57	5.09	7.29	5.08	6.63
6.00	12.37	6.01	11.15	6.09	9.94	6.02	8.50	6.24	7.95
7.03	14.21	7.11	12.92	7.07	11.33	7.00	9.73	7.15	8.96
8.09	16.09	8.10	14.46	8.09	12.74	8.02	10.98	8.10	10.00
9.07	17.75	9.12	16.02	9.15	14.18	9.07	12.25	9.08	11.05

Table 3.2. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
10.08	19.43	10.01	17.33	10.03	15.34	10.16	13.54	10.09	12.11
11.14	21.13	11.11	18.93	11.16	16.80	11.00	14.52	11.13	13.18
12.08	22.60	12.06	20.27	12.10	17.99	12.16	15.83	12.20	14.26
13.06	24.10	13.05	21.63	13.07	19.18	13.05	16.83	13.30	15.36
14.07	25.61	14.07	23.00	14.07	20.39	14.28	18.17	14.05	16.09
15.13	27.14	15.13	24.39	15.10	21.61	15.23	19.18	15.21	17.20
16.05	28.43	16.01	25.52	16.17	22.84	16.21	20.20	16.40	18.32
17.19	30.00	17.14	26.93	17.27	24.08	17.21	21.23	17.21	19.07
18.18	31.33	18.08	28.08	18.11	25.02	18.24	22.26	18.04	19.82

Table 3.2. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C_1	Γ_1	C_1	Γ_1	C_1	Γ_1	C_1	Γ_1	C_1	Γ_1
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
19.21	32.67	19.05	29.24	19.28	26.28	19.29	23.30	19.31	20.96
20.06	33.76	20.04	30.40	20.18	27.23	20.01	24.00	20.18	21.72
21.16	35.13	21.07	31.58	21.10	28.19	21.12	25.05	21.07	22.49
22.07	36.24	22.14	32.77	22.05	29.15	22.26	26.11	22.43	23.64
23.01	37.36	23.24	33.97	23.02	30.13	23.03	26.82	23.36	24.41
24.24	38.77	24.09	34.87	24.02	31.10	24.22	27.90	24.31	25.19
25.25	39.92	25.25	36.09	25.04	32.08	25.03	28.61	25.28	25.97
26.03	40.78	26.15	37.00	26.09	33.07	26.28	29.69	26.27	26.75
27.11	41.95	27.08	37.93	27.17	34.06	27.13	30.41	27.27	27.53

Table 3.2. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
28.22	43.12	28.03	38.86	28.28	35.06	28.43	31.50	28.30	28.31
29.08	44.01	29.00	39.79	29.03	35.73	29.32	32.23	29.35	29.10
30.26	45.20	30.00	40.73	30.19	36.73	30.23	32.95	30.41	29.88
31.17	46.10	31.03	41.67	31.39	37.74	31.15	33.68	31.50	30.67
32.11	47.00	32.08	42.62	32.20	38.42	32.09	34.41	32.05	31.06
33.07	47.91	33.16	43.58	33.03	39.09	33.04	35.14	33.17	31.85
34.06	48.83	34.28	44.53	34.29	40.11	34.02	35.87	34.30	32.63
35.07	49.75	35.03	45.17	35.16	40.78	35.00	36.60	35.46	33.41
36.11	50.67	36.20	46.13	36.04	41.46	36.01	37.33	36.04	33.80

Table 3.2. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C_1	Γ_1	C_1	Γ_1	C_1	Γ_1	C_1	Γ_1	C_1	Γ_1
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
37.18	51.59	37.39	47.09	37.38	42.47	37.03	38.05	37.22	34.58
38.27	52.52	38.20	47.73	38.29	43.15	38.07	38.77	38.41	35.34
39.01	53.13	39.02	48.37	39.22	43.81	39.12	39.49	39.01	35.72
40.14	54.05	40.27	49.32	40.16	44.48	40.18	40.20	40.22	36.48
41.29	54.97	41.12	49.95	41.10	45.14	41.25	40.90	41.44	37.22
42.07	55.57	42.40	50.88	42.06	45.79	42.32	41.60	42.05	37.59
43.24	56.46	43.27	51.50	43.02	46.43	43.40	42.28	43.26	38.30
44.02	57.03	44.13	52.10	44.45	47.37	44.48	42.94	44.48	39.00
45.17	57.88	45.42	52.98	45.41	47.98	45.02	43.27	45.08	39.35

Table 3.2. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁	C ₁	Γ ₁
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
46.30	58.67	46.27	53.54	46.35	48.57	46.08	43.90	46.27	40.01
47.02	59.17	47.11	54.08	47.28	49.14	47.12	44.51	47.44	40.64
48.03	59.85	48.31	54.85	48.18	49.68	48.14	45.09	48.01	40.95
49.21	60.62	49.06	55.31	49.05	50.18	49.13	45.64	49.12	41.53
50.17	61.22	50.08	55.92	50.25	50.86	50.06	46.15	50.18	42.07

Table 3.3. Single-solute equilibrium data of 2-phenyl ethanol

measured by FACP at different temperatures.

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
1.00	3.74	1.01	3.28	1.01	2.93	1.01	2.38	1.07	2.44
2.01	7.26	2.01	6.34	2.03	5.68	2.01	4.70	2.04	4.38
3.01	10.61	3.00	9.26	3.06	8.30	3.08	7.07	3.08	6.40
4.03	13.86	4.02	12.10	4.01	10.65	4.04	9.15	4.08	8.29
5.02	16.87	5.04	14.83	5.02	13.04	5.05	11.26	5.03	10.01
6.03	19.77	6.06	17.43	6.00	15.29	6.01	13.20	6.01	11.75
7.05	22.59	7.02	19.77	7.04	17.57	7.03	15.17	7.05	13.53
8.03	25.17	8.04	22.17	8.06	19.72	8.10	17.18	8.14	15.33
9.03	27.67	9.05	24.45	9.05	21.73	9.11	19.02	9.14	16.94

Table 3.3. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
10.04	30.08	10.05	26.60	10.09	23.77	10.06	20.69	10.03	18.34
11.04	32.39	11.02	28.63	11.09	25.67	11.05	22.38	11.11	19.99
12.04	34.59	12.06	30.70	12.04	27.41	12.09	24.11	12.08	21.43
13.04	36.69	13.07	32.65	13.04	29.18	13.05	25.64	13.10	22.89
14.01	38.67	14.05	34.46	14.09	30.98	14.05	27.20	14.15	24.37
15.06	40.69	15.08	36.31	15.08	32.61	15.09	28.78	15.07	25.62
16.07	42.60	16.06	38.00	16.11	34.26	16.03	30.15	16.02	26.89
17.06	44.37	17.10	39.73	17.06	35.74	17.01	31.54	17.00	28.17
18.10	46.18	18.07	41.29	18.06	37.24	18.02	32.96	18.03	29.46

Table 3.3. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C_2	Γ_2	C_2	Γ_2	C_2	Γ_2	C_2	Γ_2	C_2	Γ_2
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
19.10	47.85	19.10	42.88	19.10	38.76	19.09	34.39	19.09	30.77
20.04	49.37	20.04	44.30	20.04	40.08	20.01	35.60	20.20	32.10
21.03	50.91	21.03	45.74	21.02	41.43	21.16	37.07	21.12	33.18
22.08	52.50	22.07	47.22	22.04	42.80	22.17	38.32	22.07	34.26
23.06	53.92	23.01	48.50	23.12	44.19	23.00	39.32	23.05	35.35
24.09	55.37	24.17	50.03	24.05	45.37	24.08	40.60	24.06	36.46
25.02	56.64	25.03	51.14	25.02	46.56	25.21	41.89	25.11	37.57
26.16	58.16	26.12	52.50	26.04	47.77	26.14	42.93	26.20	38.70
27.02	59.26	27.07	53.65	27.10	48.99	27.11	43.98	27.04	39.55

Table 3.3. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
28.10	60.62	28.06	54.82	28.20	50.24	28.11	45.05	28.19	40.69
29.05	61.77	29.10	56.01	29.12	51.24	29.15	46.12	29.08	41.55
30.05	62.94	30.18	57.21	30.07	52.26	30.22	47.21	30.00	42.42
31.08	64.13	31.09	58.19	31.06	53.29	31.06	48.03	31.27	43.59
32.17	65.33	32.02	59.18	32.09	54.34	32.21	49.14	32.25	44.47
33.07	66.31	33.24	60.43	33.15	55.39	33.10	49.97	33.25	45.35
34.01	67.30	34.00	61.19	34.26	56.45	34.01	50.82	34.29	46.24
35.23	68.55	35.04	62.21	35.11	57.25	35.28	51.95	35.36	47.14
36.25	69.56	36.13	63.24	36.28	58.33	36.25	52.80	36.09	47.74

Table 3.3. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
37.03	70.33	37.25	64.27	37.19	59.14	37.25	53.65	37.20	48.64
38.11	71.36	38.11	65.05	38.12	59.95	38.28	54.51	38.35	49.54
39.23	72.38	39.30	66.09	39.07	60.76	39.34	55.37	39.13	50.15
40.08	73.15	40.21	66.87	40.05	61.57	40.06	55.94	40.33	51.04
41.25	74.18	41.14	67.64	41.04	62.38	41.15	56.80	41.14	51.64
42.14	74.93	42.09	68.42	42.06	63.19	42.27	57.64	42.37	52.53
43.03	75.67	43.06	69.18	43.08	63.98	43.02	58.20	43.20	53.12
44.20	76.63	44.03	69.93	44.12	64.76	44.16	59.03	44.04	53.69
45.06	77.30	45.00	70.67	45.16	65.52	45.30	59.83	45.30	54.54

Table 3.3. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂	C ₂	Γ ₂
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
46.15	78.13	46.27	71.59	46.18	66.25	46.05	60.35	46.14	55.10
47.15	78.87	47.19	72.24	47.16	66.93	47.15	61.09	47.39	55.89
48.04	79.50	48.06	72.84	48.09	67.56	48.19	61.78	48.19	56.40
49.11	80.23	49.13	73.55	49.22	68.30	49.16	62.39	49.34	57.09
50.04	80.82	50.06	74.14	50.21	68.91	50.03	62.93	50.05	57.51

Table 3.4. Single-solute equilibrium data of 2-methyl benzyl alcohol

measured by FACP at different temperatures.

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C_3	Γ_3	C_3	Γ_3	C_3	Γ_3	C_3	Γ_3	C_3	Γ_3
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
1.02	4.72	1.00	4.06	1.01	3.62	1.04	3.27	1.02	3.08
2.03	8.74	2.03	7.60	2.05	6.74	2.03	5.83	2.05	5.38
3.03	12.51	3.03	10.90	3.05	9.62	3.02	8.28	3.03	7.47
4.01	16.04	4.04	14.11	4.06	12.39	4.08	10.82	4.09	9.68
5.01	19.47	5.01	17.04	5.05	15.03	5.03	13.02	5.10	11.72
6.04	22.84	6.04	20.03	6.03	17.54	6.03	15.26	6.04	13.58
7.01	25.86	7.03	22.78	7.08	20.11	7.08	17.54	7.03	15.47
8.05	28.97	8.02	25.43	8.02	22.36	8.10	19.67	8.06	17.40
9.02	31.73	9.02	27.98	9.03	24.68	9.06	21.64	9.02	19.13

Table 3.4. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
10.06	34.58	10.01	30.44	10.01	26.86	10.08	23.66	10.02	20.90
11.06	37.19	11.00	32.80	11.06	29.11	11.04	25.49	11.08	22.72
12.00	39.56	12.06	35.23	12.07	31.20	12.04	27.36	12.03	24.31
13.01	42.01	13.02	37.36	13.02	33.14	13.10	29.29	13.03	25.93
14.02	44.37	14.05	39.55	14.04	35.12	14.09	31.03	14.07	27.59
15.02	46.62	15.03	41.59	15.11	37.16	15.12	32.80	15.16	29.29
16.09	48.95	16.08	43.69	16.12	39.02	16.05	34.35	16.11	30.73
17.04	50.95	17.08	45.63	17.06	40.69	17.02	35.93	17.10	32.19
18.06	53.01	18.02	47.40	18.04	42.41	18.03	37.55	18.13	33.69

Table 3.4. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C_3	Γ_3	C_3	Γ_3	C_3	Γ_3	C_3	Γ_3	C_3	Γ_3
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
19.03	54.92	19.01	49.23	19.07	44.16	19.09	39.19	19.20	35.21
20.06	56.89	20.07	51.11	20.00	45.69	20.01	40.59	20.09	36.45
21.04	58.70	21.05	52.80	21.14	47.52	21.17	42.31	21.01	37.70
22.07	60.57	22.07	54.53	22.16	49.13	22.17	43.76	22.21	39.30
23.04	62.25	23.15	56.30	23.05	50.49	23.01	44.94	23.21	40.60
24.05	63.98	24.13	57.86	24.17	52.16	24.09	46.45	24.24	41.91
25.13	65.77	25.16	59.45	25.14	53.58	25.23	47.98	25.04	42.91
26.10	67.34	26.05	60.81	26.16	55.03	26.17	49.23	26.14	44.26
27.13	68.95	27.17	62.47	27.22	56.50	27.15	50.49	27.28	45.63

Table 3.4. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
28.03	70.33	28.16	63.90	28.10	57.70	28.16	51.78	28.16	46.67
29.16	72.04	29.19	65.35	29.01	58.92	29.21	53.08	29.06	47.72
30.16	73.50	30.05	66.54	30.20	60.47	30.02	54.07	30.31	49.13
31.20	74.99	31.16	68.05	31.19	61.73	31.14	55.41	31.27	50.20
32.08	76.22	32.10	69.28	32.21	63.01	32.01	56.42	32.26	51.28
33.22	77.79	33.07	70.53	33.01	63.98	33.20	57.79	33.28	52.38
34.18	79.07	34.07	71.81	34.10	65.30	34.12	58.83	34.33	53.48
35.18	80.39	35.12	73.11	35.24	66.64	35.07	59.88	35.04	54.22
36.22	81.72	36.21	74.44	36.12	67.65	36.04	60.94	36.14	55.34

Table 3.4. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
37.02	82.75	37.05	75.44	37.02	68.67	37.05	62.00	37.26	56.46
38.14	84.13	38.22	76.80	38.27	70.06	38.08	63.08	38.03	57.22
39.00	85.19	39.12	77.84	39.24	71.11	39.13	64.16	39.21	58.35
40.20	86.61	40.05	78.88	40.23	72.17	40.22	65.26	40.01	59.12
41.12	87.70	41.01	79.94	41.25	73.23	41.34	66.36	41.24	60.27
42.07	88.79	42.32	81.36	42.30	74.31	42.10	67.10	42.08	61.03
43.04	89.89	43.33	82.44	43.01	75.03	43.26	68.20	43.36	62.19
44.03	90.99	44.02	83.15	44.10	76.11	44.05	68.94	44.23	62.95
45.04	92.09	45.06	84.22	45.21	77.19	45.25	70.05	45.11	63.72

Table 3.4. (continued)

<u>T = 20.0 °C</u>		<u>T = 30.0 °C</u>		<u>T = 40.0 °C</u>		<u>T = 50.0 °C</u>		<u>T = 60.0 °C</u>	
C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃	C ₃	Γ ₃
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
46.05	93.17	46.12	85.29	46.34	78.26	46.06	70.78	46.45	64.86
47.06	94.24	47.19	86.34	47.10	78.97	47.29	71.87	47.35	65.61
48.07	95.28	48.26	87.38	48.24	80.03	48.11	72.58	48.25	66.35
49.06	96.28	49.33	88.38	49.00	80.71	49.35	73.64	49.15	67.08
50.01	97.23	50.02	89.03	50.14	81.72	50.17	74.32	50.05	67.80

expressions [Jacobson *et al.*, 1987] in order to derive the binary solute adsorption isotherm data.

This procedure was applied to all the binary solute mixtures, with the exception of the 1:3 mixtures of PE and MBA. In this case, the intermediate subplateau was very narrow. This situation prevented us to calculate the exact concentration at the subplateau via the calibration polynomial. In order to evaluate the concentration of PE in the subplateau, fractions were collected every 3 s (ca. 50 μ l) in this region and analyzed off-line. For quantitation, a linear calibration graph based on the area of the peak was established for each compound via the external standard method. The collected fractions were diluted prior to analysis. The analyses of diluted samples were performed at 27°C. The injected amount was 2 μ l. The flow rate was 1 ml/min. The signal was detected at 220 nm. The adsorption data for the mixtures of BA and PE are presented in Table 3.5, the adsorption data for the mixtures of BA and MBA are presented in Table 3.6 and the adsorption data for the mixtures of PE and MBA are presented in Table 3.7.

At constant temperature, it is possible to relate the spreading pressure and the excess adsorption of an N-component system via the expression [Gibbs, 1961; Sircar *et al.*, 1972]

$$Ad\pi = \sum_{i=1}^N \Gamma_i d\mu_i^b \quad (3.1)$$

where A is the specific surface area of the adsorbent, π the spreading pressure, Γ_i the excess concentration of the i -th component in the adsorbed phase, and μ_i^b

Table 3.5. Binary-solute equilibrium data of

benzyl alcohol and 2-phenyl ethanol

C_1	C_2	Γ_1	Γ_2
(g/l)	(g/l)	(g/l)	(g/l)
2.50	2.50	4.32	7.29
5.00	5.00	8.02	13.49
7.50	7.50	11.24	18.70
10.00	10.00	13.96	23.29
12.50	12.50	16.56	27.40
15.00	15.00	19.02	30.41
17.50	17.50	21.06	34.04
20.00	20.00	23.22	37.26
22.50	22.50	24.86	38.84
25.00	25.00	26.60	41.44
3.75	1.25	6.64	3.70
7.50	2.50	12.29	6.82
11.25	3.75	17.38	9.55
15.00	5.00	22.11	11.99
18.75	6.25	26.08	13.96
22.50	7.50	29.72	15.92

Table 3.5. (continued)

C_1	C_2	Γ_1	Γ_2
(g/l)	(g/l)	(g/l)	(g/l)
26.25	8.75	33.19	17.50
30.00	10.00	36.62	19.04
33.75	11.25	40.35	20.65
37.50	12.50	41.35	21.40
1.25	3.75	2.08	11.04
2.50	7.50	3.80	19.73
3.75	11.25	5.46	27.74
5.00	15.00	6.71	33.90
6.25	18.75	8.03	39.30
7.50	22.50	9.21	44.69
8.75	26.25	9.98	48.54
10.00	30.00	10.93	52.60
11.25	33.75	11.72	56.40
12.50	37.50	12.26	59.08

Table 3.6. Binary-solute equilibrium data of
benzyl alcohol and 2-methyl benzyl alcohol

C_1	C_3	Γ_1	Γ_3
(g/l)	(g/l)	(g/l)	(g/l)
2.50	2.50	4.73	8.77
5.00	5.00	8.16	15.41
7.50	7.50	11.41	21.37
10.00	10.00	14.30	26.58
12.50	12.50	16.87	30.99
15.00	15.00	18.83	34.93
17.50	17.50	20.84	38.36
20.00	20.00	22.75	41.37
22.50	22.50	24.71	44.38
25.00	25.00	26.24	46.92
3.75	1.25	8.30	5.09
7.50	2.50	14.92	9.18
11.25	3.75	19.97	12.12
15.00	5.00	22.80	13.56
18.75	6.25	26.74	16.01
22.50	7.50	30.20	18.08

Table 3.6. (continued)

C_1	C_3	Γ_1	Γ_3
(g/l)	(g/l)	(g/l)	(g/l)
26.25	8.75	33.77	19.90
30.00	10.00	36.98	21.64
33.75	11.25	39.81	23.12
37.50	12.50	42.23	24.32
1.25	3.75	2.03	13.36
2.50	7.50	3.82	23.01
3.75	11.25	5.40	31.28
5.00	15.00	6.88	38.63
6.25	18.75	7.87	44.69
7.50	22.50	8.73	50.24
8.75	26.25	9.87	54.66
10.00	30.00	10.68	59.18
11.25	33.75	11.26	63.34
12.50	37.50	12.40	66.78

Table 3.7. Binary-solute equilibrium data of

2-phenyl ethanol and 2-methyl benzyl alcohol

C_2	C_3	Γ_2	Γ_3
(g/l)	(g/l)	(g/l)	(g/l)
2.50	2.50	7.74	8.70
5.00	5.00	14.02	15.75
7.50	7.50	19.36	21.78
10.00	10.00	22.87	25.75
12.50	12.50	26.70	29.79
15.00	15.00	29.52	33.29
17.50	17.50	32.00	36.44
20.00	20.00	34.58	39.18
22.50	22.50	36.08	41.30
25.00	25.00	38.40	44.18
3.75	1.25	11.11	4.14
7.50	2.50	20.16	7.53
11.25	3.75	27.77	10.38
15.00	5.00	34.15	12.74
18.75	6.25	39.33	14.81
22.50	7.50	44.09	16.64

Table 3.7. (continued)

C_2	C_3	Γ_2	Γ_3
(g/l)	(g/l)	(g/l)	(g/l)
26.25	8.75	48.22	18.22
30.00	10.00	51.42	19.59
33.75	11.25	55.22	20.96
37.50	12.50	58.37	22.09
1.25	3.75	3.67	12.43
2.50	7.50	6.63	22.19
3.75	11.25	9.01	30.51
5.00	15.00	11.18	37.40
6.25	18.75	13.18	43.15
7.50	22.50	14.45	48.39
8.75	26.25	15.71	53.58
10.00	30.00	16.91	57.12
11.25	33.75	18.75	61.03
12.50	37.50	19.76	65.24

the chemical potential of the i -th component in the bulk liquid phase.

In the same time, the Gibbs-Duhem equation for the same system must hold for the bulk liquid phase [Smith *et al.*, 1996]

$$\sum_{i=1}^N x_i^b d\mu_i^b = 0 \quad (3.2)$$

where x_i^b is the mole fraction of the i -th component in the bulk liquid phase.

The combination of Eqs. (3.1) and (3.2) is the basis for the application of a thermodynamic consistency test for binary liquid mixtures [Sircar and Myers, 1971]. Assume that we have a binary solute mixture of BA and PE. Since the solutes are sufficiently dilute (*i.e.*, $x_i^b < 0.005$), the activities of the two major components of the mobile phase (methanol and water) are nearly constant, thus Eqs (3.1) and (3.2) can be approximated by the expressions

$$Ad\pi = \Gamma_1 d\mu_1^b + \Gamma_2 d\mu_2^b \quad (3.3)$$

and

$$x_1^b d\mu_1^b + x_2^b d\mu_2^b = 0 \quad (3.4)$$

respectively. From the last expression it follows that

$$d\mu_2^b = -\frac{x_1^b}{x_2^b} d\mu_1^b \quad (3.5)$$

From the definition of the liquid-phase chemical potential we have

$$d\mu_1^b = RT d\ln(\gamma_1^b x_1^b) \quad (3.6)$$

where γ_1^b is the activity coefficient of BA in the bulk liquid phase.

By inserting Eqs (3.5) and (3.6) in Eq (3.3) and rearranging, it follows that

$$\frac{A}{RT}d\pi = \frac{1}{\gamma_1^b} \left(\frac{\Gamma_1}{x_1^b} - \frac{\Gamma_2}{x_2^b} \right) d(\gamma_1^b x_1^b) \quad (3.7)$$

The integration of this last expression can be accomplished between any two points, α and β , of the binary solute domain, i. e.

$$\Pi = \frac{A(\pi_\beta - \pi_\alpha)}{RT} = \int_{(x_i^b, \Gamma_i)_\alpha}^{(x_i^b, \Gamma_i)_\beta} \frac{1}{\gamma_1^b} \left(\frac{\Gamma_1}{x_1^b} - \frac{\Gamma_2}{x_2^b} \right) d(\gamma_1^b x_1^b) \quad (3.8)$$

Although Eq (3.8) holds for the mixture of BA and PE, similar expressions can be written for each pair of solutes : BA-PE, BA-MBA or PE-MBA. The consistency test is the application of the integrals defined by Eq (3.8) through a closed loop. The closed loop applied here is defined by four paths in the domain of binary solute adsorption (see Figure 3.2), specifically,

Path A (Π_A). This path was applied to the 1:3 mixtures. It starts at some value of the total solute concentration, say 5 g/l (point I, $\alpha = I$), and ends at the next higher value of the total solute concentration, i.e., 10 g/l (point II, $\beta = II$).

Path B (Π_B). This path was applied to all the mixtures having the same total concentration (10 g/l in our example). It starts at point II for the 1:3 mixture ($\alpha = II$), passes through the 1:1 mixture and ends at the 3:1 mixture (point III, $\beta = III$).

Path C (Π_C). This path was applied to the 3:1 mixtures. It starts at point

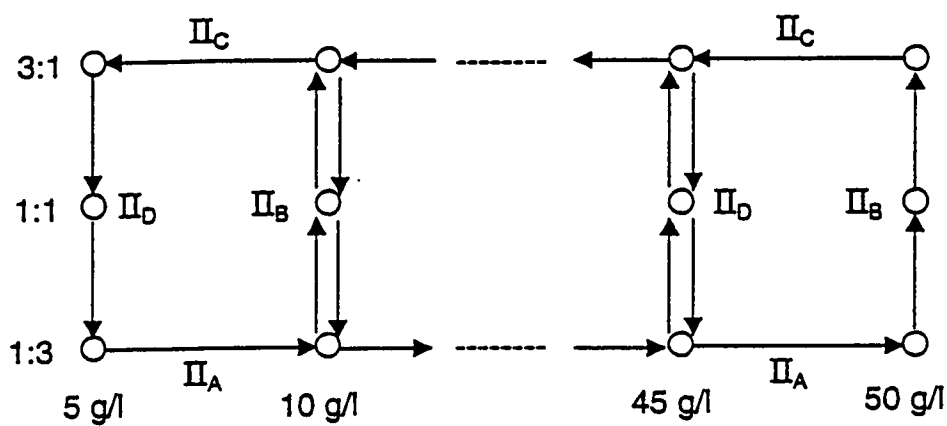


Figure 3.2 Integration paths in the domain of binary solute adsorption applied in the thermodynamic consistency test.

III (10 g/l in our example, $\alpha = III$) and ends at the next lower value of the total solute concentration (5 g/l, point IV, $\beta = IV$).

Path D (Π_D). This path was also applied to all the mixtures having a constant total concentration (5 g/l in our example). It starts at point IV ($\alpha = IV$) for the 3:1 mixture, passes through the 1:1 mixture and ends at the 1:3 mixture (point I, $\beta = I$), thus closing the loop.

Theoretically, the sum of the four integrals of this closed loop should be zero. In practice we observe a slight deviation from zero produced by the experimental error, thus

$$\Pi_A + \Pi_B + \Pi_C + \Pi_D = \epsilon \quad (3.9)$$

The first two integrals are positive, the last two are negative. The consistency is evaluated via the expression

$$\delta = 100 \frac{\epsilon}{\Pi_{max}} \quad (3.10)$$

where Π_{max} is the largest sum of either positive or negative integrals. The consistency test, Eq. (3.10) was applied to the three solute binaries. Nine closed loops were calculated for each binary, the first starting at 5 g/l and the last starting at 45 g/l.

3.1.3.3 Ternary solute isotherm data.

In the case of the ternary solute mixtures two subplateaus are observed (see

Figure 3.3). The first one is pure BA, thus the concentration on this first subplateau was derived from the absorbance via the correlation polynomial. The concentrations of BA and PE in the second subplateau were determined via fraction collection and subsequent off-line analysis, as described above. In the case of the ternary solute mixtures, the following equations were employed in order to calculate the adsorbed amounts. The adsorbed amounts are basically volume excess concentrations [Slaats *et al.*, 1981].

a) For the first component

$$\Gamma_1 = \frac{(V_3 - V_o)C_1^F - (V_3 - V_2)C_1^2 - (V_2 - V_1)C_1^1}{V_{sp}} \quad (3.11)$$

where V_1 , V_2 and V_3 are the breakthrough volumes of the first, second, and third shocks, respectively; C_1^1 and C_1^2 are the concentrations of BA in the first and second subplateaus, respectively; V_o is the system hold-up volume, C_1^F is the concentration of BA in the feed, and V_{sp} is the volume of the stationary phase. The system hold-up volume was determined using thiourea (Aldrich, Milwaukee, WI, USA) as a nonretained tracer.

b) For the second component

$$\Gamma_2 = \frac{(V_3 - V_o)C_2^F - (V_3 - V_2)C_2^2}{V_{sp}} \quad (3.12)$$

where C_2^F is the concentration of PE in the feed and C_2^2 is the concentration of PE in the second subplateau.

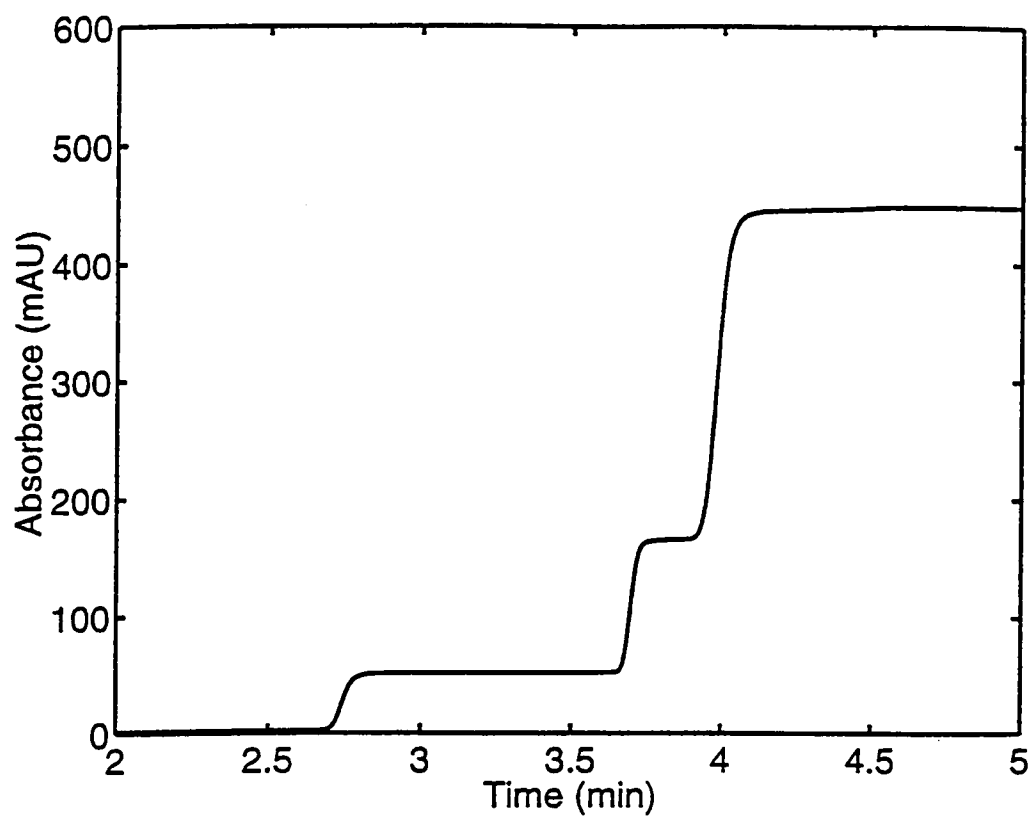


Figure 3.3 Frontal breakthrough curve of a ternary solute mixture

c) For the third component

$$\Gamma_3 = \frac{(V_3 - V_o)C_3^F}{V_{sp}} \quad (3.13)$$

where C_3^F is the concentration of MBA in the feed

These equations are straightforward extensions of the expression reported before [Jacobson *et al.*, 1987] for binary solute mixtures. Ternary-solute adsorption data are presented in Table 3.8.

3.1.3.4 Multisolute Band Profiles and System Peaks.

Multisolute band profiles were acquired at 30°C. The solutions were prepared and used on the same day. The detector signal was recorded at 275 nm. The single solute band profiles were derived from the detector trace, converted to units of concentrations using the same calibration polynomial determined from the FA plateaus. The multisolute profiles were obtained by collecting and analyzing successive fractions of the column effluent as described above.

3.2 Models.

3.2.1 Adsorbed Solution Theory Models.

In the study of all these models, we assume the existence of two phases in equilibrium : the adsorbed phase and the bulk liquid phase. Both phases are

Table 3.8. Ternary-solute equilibrium data

C_1	C_2	C_3	Γ_1	Γ_2	Γ_3
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
1.67	1.67	1.67	2.86	5.08	5.64
3.33	3.33	3.33	5.22	9.09	10.14
5.00	5.00	5.00	7.06	12.32	14.04
6.67	6.67	6.67	9.06	15.37	17.53
8.33	8.33	8.33	10.23	17.60	20.09
10.00	10.00	10.00	11.63	19.74	22.74
11.67	11.67	11.67	12.53	21.57	24.77
13.33	13.33	13.33	14.14	23.54	27.03
15.00	15.00	15.00	14.90	25.81	28.77
16.67	16.67	16.67	16.77	27.08	30.59
3.00	1.00	1.00	5.87	3.41	3.81
6.00	2.00	2.00	10.53	6.10	6.96
9.00	3.00	3.00	15.25	8.50	9.74
12.00	4.00	4.00	16.70	9.39	10.85
15.00	5.00	5.00	20.11	11.24	12.88
18.00	6.00	6.00	23.78	13.22	14.38

Table 3.8. (continued)

C_1	C_2	C_3	Γ_1	Γ_2	Γ_3
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
21.00	7.00	7.00	24.44	13.53	15.73
24.00	8.00	8.00	26.42	14.54	16.99
27.00	9.00	9.00	28.30	15.39	18.12
30.00	10.00	10.00	31.17	16.84	19.04
1.00	3.00	1.00	1.68	8.95	3.34
2.00	6.00	2.00	3.01	15.97	6.03
3.00	9.00	3.00	4.19	21.87	8.30
4.00	12.00	4.00	5.31	27.26	10.58
5.00	15.00	5.00	6.00	30.92	11.99
6.00	18.00	6.00	6.84	34.84	13.40
7.00	21.00	7.00	7.56	38.43	14.67
8.00	24.00	8.00	8.32	41.48	15.89
9.00	27.00	9.00	8.69	44.29	16.89
10.00	30.00	10.00	7.49	50.23	17.95
1.00	1.00	3.00	1.64	3.07	10.07
2.00	2.00	6.00	2.89	5.33	18.33

Table 3.8. (continued)

C_1	C_2	C_3	Γ_1	Γ_2	Γ_3
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
3.00	3.00	9.00	4.05	7.25	25.03
4.00	4.00	12.00	5.06	9.03	30.74
5.00	5.00	15.00	6.00	10.74	35.34
6.00	6.00	18.00	6.58	11.64	39.70
7.00	7.00	21.00	7.22	13.31	44.01
8.00	8.00	24.00	8.19	14.22	47.34
9.00	9.00	27.00	8.70	15.18	49.93
10.00	10.00	30.00	8.95	15.79	53.42

composed of solutes and a solvent. The distribution of the i -th component between the adsorbed phase and the bulk liquid phase can be described by the following equilibrium equation [Minka and Myers, 1973]

$$\gamma_i^a x_i^a e^{\frac{A(\pi - \pi_i^o)}{n_i^\infty RT}} = \gamma_i^b x_i^b \quad (3.14)$$

where γ_i^a is the activity coefficient of the i -th component in the adsorbed phase, x_i^a is the mole fraction of the i -th component in the adsorbed phase, π_i^o the spreading pressure at the interface between the adsorbent and pure i -th liquid, and n_i^∞ the capacity of the adsorbed layer for the i -th component.

We can visualize the adsorbed phase as a lattice composed of a fixed number of adsorption sites, with a molar density equal to n^∞ [Martire, 1992; Tijssen *et al.*, 1993]. Let one molecule of each solute occupy one site in the lattice. Then the capacity of the adsorbed layer for the i -th solute is simply

$$n_i^\infty = n^\infty \quad (3.15)$$

Then Eq. (3.14) becomes

$$\gamma_i^a x_i^a e^{\frac{A(\pi - \pi_i^o)}{n^\infty RT}} = \gamma_i^b x_i^b \quad (3.16)$$

For the pure solvent in contact with the adsorbent, we assume a reference value of the spreading pressure equal to zero, thus $\pi_i^o = \pi_s^o = 0$. Then Eq (3.16) reduces to

$$\gamma_i^s x_i^s e^{\frac{A\pi}{n^\infty RT}} = \gamma_s^b x_s^b \quad (3.17)$$

Thus, in the case of a pure or nearly pure solvent, Eq. (3.17) allows the derivation of the spreading pressure as

$$\pi = \frac{RTn^\infty}{A} \ln \frac{\gamma_s^b x_s^b}{\gamma_s^a x_s^a} \quad (3.18)$$

for the solute, Eq. (3.14) can be rearranged into

$$\exp\left[-\frac{A}{RTn^\infty} \pi_i^o\right] = \frac{\gamma_i^b x_i^b}{\gamma_i^a x_i^a} \exp\left[-\frac{A}{RTn^\infty} \pi\right] \quad (3.19)$$

The equilibrium equation, Eq. (3.19), must apply also under infinite dilution conditions for the solutes. Under these conditions:

a) The spreading pressure approaches zero, the reference value for the pure solvent.

b) The ratio $\frac{x_i^a}{x_i^b}$ approaches the value of the Henry constant,

$$\lim_{x_i^b \rightarrow 0} \frac{x_i^a}{x_i^b} = K_i^x \quad (3.20)$$

Note that the above definition of the Henry constant is based on a ratio of mole fractions. The relationship with the Henry constant defined earlier (Eq. 2.25) as a ratio of molar concentrations (K_i^c) is simply

$$K_i^x = K_i^c \frac{\rho_b}{n^\infty} \quad (3.21)$$

where ρ_b is the molar density of the bulk liquid phase.

c) The activity coefficients in both phases approach the values at infinite dilution, i.e. $\gamma_i^{b,\infty}$ and $\gamma_i^{a,\infty}$. Thus, at infinite dilution, Eq (3.19) becomes

$$\exp\left[-\frac{A}{RTn^\infty}\pi_i^o\right] = \frac{\gamma_i^{b,\infty}}{K_i^x \gamma_i^{a,\infty}} \quad (3.22)$$

Inserting both the RHS of Eq (3.22) and the expression for the spreading pressure from Eq (3.18) in Eq (3.16) and rearranging we obtain

$$\frac{\gamma_i^a x_i^a}{\gamma_s^a x_s^a} \frac{\gamma_i^{b,\infty}}{K_i^x \gamma_i^{a,\infty}} = \frac{\gamma_i^b x_i^b}{\gamma_s^b x_s^b} \quad (3.23)$$

Note that the mole fraction of the i-th solute in the adsorbed phase is equal to the fractional coverage θ_i of the adsorbed phase by that solute, thus

$$\theta_i = x_i^a = \frac{\Gamma_i}{n^\infty} \quad (3.24)$$

The coverage of free sites in the adsorbed layer is

$$1 - \sum_{k=1}^{N_s} \theta_k = x_s^a \quad (3.25)$$

Note that the summation here is performed only over the solute species. N_s is the number of solutes in the system.

Substitution of Eqs (3.21), (3.24) and (3.25) in Eq (3.23) gives

$$\frac{\gamma_i^a \theta_i}{\gamma_s^a (1 - \sum_{k=1}^{N_s} \theta_k)} \frac{n^\infty \gamma_i^{b,\infty}}{\rho_b K_i^c \gamma_i^{a,\infty}} = \frac{\gamma_i^b x_i^b}{\gamma_s^b x_s^b} \quad (3.26)$$

The above expression constitutes the nonideal adsorbed solution model.

If the mobile phase is sufficiently dilute, the mole fraction of the solvent in the bulk liquid phase is practically one, $x_s^b \approx 1$ and both phases are considered to be ideal (all the activity coefficients are equal to 1). Then, Eq. 3.26 reduces to

$$\frac{\theta_i}{1 - \sum_{k=1}^{N_s} \theta_k} = \frac{\rho_b K_i^c x_i^b}{n^\infty} \quad (3.27)$$

Recall that $\rho_b x_i^b = C_i$, where C_i is the molar concentration of the i -th solute in the bulk liquid. By defining $K_i^L = K_i^c/n^\infty$, we can reduce Eq. (3.27) to the well-known multicomponent Langmuir model [Schwab, 1928]

$$\frac{\theta_i}{1 - \sum_{k=1}^{N_s} \theta_k} = K_i^L C_i \quad (3.28)$$

where K_i^L is the Langmuir equilibrium constant for the i -th solute. The above equation is usually rearranged as

$$\frac{\Gamma_i}{n^\infty} = \frac{K_i^L C_i}{1 + \sum_{i=1}^{N_s} K_i^L C_i} \quad (3.29)$$

Nonidealities in the adsorbed phase can be accounted using the Wilson model for multicomponent systems [Wilson, 1964].

$$\ln \gamma_i^a = 1 - \ln \sum_{j=1}^N x_j^a \Lambda_{ij} - \sum_{k=1}^N \frac{x_k^a \Lambda_{ki}}{\sum_{j=1}^N x_j^a \Lambda_{kj}} \quad (3.30)$$

where Λ_{ij} are the constants of the model. Note that the summation here is performed over all species, including the solvent present in the adsorbed phase.

The limit of the selectivity of solute 1 with respect to solute 2 at infinite dilution is given by the ratio of the corresponding Henry constants, *i.e.*,

$$\lim_{x_1^b, x_2^b \rightarrow 0} S_{1,2} = \lim_{x_1^b, x_2^b \rightarrow 0} \frac{x_1^a/x_1^b}{x_2^a/x_2^b} = \frac{K_1^x}{K_2^x} \quad (3.31)$$

From Eq (3.23) the selectivity $S_{1,2}$ for a binary solute mixture is

$$S_{1,2} = \frac{x_1^a/x_1^b}{x_2^a/x_2^b} = \frac{\gamma_1^b \gamma_s^a x_s^a \gamma_1^{a,\infty} K_1^x \gamma_2^{b,\infty} \gamma_s^b x_s^b \gamma_2^a}{\gamma_1^{b,\infty} \gamma_s^b x_s^b \gamma_1^a K_2^x \gamma_2^b \gamma_s^a x_s^a \gamma_2^{a,\infty}} \quad (3.32)$$

At infinite dilution for the solutes, we have

- a) In the liquid phase : $x_1^b \rightarrow 0$, $x_2^b \rightarrow 0$, $x_s^b \rightarrow 1$, $\gamma_1^b \rightarrow \gamma_1^{b,\infty}$, $\gamma_2^b \rightarrow \gamma_2^{b,\infty}$, $\gamma_s^b \rightarrow 1$.
- b) In the adsorbed phase : $x_1^a \rightarrow 0$, $x_2^a \rightarrow 0$, $x_s^a \rightarrow 1$, $\gamma_1^a \rightarrow \gamma_1^{a,\infty}$, $\gamma_2^a \rightarrow \gamma_2^{a,\infty}$, $\gamma_s^a \rightarrow 1$.

Incorporating these limits into Eq. (3.32) we arrive at Eq. (3.31), *i.e.*, Eq. (3.23) complies with Henry Law at low solute concentration and the selectivity extrapolates to a unique limit.

The calculation of multisolute equilibria via the Wilson model, using the parameters identified from the single solute adsorption data, is not straightforward because of the unavailability of the $\Lambda_{i,j}$ constants for the solute-solute interactions. On the other hand, it was found previously for adsorption systems that the parameters $\Lambda_{i,j}$ and $\Lambda_{j,i}$ are strongly correlated and the product $\Lambda_{i,j}\Lambda_{j,i}$ is close to one [Cochran *et al.*, 1985]. To overcome this problem, we may use a Flory-Huggins [Flory, 1953] type expression to represent the activity coefficients in the adsorbed phase, *i.e.*,

$$\ln \gamma_i^a = 1 - \ln \sum_{j=1}^N \frac{\alpha_j}{\alpha_i} x_j^a - \frac{1}{\sum_{j=1}^N \frac{\alpha_j}{\alpha_i} x_j^a} \quad (3.33)$$

where α_i are the constants of the model. We further assume that, for the solvent present in the adsorbed phase, $\alpha_s = 1$. Note that, in this study, the constants α_i will account not just for the differences in size of the adsorbate molecules, as originally suggested by Flory and Huggins [Flory, 1953], but also for the solute-solute and solute-solvent interactions in the adsorbed phase. At infinite dilution, the activity coefficients are simply

$$\gamma_i^{a,\infty} = \alpha_i \exp(1 - \alpha_i) \quad (3.34)$$

In this study the solutes are present in the bulk liquid in small quantities ($x_i^b < 0.01$), thus the activity of the solvent is very close to unity ($\gamma_s^b x_s^b \approx 1$).

Taking into account the aforementioned simplifications Eq (3.26) becomes

$$\frac{\gamma_i^a \theta_i}{\gamma_s^a (1 - \sum_{k=1}^{N_s} \theta_k)} \frac{n^\infty \gamma_i^{b,\infty}}{\rho_b K_i^c \gamma_i^{a,\infty}} = \gamma_i^b x_i^b \quad (3.35)$$

In the present study, the nonidealities in the bulk liquid phase are estimated via the UNIFAC method [Hansen *et al.*, 1991].

Regression of the experimental data to the adsorption isotherm models was performed using the optimization routine E04UPF of the NAG Library (NAG, 1993) for the minimization of a function subject to constraints using a sequential quadratic programming method. The numerical inversion of the model with respect to the surface coverage was accomplished using a modification of the Powell hybrid method for the solution of nonlinear equations. These last algorithm is implemented in the routine C05NBF, also from the NAG Library.

When fitting the single solute data, the response surface of the optimization problem often exhibits several minima (global and/or local), since the model exhibits a significant degree of nonlinear behavior. To avoid to be trapped in local minima, we carried out the identification process several times, using a different initial guess vector each time. This is a convenient empirical way to determine if the solution converges toward the global minima. The procedure calculates the values of the isotherm parameters which minimize the residual sum of squares between experimental and calculated values for the joint single solute data of BA, PE and MBA.

The selection of the most adequate model was performed using the Fisher's test. The model that correlated best the data is the one which exhibits the highest value of the following Fisher parameter [Ajnazarova and Kafarov, 1985]

$$F = \frac{(n-l) \sum_{j=1}^n (q_{ex,j} - \overline{q_{ex}})^2}{(n-1) \sum_{j=1}^n (q_{ex,j} - q_{t,j})^2} \quad (3.36)$$

where n is the total number of experimental points, l is the number of adjusted parameters of the model, $\overline{q_{ex}}$ is the mean value of the vector $\vec{q_{ex}}$, which contains the experimental data as elements $q_{ex,j}$ and $q_{t,j}$ is the theoretical value of the adsorbed amount calculated by the model. The second factor in the RHS of Eq. (3.36) contains the residual sum of squares in the denominator. So, the higher F_{calc} , the better the model correlates the data. The first term in the numerator of the RHS of Eq. (3.36) decreases with increasing number of the parameters

in the model. So, Eq. (3.36) shows to which extent the introduction of a new parameter in the model can actually decrease in a significant way the residual sum of squares. Thus, Eq. (3.36) allows the comparison of models having different number of parameters (Ajnazarova and Kafarov, 1985).

3.2.2 Liquid-Liquid Equilibria Models.

The equilibrium in a liquid-liquid system is characterized by the expression [Prausnitz *et al.*, 1986]

$$\gamma_i^{sp} x_i^{sp} = \gamma_i^b x_i^b \quad (3.37)$$

where γ_i^{sp} is the activity coefficient and x_i^{sp} the mole fraction of component i in the stationary phase.

The UNIFAC model [Hansen *et al.*, 1991] was applied in this study to account for the nonidealities in both the stationary and the mobile bulk liquids. Both single-solute and multisolute data can be predicted using Eq (3.37), provided the nature of the stationary phase is specified. In order to compare the model estimates with experimental data, a representation of the stationary phase composition in terms of molar concentrations is needed. The molar concentration of the solute in the stationary phase is calculated from the corresponding mole fraction via the expression

$$C_i^{sp} = x_i^{sp} \rho_{sp} \quad (3.38)$$

where ρ_{sp} is the density of the stationary phase. ρ_{sp} is assumed to be equal to

the density of the liquid employed to model the stationary phase, for example 1-octanol, since the mole fractions of the solutes in this phase are very low.

From Eq (3.37), it follows that the distribution coefficient of the i -th component in terms of mole fractions is

$$D_i^x = \frac{x_i^{sp}}{x_i^b} = \frac{\gamma_i^b}{\gamma_i^{sp}} \quad (3.39)$$

On the other hand, the distribution coefficient based on molar concentrations is

$$D_i^c = \frac{C_i^{sp}}{C_i} = \frac{\gamma_i^b \rho_{sp}}{\gamma_i^{sp} \rho_b} \quad (3.40)$$

and, at infinite dilution, it becomes

$$D_i^{c,\infty} = \frac{\gamma_i^{b,\infty} \rho_{sp}}{\gamma_i^{sp,\infty} \rho_b} \quad (3.41)$$

3.3 Discussion.

3.3.1 Thermodynamic consistency of the experimental data.

Single solute isotherm data determined from FA and FACP experiments at 30° C are presented in Figure 3.4 for all the solutes. Note the good agreement between the data obtained by the two different methods. Recall that FA extracts the equilibrium data using the adsorption branch of the experiment while FACP derives the same data from the desorption branch of the experiment, assuming in this last case that equilibrium is attained instantaneously [Guiochon *et al.*, 1992].

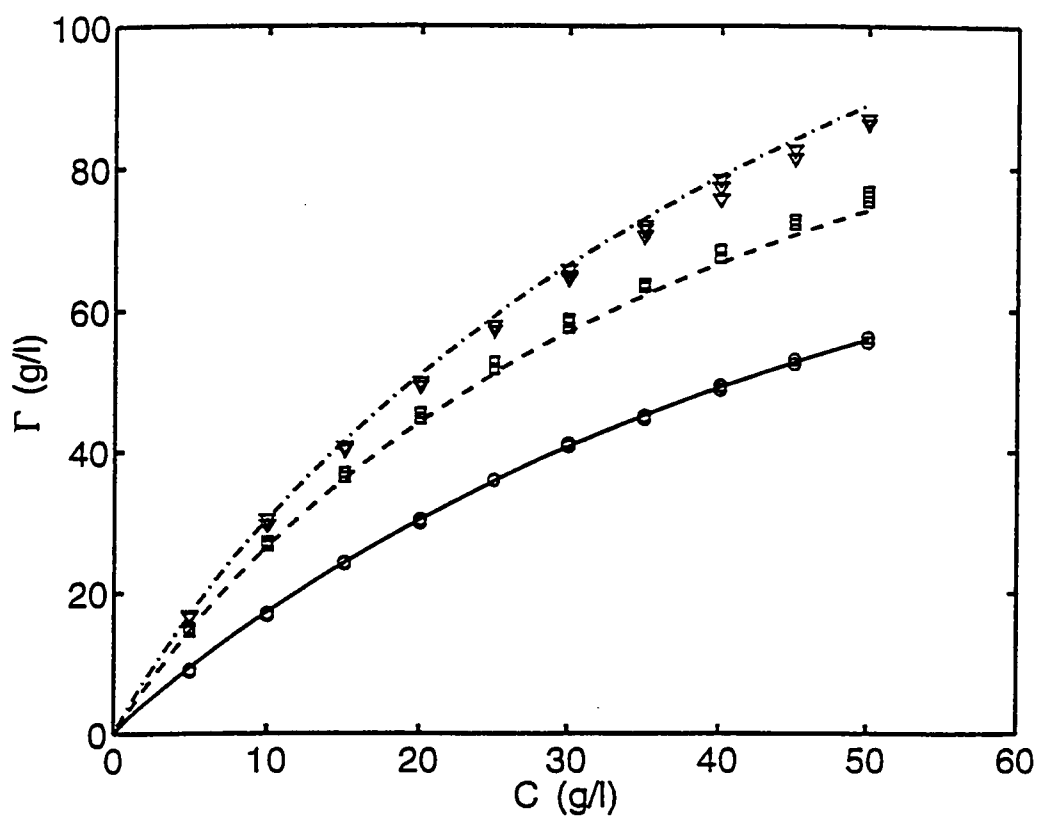


Figure 3.4 Single solute adsorption data at 30 °C obtained via FA (points) and FACP (lines). It is shown the data for BA (circles and solid line), PE (squares and dashed line) and MBA (triangles and dashed-dotted line)

The coincidence between FA and FACP demonstrates the excellent thermodynamic consistency of the measured single solute data (in part a consequence of the use of highly efficient columns, as mentioned earlier).

The results of the analysis of the binary solute data for thermodynamic consistency are presented in Figure 3.5. Note that errors are provided for each closed loop integral at every level of total solute concentration. Because the average relative deviations are small (*ca.* 5%) and comparable to these errors, the data exhibit a very good thermodynamic consistency for the three solute binaries.

3.3.2 Thermodynamic functions of adsorption.

The values of several thermodynamic functions of adsorption derived from low concentration data at different temperatures are presented in Table 3.9. Note that the values of K_i^c and ΔG_i^o increase from benzyl alcohol to 2-methyl benzyl alcohol. This trend reflects the fact that benzyl alcohol is the least retained while 2-methyl benzyl alcohol is the most. The Van't Hoff plots of the Henry constants for the different solutes studied are shown in Figure 3.6. Note that also the values of ΔH_i^o slightly increase when moving from benzylalcohol to 2-methylbenzylalcohol, although all the values are about -10 kJ/mol. These values of ΔH_i^o are similar to those reported for compounds having similar molecular weight and functional groups in reversed-phase systems [Miyabe and Suzuki, 1992].

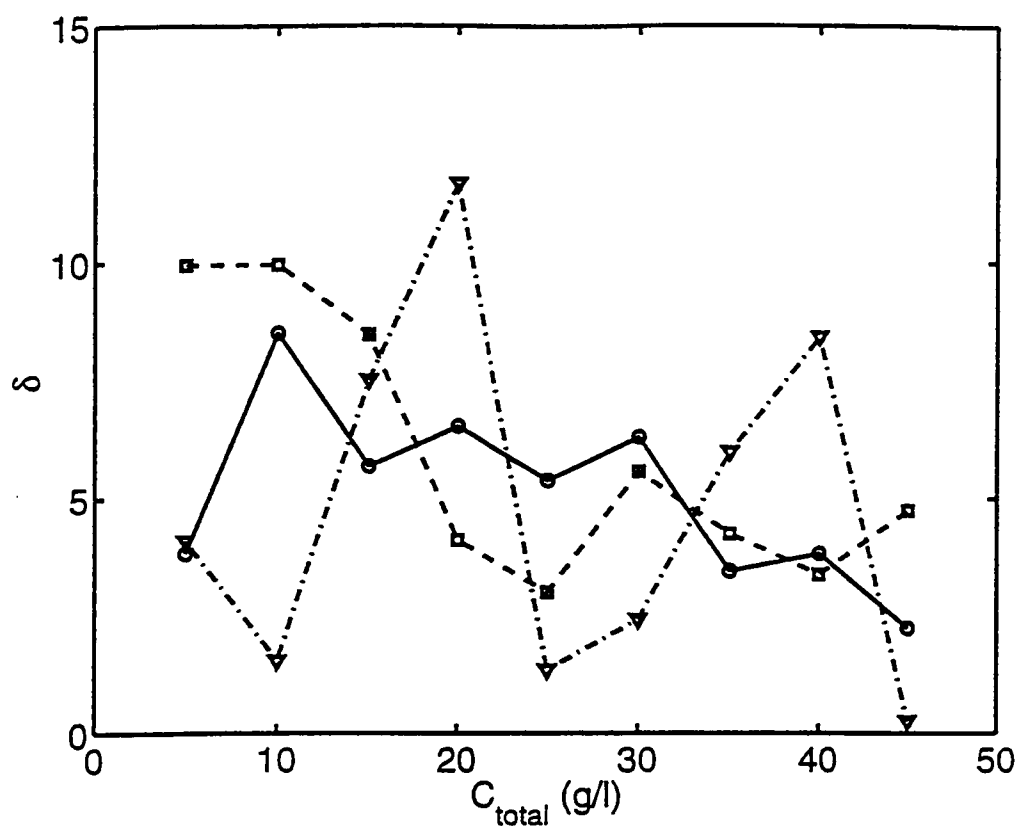


Figure 3.5 Thermodynamic consistency test for the three binary solute mixtures studied. The abscissa shows the total solute concentration in the mixture. Data presented for the BA-PE mixture (circles and solid line), BA-MBA mixture (squares and dashed line) and PE-MBA (triangles and dashed-dotted line). The average errors are 5.08 %, 5.94 % and 4.81 % for the BA-PE, BA-MBA and PE-MBA mixtures, respectively.

Table 3.9. Values of the thermodynamic functions of adsorption
derived from low concentration data

T	K^{exp}_1	$-\Delta G^\circ_1$	$-\Delta S^\circ_1$	K^{exp}_2	$-\Delta G^\circ_2$	$-\Delta S^\circ_2$	K^{exp}_3	$-\Delta G^\circ_3$	$-\Delta S^\circ_3$
(K)		(kJ/mol)	(J/mol K)		(kJ/mol)	(J/mol K)		(kJ/mol)	(J/mol K)
293.15	2.032	1.73	25.42	3.501	3.05	25.49	3.998	3.38	26.53
303.15	1.828	1.51	25.3	3.090	2.84	25.35	3.494	3.15	26.40
313.15	1.622	1.26	25.3	2.707	2.59	25.34	3.035	2.89	26.39
323.15	1.446	0.99	25.34	2.373	2.32	25.39	2.644	2.61	26.44
333.15	1.295	0.72	25.41	2.088	2.04	25.48	2.311	2.32	26.52

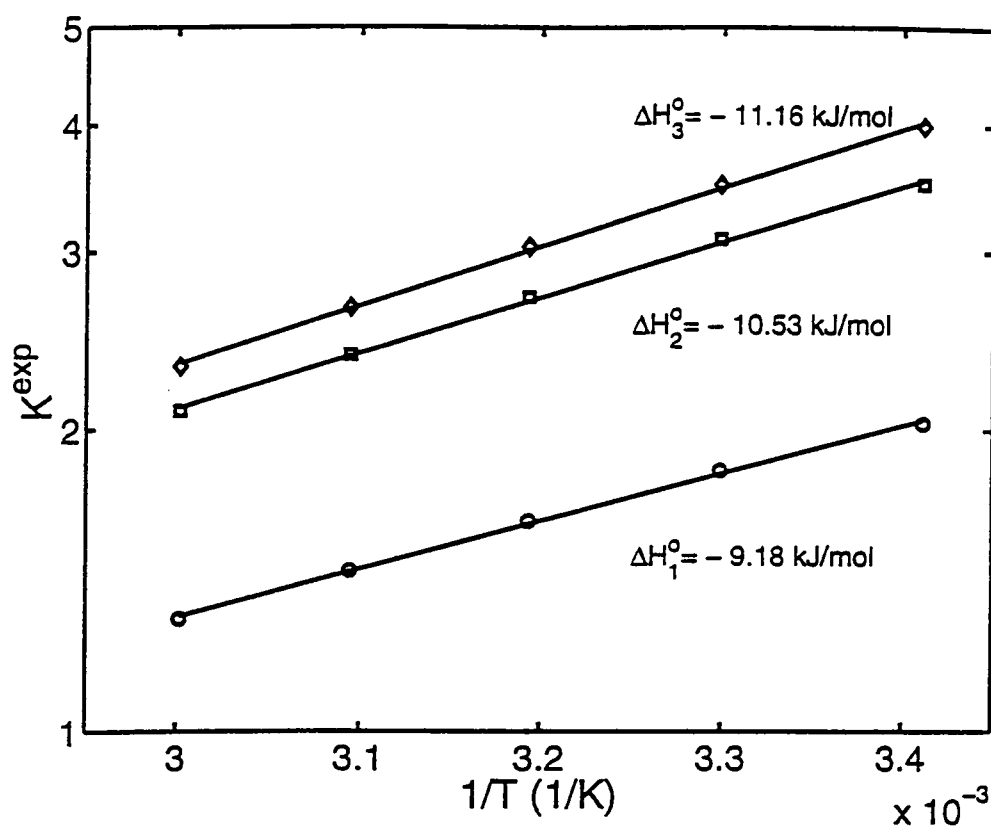


Figure 3.6. Van't Hoff plots of the experimental Henry constants determined for the different solutes. Data for BA (circles), PE (squares) and MBA (diamonds).

The trend observed in the values of ΔG_i° and ΔH_i° roughly correlates with the hydrocarbonaceous area of the molecules [Snyder, 1968]. These areas are 53.98, 61.63, and 62.90 Å² for BA, PE, and MBA, respectively. The hydrocarbonaceous area of the adsorbates is believed to be a crude measure of the adsorbate-adsorbent interactions in RPLC [Horváth *et al.*, 1976]. The values of ΔS_i° are close for all the adsorbates at the different temperatures, about 25-26 J/mol K. This is possibly a result of the similarities in size and structure among these solutes.

Single solute adsorption data of BA determined from FACP experiments at different temperatures are presented in Figure 3.7 (symbols). A similar temperature dependence is also observed for PE and MBA. From the adsorption data at different temperatures, Clausius-Clapeyron plots were constructed. The plots for BA are presented in Figure 3.8. Similar plots were constructed for PE and MBA. From these plots, the isosteric heats of adsorption were derived at different loadings for all the solutes. They are presented in Table 3.10. Note that the values of the isosteric heats are basically constant for each adsorbate at different loadings. This constancy of the isosteric heats of adsorption was reported previously for other RPLC systems [Miyabe and Suzuki, 1992].

The results obtained here provide evidence that the surface is nearly homogeneous under the conditions of this study. Adsorbate-adsorbate interactions may also contribute to the value of the isosteric heats but since we employ activities

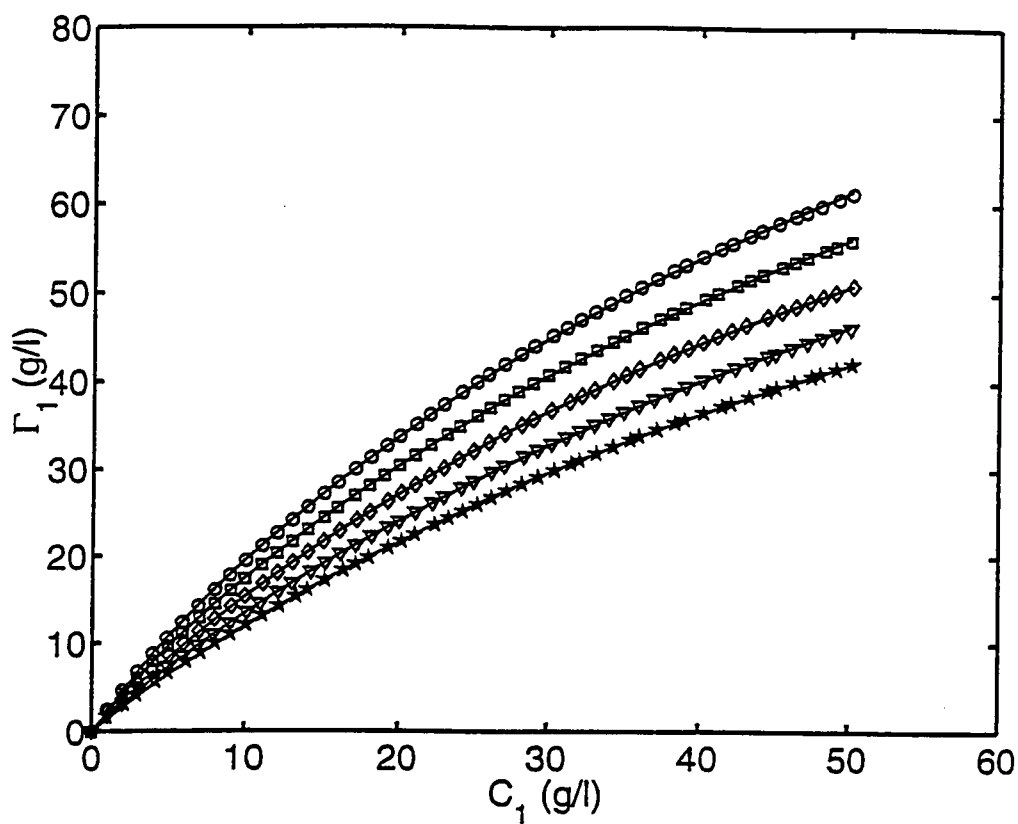


Figure 3.7. Single solute BA adsorption data (points) at different temperatures : 20 °C (circles), 30 °C (squares), 40 °C (diamonds), 50 °C (triangles), 60 °C (stars). The solid lines are the correlations given by the FH model.

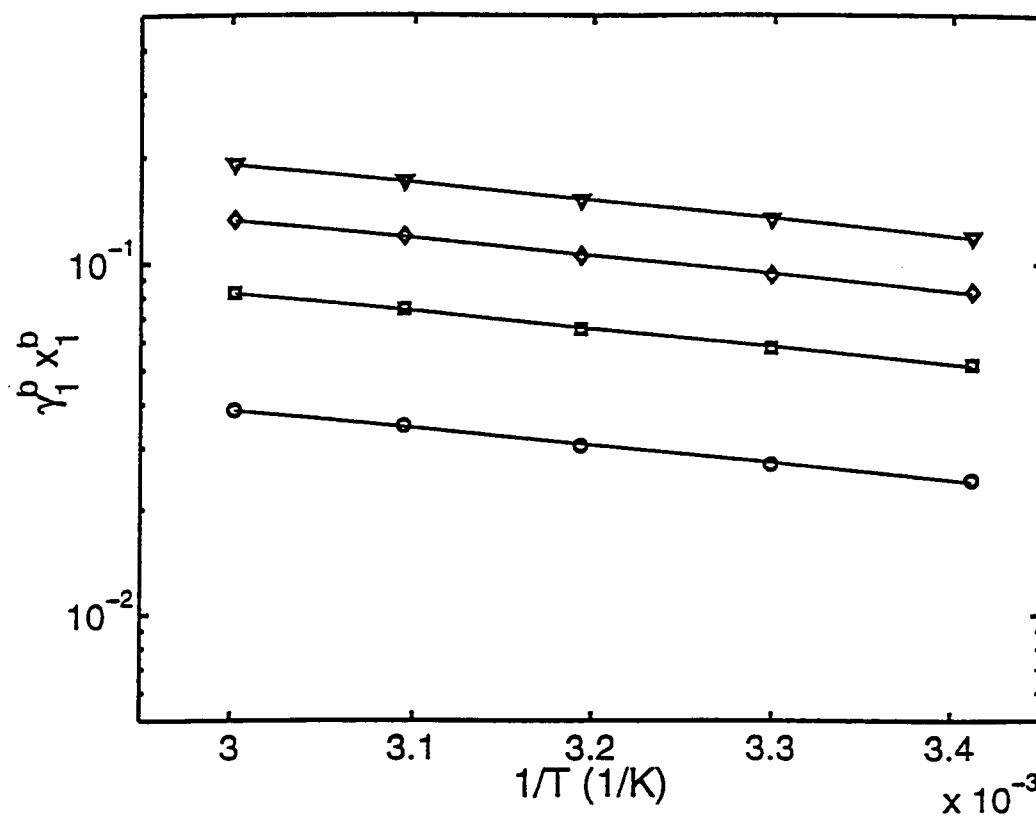


Figure 3.8. Clausius-Clapeyron plots for BA. Data at different loadings of the adsorbed phase : 10 g/l (circles), 20 g/l (squares), 30 g/l (diamonds) and 40 g/l (triangles).

Table 3.10. Isosteric heats of adsorption for
different adsorbates at different loadings

Γ	Q_{1}^{iso}	Q_{2}^{iso}	Q_{3}^{iso}
(g/l)	(kJ/mol)	(kJ/mol)	(kJ/mol)
10	9.50	9.99	10.12
20	9.57	10.01	10.13
30	9.63	10.02	10.13
40	9.67	10.03	10.13
50	-	10.01	10.10
60	-	-	10.06

in eq. (2.29), the main contribution should come from the adsorbate-adsorbent interactions. Moreover, note that the values presented in Table 3.10 are all approximately equal to 10 kJ/mol. This is basically the same value determined from the Van't-Hoff plots at low concentrations for the standard heat of adsorption, see Figure 3.6. Thus, a very good agreement is observed between data obtained at low and high concentrations of the solutes, further comforting the conclusion of an homogeneous adsorbent surface.

3.3.3 Adsorption isotherm models.

The single solute adsorption data at different temperatures were fitted to the nonideal model, Eq. (3.35), using both the Wilson model, Eq. (3.30), and the Flory-Huggins (FH) model, Eq. (3.33), to account for the nonidealities in the adsorbed phase. The results of the identification for the Wilson and FH models are presented in Tables 3.11 and 3.12, respectively. The F-values presented in these tables show that for the experimental data under consideration, the FH model provided a correlation with basically the same accuracy as the Wilson model. Figure 3.7 presents the correlation of the FACP data for BA provided by the FH model (lines). Note that the model provides an excellent representation of the data. For the sake of comparison, the same data were fitted to the Langmuir model, Eq. (3.29). These results are presented in Table 3.13. Note that the correlation provided by the Langmuir model is not as good the one provided by

Table 3.11. Results of the fit of FACP data to the Wilson model.

T	n^∞	K_1^c	K_2^c	K_3^c	Λ_{1s}	Λ_{s1}	Λ_{2s}	Λ_{s2}	Λ_{3s}	Λ_{s3}	F
(K)	(mol/l)										
293.15	7.105	2.214	3.749	4.629	0.093	4.705	0.071	5.310	0.417	3.094	14791.65
303.15	3.265	2.050	3.099	3.902	0.221	3.087	0.107	3.982	0.454	2.283	35792.56
313.15	5.122	1.762	2.798	3.461	0.701	2.259	0.108	4.364	0.324	2.991	6494.31
323.15	5.149	1.500	2.409	2.935	0.169	3.64	0.121	4.189	0.407	2.720	6178.90
333.15	4.188	1.369	2.228	2.450	0.368	2.665	0.201	3.489	0.524	2.217	14450.59

Table 3.12. Results of the fit of the single solute adsorption data to the FH model.

T	n^∞	K_1^c	K_2^c	K_3^c	α_1	α_2	α_3	F
(K)	(mol/l)							
FACP data								
293.15	2.486	2.338	4.282	4.409	2.047	2.518	1.930	8220.06
303.15	2.429	2.071	3.628	3.781	2.055	2.449	1.865	10712.07
313.15	2.535	1.750	2.895	3.164	0.138	0.001	0.333	15791.61
323.15	2.654	1.532	2.593	2.785	2.061	2.389	1.907	15260.29
333.15	2.000	1.338	2.152	2.372	0.398	0.257	1.326	10567.80
FA data								
303.15	2.277	2.015	3.574	3.674	1.876	2.246	1.787	2271.17

Table 3.13. Results of the fit of the single solute adsorption data to the Langmuir model.

T	n^∞	$K_1^L \times 10^2$	$K_2^L \times 10^2$	$K_3^L \times 10^2$	F
(K)	(g/l)	(l/g)	(l/g)	(l/g)	
FACP data					
293.15	161.1	1.277	2.128	2.820	479.12
303.15	154.69	1.180	1.936	2.542	533.58
313.15	150.35	1.060	1.762	2.252	658.38
323.15	146.47	0.951	1.563	1.969	921.26
333.15	140.38	0.882	1.434	1.795	933.10
FA data					
303.15	154.40	1.178	2.006	2.452	616.35

the FH model, as indicated by the corresponding values of F in Tables 3.12 and 3.13. The RPLC system analyzed in this study is nonideal in both the mobile and the stationary phases and it is clear that the assumptions implicit in the Langmuir model are not met.

The values of the Henry constant identified from the fit of the data reflect the trend observed under analytical conditions in terms of retention order, benzylalcohol being the least retained and 2-methyl benzylalcohol being the most. Note that for the FH model, the value of n^∞ is in the range of 2.0-2.7 mol/l (see Table 3.12). Surprisingly, this range includes the value of the concentration of the C_{18} chains in the packing, which is about 2.4 mol/l. The latter value was calculated from the manufacturer's data for the bonding density, $3.16 \mu\text{mol } C_{18}/\text{m}^2$, and the specific surface area, $340 \text{ m}^2/\text{g}$. We assumed a density of the silica approximately equal to 2.3 g/ml [Unger, 1979].

Single, binary, and ternary solute adsorption data measured by FA (Tables 3.1 and 3.5-3.8) are presented graphically in Figures 3.9 to 3.12 (the symbols show the experimental data). Also in Figures 3.9 to 3.12, we present the correlation of the single solute FA data provided by the FH model (solid lines). Note that this model provides an excellent representation of the single solute data, as well as of the binary and ternary data. Based on the parameters identified from the single solute data, the multisolute data could be predicted, as illustrated in Figures 3.9 to 3.12 (solid lines). Note that the FH model accurately predicts

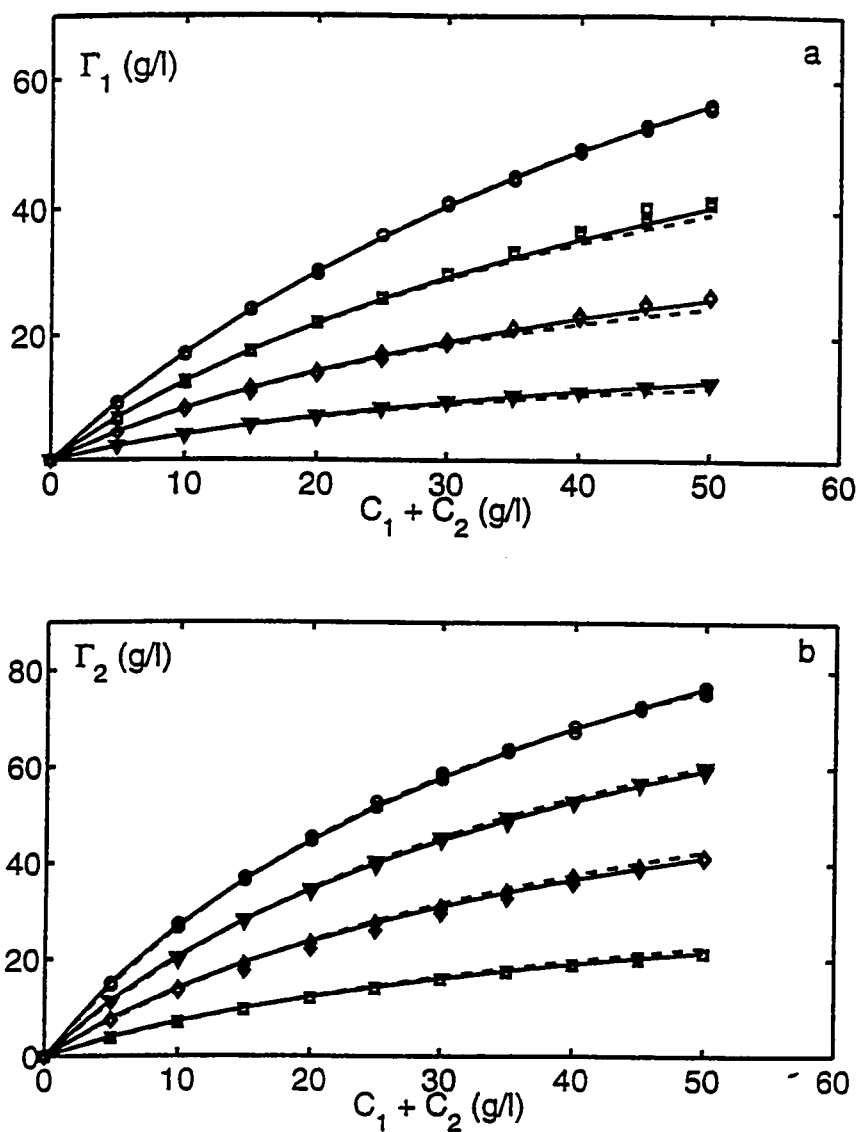


Figure 3.9. Adsorbed amount of BA (a) and PE (b) determined via FA in their mixtures. Symbols: data for single solute, circles; data for 3:1 mixtures (Three parts of BA and one part of PE in the mobile phase), squares; data for 1:1 mixtures, diamonds; and data for 1:3 mixtures, triangles. The solid lines are the calculated amounts via the FH model which uses the parameters determined from single solute data. The dashed lines are the calculated adsorbed amounts via the IAS model.

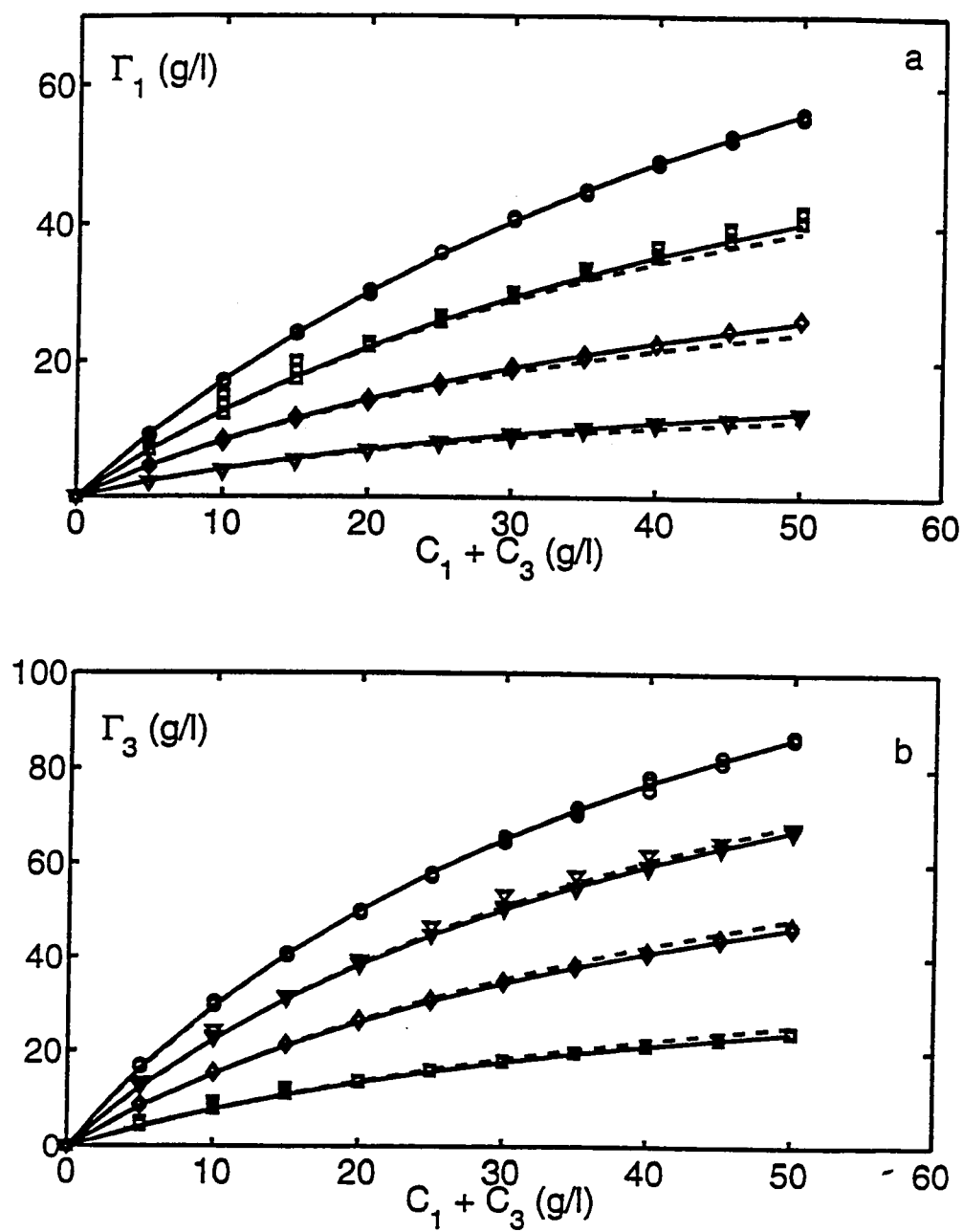


Figure 3.10. Adsorbed amount of BA (a) and MBA (b) determined via FA in mixtures containing BA and MBA. Identical convention as in Figure 3.9.

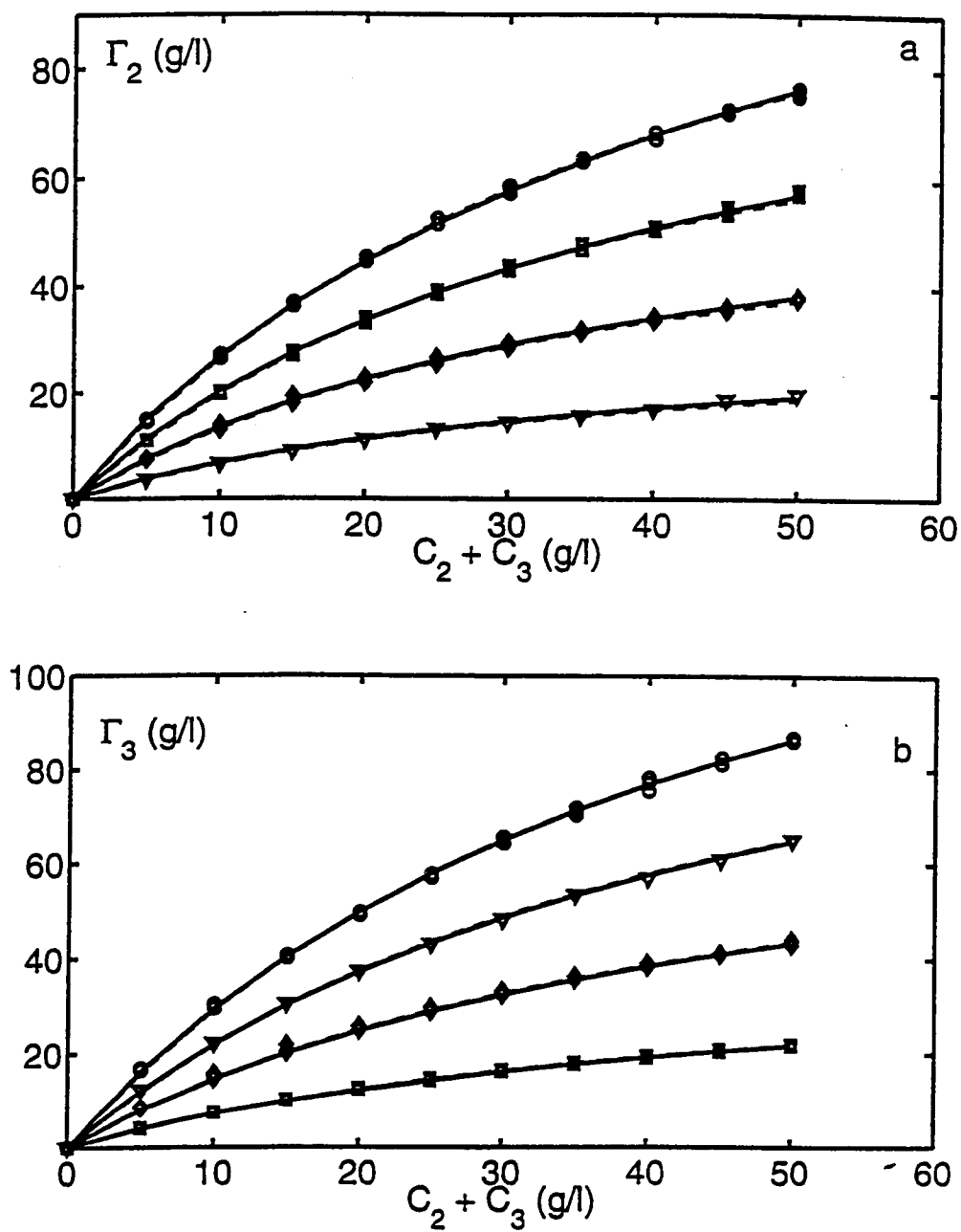


Figure 3.11. Adsorbed amount of PE (a) and MBA (b) determined via FA in mixtures containing PE and MBA. Identical convention as in Figure 3.9.

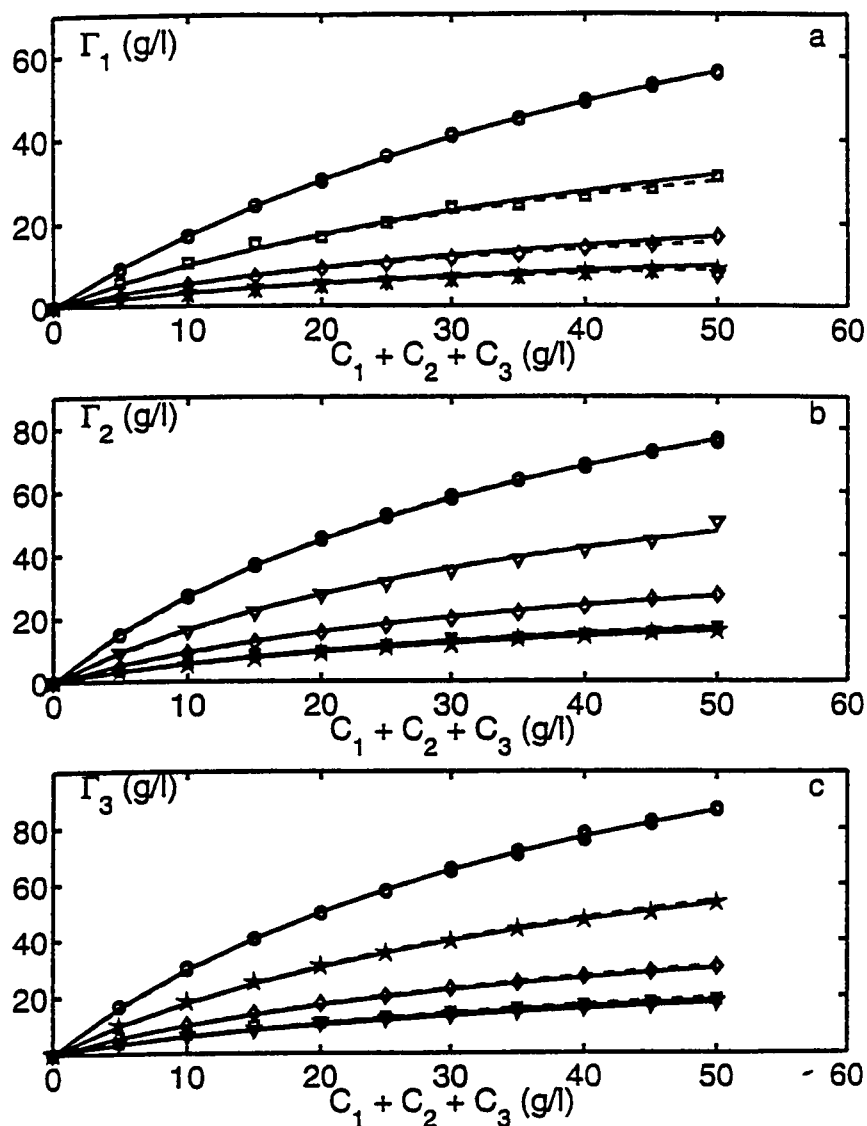


Figure 3.12. Adsorbed amount of BA (a), PE (b) and MBA (c) determined via FA their mixtures. The mobile phase concentration is expressed via the relative composition BA:PE:MBA. Symbols: data for single solute, o; data for the 1:1:1 mixtures, diamonds; data for 3:1:1 mixtures, squares; data for 1:3:1 mixtures, triangles; and data for the 1:1:3 mixtures, stars. The solid lines are the calculated adsorbed amounts via the FH model which uses the single solute determined parameters. The dashed lines are the calculated adsorbed amounts via the IAS model.

the binary and ternary solute adsorption data, based solely on the single solute identified parameters. A comparison of the quality of the predictions made with this and other models, *i.e.*, the Langmuir model and the IAS theory [Myers and Prausnitz, 1965; Radke and Prausnitz, 1972] is presented in Table 3.14. The prediction given by the FH model is the best.

In Figures 3.9 to 3.12, the prediction of the IAS theory is also presented (dashed lines). It is worth noting that the prediction of the IAS model is very close to the one provided by the FH model. In some cases however, the IAS model deviates slightly at high concentrations from the experimental competitive data. As a result, the value of the total residuals produced by the IAS model is greater than the value corresponding to the FH model (see Table 3.14).

Figures 3.13 and 3.14 show that the activity coefficients of the solutes in both phases are fairly constant over the concentration range studied. Note in Figure 3.13 that the values of γ_i^a are less than unity. Thus, the adsorbed phase shows negative deviations from solution ideality. On the other hand, Figure 3.14 shows that the values of γ_i^b are greater than unity, thus the bulk liquid phase shows positive deviations from ideal-solution behavior. These results show that the solutes will distribute in the adsorbed phase not only as a result of net repulsive interactions in the mobile phase but also as a result of net attractive interactions in the adsorbed phase, as suggested elsewhere [Carr *et al.*, 1993]. Of course, the observed deviations from ideality are linked to the nature of the chosen standard

Table 3.14. Prediction of the multisolute adsorption data based on the single solute parameters using different models. The values shown in the table are the sum of squares of the differences between the experimental and calculated values of the adsorbed amount. Values in parentheses correspond to the competitive data.

Model	BA-PE			BA-MBA		
	BA	PE	Sub-total	BA	MBA	Sub-total
Langmuir	17.36	22.39	162.05	17.36	33.68	523.96
	(44.70)	(77.61)		(206.46)	(266.46)	
FH	2.33	6.94	50.89	2.33	9.93	95.30
	(18.41)	(23.22)		(36.56)	(46.48)	
IAS	1.90	4.93	143.99	1.90	11.81	200.08
	(76.76)	(67.23)		(109.32)	(90.76)	

Table 3.14. (Continued)

Model	PE-MBA			BA	BA-PE-MBA			TOTAL
	PE	MBA	Sub-total		PE	MBA	Sub-total	
Langmuir	22.39 (84.64)	33.68 (67.98)	208.69	17.36 (15.03)	22.39 (18.28)	33.68 (15.03)	174.99	1069.69
FH	6.94 (13.33)	9.93 (12.19)	42.39	2.33 (25.21)	6.94 (17.19)	9.93 (25.21)	67.68	256.26
IAS	4.93 (20.74)	11.81 (22.51)	43.25	1.90 (11.31)	4.93 (24.50)	11.81 (21.79)	59.50	446.82

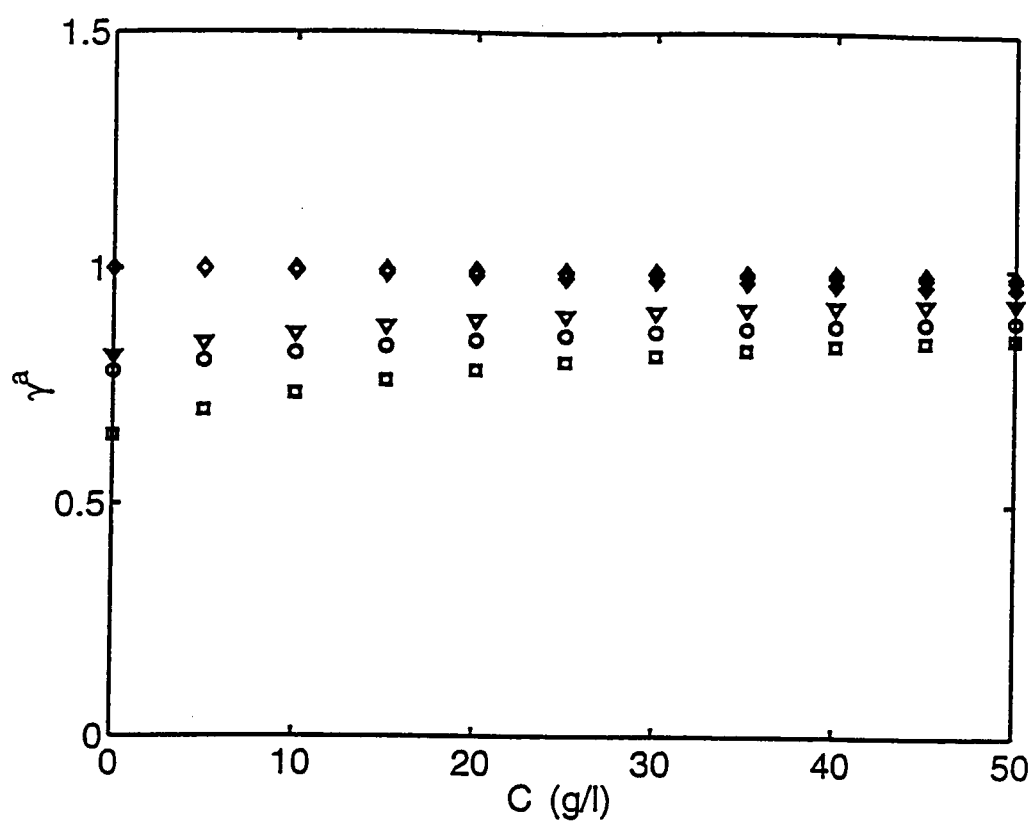


Figure 3.13. Activity coefficients in the adsorbed phase. Data for BA (circles), PE (squares), MBA (triangles) and solvent (diamonds).

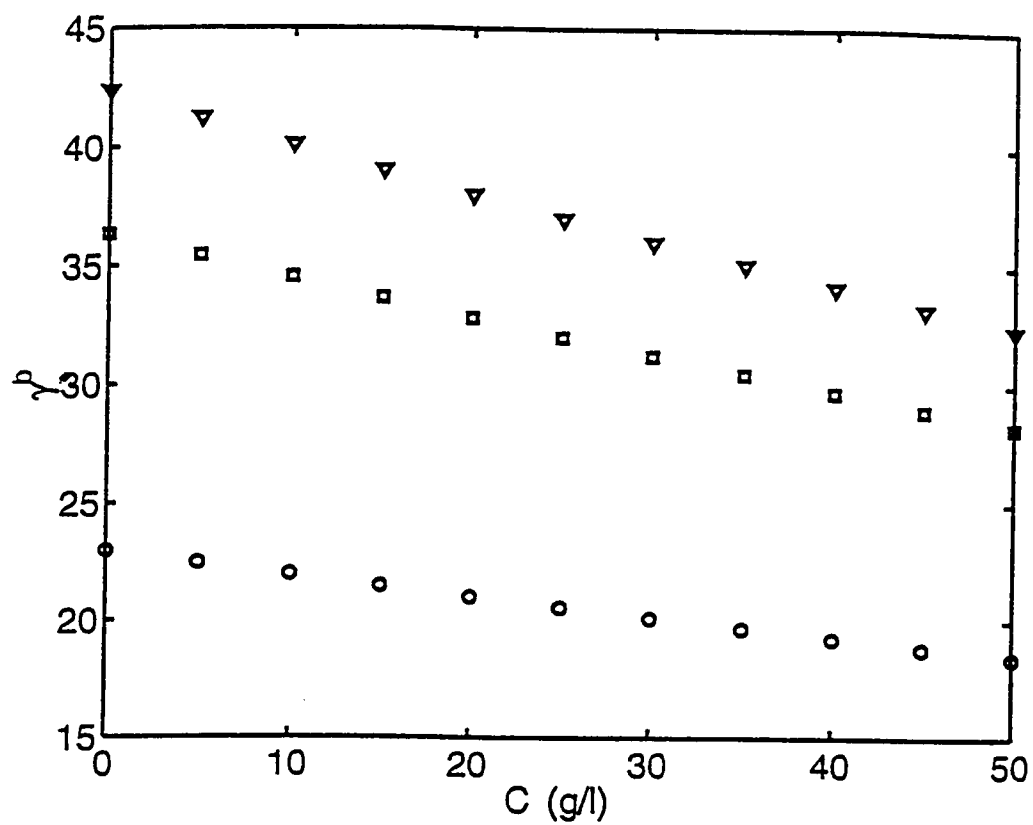


Figure 3.14. Activity coefficients in the mobile phase. Data for BA (circles), PE (squares) and MBA (triangles).

state.

In this work we employ models that comply with the symmetric convention for the activity coefficients [Prausnitz *et al*, 1986]. Accordingly, the link between the nature of the interactions in both phases and the deviations from the Lewis-Randall rule should be carefully understood within the constraints imposed by the assumed standard state. On the other hand, the values of γ_s^a are practically equal to unity, thus the behavior of the solvent in the adsorbed phase is basically ideal. Eq. (3.35) can be rearranged as

$$\frac{\theta_i}{1 - \sum_{k=1}^{N_s} \theta_k} = K_i^{app} C_i \quad (3.42)$$

where

$$K_i^{app} = \frac{K_i^c \gamma_i^{a,\infty} \gamma_i^b \gamma_s^a}{n^\infty \gamma_i^a \gamma_i^{b,\infty}} \quad (3.43)$$

K_i^{app} can be interpreted as an apparent Langmuir equilibrium constant. Note that if the activity coefficients of the species do not change significantly with composition the value of K_i^{app} is roughly constant. As a first approximation, this is the case in the present study, as shown in Figures 3.13 and 3.14. Note that Eq. 3.42 is equivalent to the Langmuir model, Eq. 3.28. This fact explain why the Langmuir model was able to correlate the single solute adsorption data obtained in the present study. It could also explain why the IAS model is able to give a good representation of the competitive data. The same situation has been reported for several others systems, where the Langmuir model has successfully

correlated single solute RPLC data [Guiochon *et al.*, 1994].

3.3.4 Liquid-Liquid equilibrium models.

The liquid-liquid (L-L) equilibrium model was applied to the description of the distribution of benzylalcohol between the stationary and the mobile phases. Several hydrocarbons and alcohols were used to model the stationary phase. No partitioning of mobile phase components other than the solutes is allowed. It is assumed that the model stationary phase already accounts for the possible inclusion of the mobile phase components (*e.g.*, methanol).

The results are presented in Figure 3.15. Note that the hydrocarbon phases fail completely to account for the experimental data. It was stated previously that hydrocarbon phases could fail to describe the partitioning of polar solutes [Carr *et al.*, 1993]. On the other hand, the alcohol phases better describe the experimental data, specially in the region of low concentrations. The failure of the hydrocarbon phases and the relative success of long-chain alkanols is probably a consequence of the exclusion of methanol from the stationary phase. Table 3.15 presents the low concentration distribution constants calculated for the different alcohol stationary phases according to Eq. (3.41). These values can be compared with the experimental values of the Henry constants presented in Table 3.9. The differences between experimental and calculated values can be evaluated via the

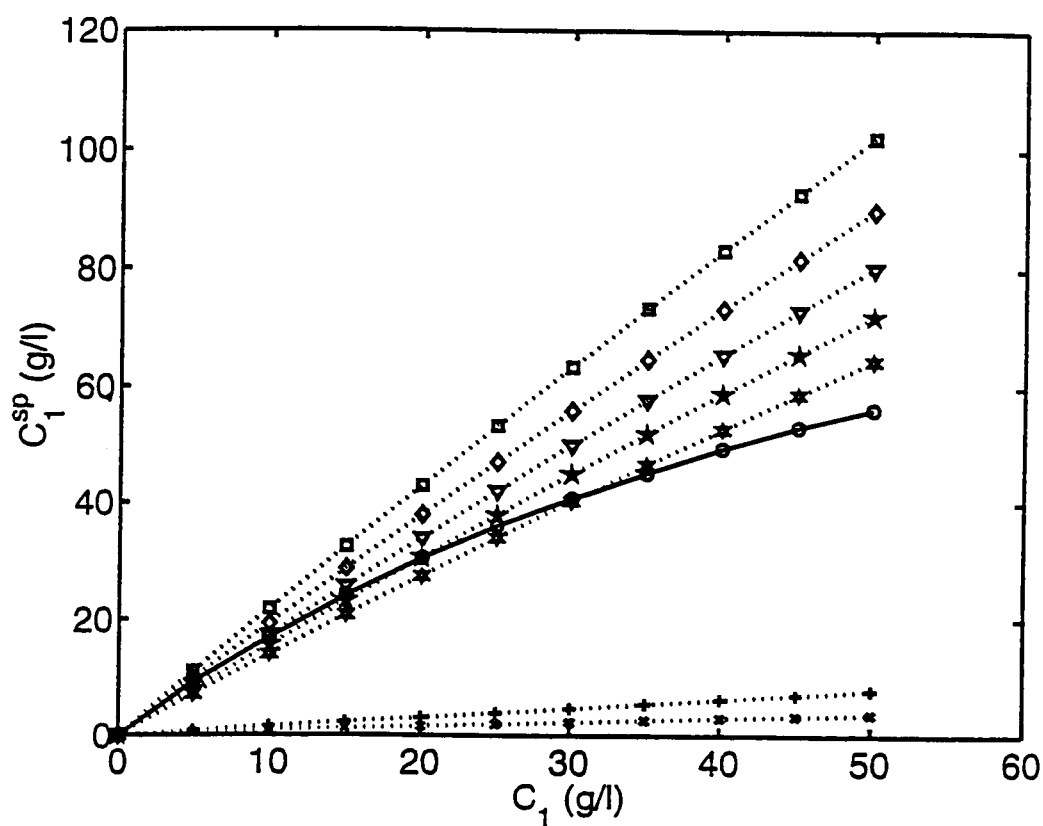


Figure 3.15. Single solute distribution data for BA calculated via the use of different model stationary phases. Experimental data as circles. Symbols for the model phases are 1-octanol (squares), 1-nonanol (diamonds), 1-decanol (triangles), 1-undecanol (pentagrams), 1-dodecanol (hexagrams), 1-pentane (straight cross) and 1-hexadecane (cross).

Table 3.15. Values of the infinite dilution distribution coefficient calculated for the different model stationary phases.

Stationary Phase	$D_1^{c,\infty}$	Δ	$D_2^{c,\infty}$	Δ	$D_3^{c,\infty}$	Δ
$C_8H_{18}O$	2.185	19.54	3.723	20.47	4.291	22.81
$C_9H_{20}O$	1.938	6.03	3.312	7.20	3.802	8.81
$C_{10}H_{22}O$	1.735	5.08	2.973	3.79	3.400	2.70
$C_{11}H_{24}O$	1.576	13.81	2.705	12.46	3.084	11.74
$C_{12}H_{26}O$	1.433	21.63	2.464	20.27	2.801	19.83
C_{18}	1.828	0.00	3.090	0.00	3.494	0.00

expression

$$\Delta = 100 \frac{|K_i^{exp} - D_i^{c,\infty}|}{K_i^{exp}} \quad (3.44)$$

Note that the best representation of the experimental data is given by 1-decanol (see Figure 3.15). This model stationary phase is able to predict the experimental Henry constants with an error lower than 5 %. Note, however, that all the model stationary phases completely fail properly to describe the curvature of the experimental data at higher concentrations of the solute. Moreover, the L-L model also fails to describe the temperature dependence of the experimental data, as shown in Figure 3.16. This situation could be in part a result of the weak temperature dependence built in the UNIFAC model, as discussed elsewhere [Park *et al.*, 1993].

The 1-decanol stationary phase was used to predict the multisolute adsorption data measured in this study. The results for BA in its mixtures with PE are shown in Figure 3.17. The model is able adequately to predict both single and multisolute adsorption data in the low concentration range, under approximately 10-15 g/l of total solute concentration in the mobile phase. However, it fails again at higher concentrations. It seems that a partition model could be a useful description of the experimental system at low solute concentrations. However, it fails adequately to represent multisolute distribution data at higher concentrations. On the other hand, the Langmuir model, the simplest possible nonlinear adsorption model readily captures the essential trend of the experimental data

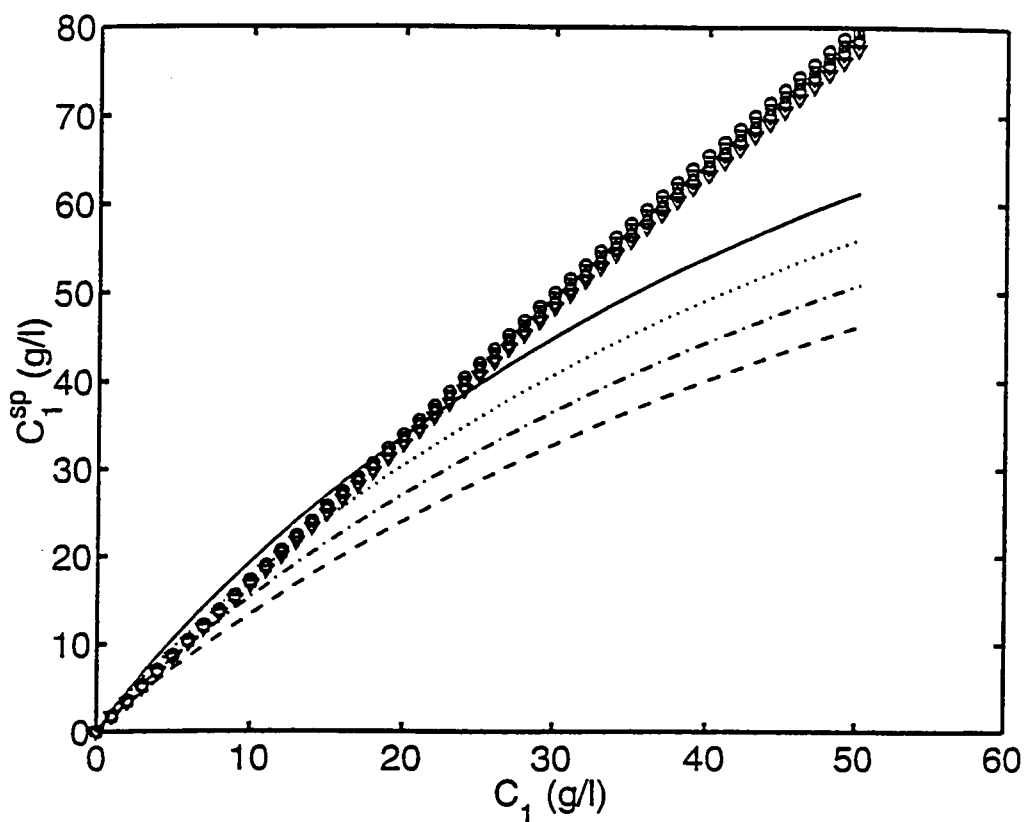


Figure 3.16. Single solute distribution data for BA at different temperatures calculated using 1-decanol as the model stationary phase. Experimental data provided as lines : 20 °C (solid), 30 °C (points), 40 °C (dashed-dotted) and 50 °C (dashed). Calculated data provided as points : 20 °C (circles), 30 °C (squares), 40 °C (diamonds) and 50 °C (triangles).

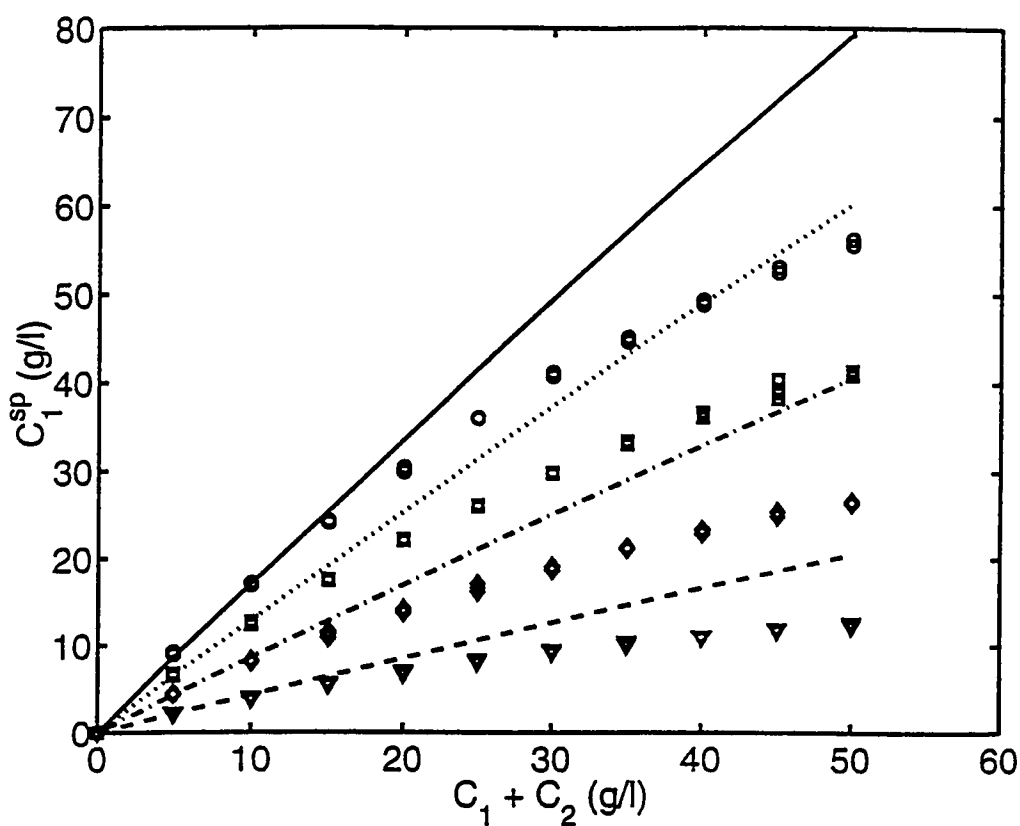


Figure 3.17. Same experimental data as in Figure 3.9a but calculations performed via the partition model which uses 1-decanol as the model stationary liquid. Calculations presented for the single solute data(solid line), 3:1 mixtures (dotted line), 1:1 mixture (dashed-dotted line) and 1:3 mixtures (dashed lines).

measured in this study.

3.3.5 Multisolute Band Profiles and System Peaks.

In addition to the knowledge of the multisolute adsorption equilibria, the calculation of nonlinear band profiles requires also the values of some of the characteristics of the separation at low concentrations, *i.e.*, under analytical conditions. The plate number for the three compounds, listed in Table 3.16, are nearly the same. They are used for the derivation of the apparent Peclet number, see equation (Eq. 2.42). At low concentrations, the distribution of the solute between the stationary phase and the mobile phase is characterized via the retention factor (Guiochon *et al.* 1994)

$$k'_i = \frac{t_{R,i} - t_o}{t_o} \quad (3.45)$$

where k'_i is the retention factor (equal to the product of the phase ratio and the initial slope of the isotherm). The values of k'_i are also presented in Table 3.16.

The boundary condition or injection profile of the feed at the column inlet is also needed to calculate band profiles and system peaks. It is customary to represent this boundary condition by a rectangular injection profile. However, experimental injection devices, like the one employed in this study to introduce the large amount of feed required, produce injection profiles that deviate significantly from the ideal, rectangular injection profile. The use of the correct

Table 3.16. Parameters of the separation under analytical conditions.

Parameters	BA	PE	MBA
k'	1.274	2.160	2.440
Flow rate = 0.8 ml/min			
N	8302	9019	9098
Flow rate = 1 ml/min			
N	7396	8048	8228

boundary condition is necessary to achieve an accurate calculation of the bands under overloaded, nonlinear conditions [Katti *et al.*, 1990].

Experimental injection profiles (*i.e.*, boundary conditions) corresponding to solutes not present initially in the column (*i.e.*, under the conventional conditions of elution chromatography) have been reported [Katti *et al.*, 1990]. However, the study of system peaks requires special attention. The relevant boundary condition corresponds to the simultaneous injection of a feed sample and a vacancy of the strong additive on a concentration plateau of the strong additive. This is important to remember because the composition of the injected sample is usually different from that of the mobile phase and, accordingly, the injection produces a complex perturbation of the equilibrium established in the column prior to the injection [Golshan-Shirazi and Guiochon, 1989a].

Injection profiles were recorded with the detector connected between the injection valve and the column, thus maintaining the same pressure drop (and presumably flow behavior) as in the actual chromatographic experiment but replacing the column by a zero-volume connector. Recorded profiles corresponding to the different experimental situations encountered in the present study are presented in Figure 3.18. Note that, under the same experimental conditions, the injection of a certain amount of solute and that of an equivalent vacancy produce profiles which are mirror images, as expected.

There is a time delay of ca 5 s from the time when the injection valve is

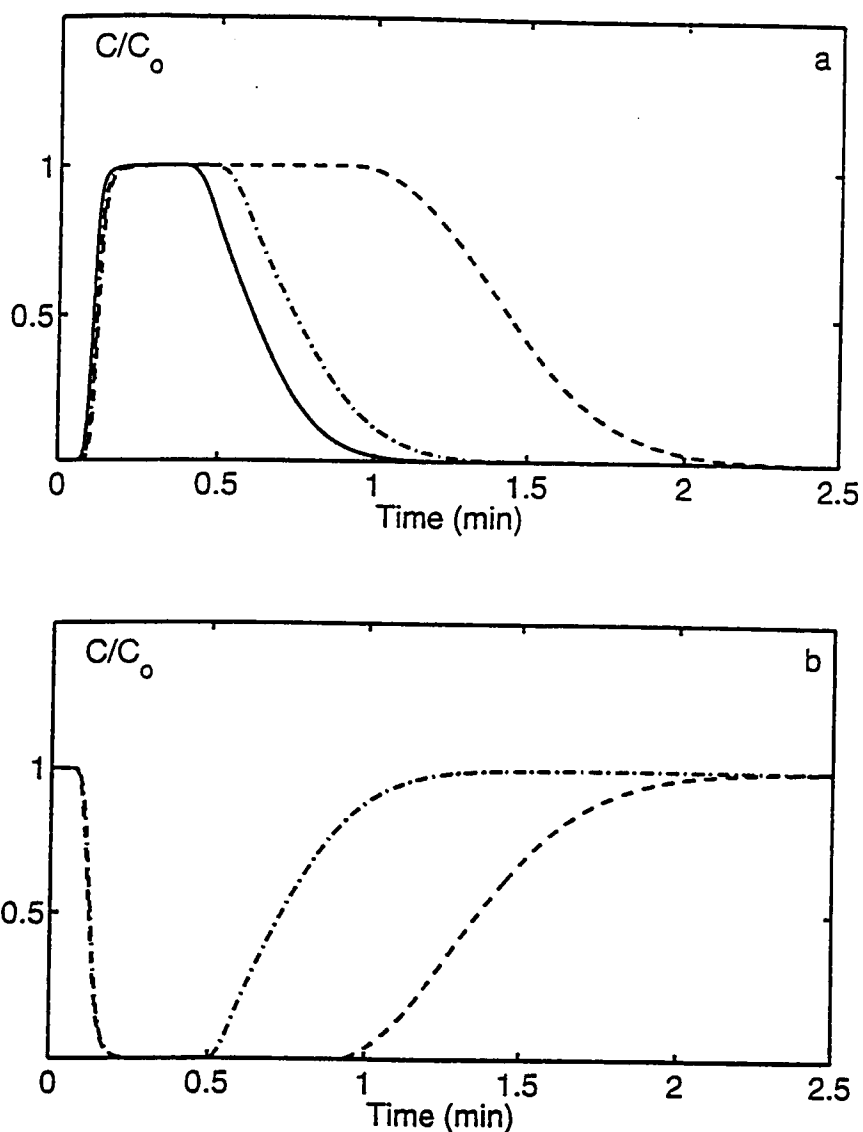


Figure 3.18. Experimental injection profiles of solutes (a) and vacancies (b). The profiles are normalized in terms of concentrations, where C_0 is the concentration of the solute present in the injected sample (a) or the concentration of additive initially present in the mobile phase (b). The solid line corresponds to a loop with a volume of 0.5 ml operated at 1 ml/min, the dashed-dotted line corresponds to a loop with a volume of 0.5 ml operated at 0.8 ml/min and the dashed line corresponds to a loop with a volume of 1.0 ml operated at 0.8 ml/min.

actuated to the time when the front of the injection profile actually reaches the column inlet. This delay is in part due to the time needed to operate the valve, in part to the transit time (estimated to be less than 1 s from the connecting tube volume and the flow rate) and, probably, in part to the pressure excursion in the loop (from atmospheric pressure during filling to about 200 bar at the end of the injection) and to mixing and possibly some back flow from the column into the loop. Note, however that the front of the injection profile is steep, without any significant dispersion.

On the other hand, the dispersion due to the Hagen-Poiseuille flow velocity distribution across the cross-section of the loop produces a significant dispersion of the rear part of the injection profiles. Unfortunately, it is this very part of the injection profile that has the major influence on the final shape of the calculated profiles (see below). The injection profiles presented in Figure 3.18 have been normalized with respect to either the total concentration of solutes in the injected sample or to the initial concentration of the additive in the mobile phase. Accordingly, they can be used for mixtures of any composition. These profiles constitute the actual boundary conditions in band profile calculations.

Single solute band profiles for BA and PE are presented in Figure 3.19. The calculated profile that assumes a rectangular injection (dashed line) produces a poor description of the rear, diffuse part of the experimental data. When the actual experimental injection profile is accounted for in the boundary condition

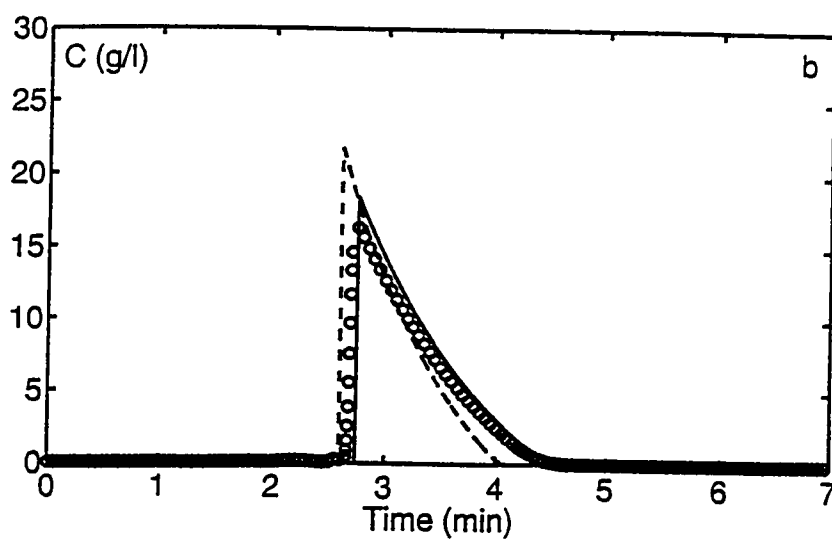
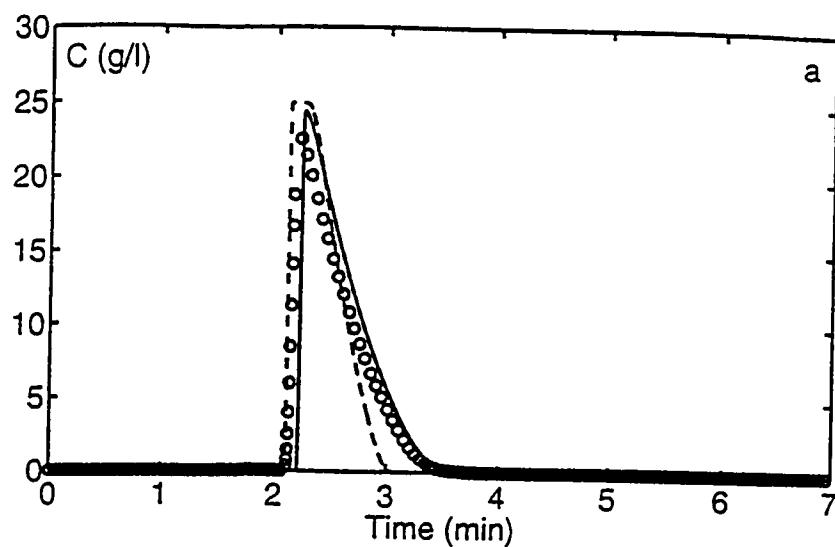


Figure 3.19. Single solute band profiles of BA (a) and PE (b). $C_0 = 25$ g/l for each phenyl alcohol in the sample. The mobile phase is a mixture of methanol and water (1:1, v/v). Flow rate is 1 ml/min. Volume injected is 0.5 ml. Presented the experimental points (circles), theoretical profile which uses a rectangular injection (dashed line) and theoretical profile which uses the experimental injection profiles (solid line).

(solid line), a better agreement between calculated and experimental (symbols) profiles is observed. The profiles of BA and PE presented here are typically langmuirian, with a shock in the front and a diffuse rear.

Analogous langmuirian profiles are observed for the multi-solute mixtures presented in Figure 3.20. For the binary mixture of BA and PE, two shocks are observed (Figure 3.20a). For the ternary mixture (Figure 3.20b), there are three shocks. There is a good agreement between the multisolute experimental (symbols) and calculated (lines) profiles. In all these cases, the mobile phase was a mixture of methanol and water (1:1, v/v). As reported previously, methanol is weakly adsorbed in this system (the retention factor of methanol in pure water is approximately 1). Accordingly, system peaks are not observed since the interactions of the solutes with the stationary phase are much stronger than those of methanol [Golshan-Shirazi and Guiochon, 1988].

When the mobile phase contains an additive which is retained, the injection of a feed sample causes a perturbation of the additive equilibrium between the two phases. Because of competition with the feed component, the amount of additive adsorbed decreases, to be restored later, when the feed components have moved on. This is the origin of additive peaks and system peaks [Guiochon *et al.*, 1994]. When the retention of the additive is higher but not much higher than that of the solutes, the profiles of system peaks become extremely unusual [Fornsted and Guiochon, 1994a].

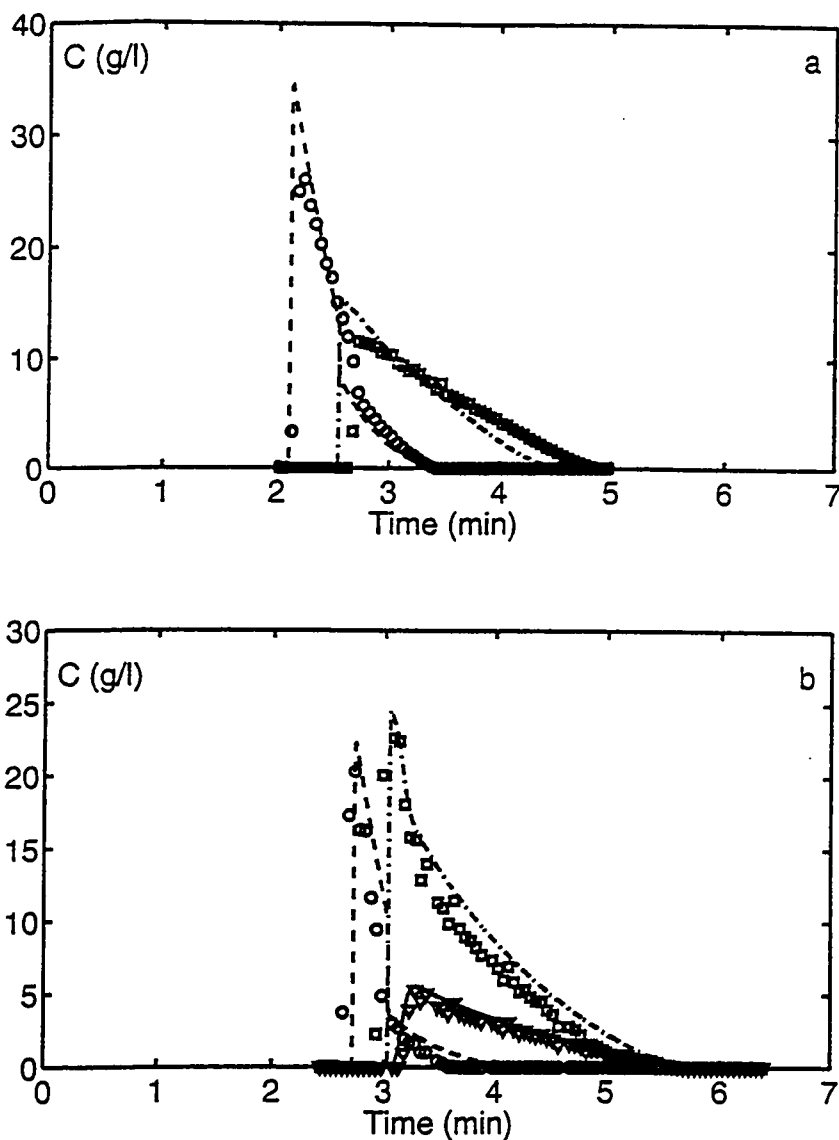


Figure 3.20. Band profiles of a binary solute mixture of BA and PE (1:1, w/w) with a total solute concentration of 50 g/l (a) and of a ternary solute mixture of BA, PE and MBA (1:3:1, w/w/w) with a total solute concentration of 50 g/l (b). The mobile phase is a mixture of methanol and water (1:1, v/v). Flow rate is 0.8 ml/min. Volume injected is 0.5 ml. Presented the experimental profiles for BA (circles), PE (squares) and MBA (triangles) along with the calculated profiles for BA (dashed line), PE (dashed-dotted line) and MBA (solid line).

Thus, we decided to use 2-methyl benzyl alcohol, the most retained of the three solutes (see Table 3.16), as the strong additive of the mobile phase and to determine the profiles of the three components upon injection of a mixture of the other two solutes. In Figure 3.21 we present the band profiles corresponding to the injection of 0.5 ml of a mixture of BA:PE=3:1 (w/w) at a total concentration of 40 g/l. Excellent agreement between the experimental results (symbols) and those of the calculations (lines) was observed for this and for subsequent experiments carried out under different experimental conditions (see Figures 3.22 to 3.25). The additive profile (Figure 3.21a) exhibits a typical shape [Guiochon *et al.*, 1994], with a positive primary system peak followed by the negative vacancy peak.

This pattern of the additive system peak roughly holds for all the chromatograms (see Figures 3.21a to 3.25). The band profile of BA, the lesser retained component, keeps a langmuirian shape, with a sharp front and a diffuse rear. It is quite similar to the one observed for the band of pure BA (cf Figures 3.19a and 3.21b), although it is wider and is eluted slightly later.

By contrast, the band profile of PE is quite different from those in Figures 3.19a and 3.20; it is diffuse at both ends but mostly so at the front, the opposite of what is expected in the case of a langmuirian behavior. The profile of PE could easily be ascribed to an anti-langmuirian isotherm since this association is well known in the case of single component bands [Guiochon *et al.*, 1994]. However,

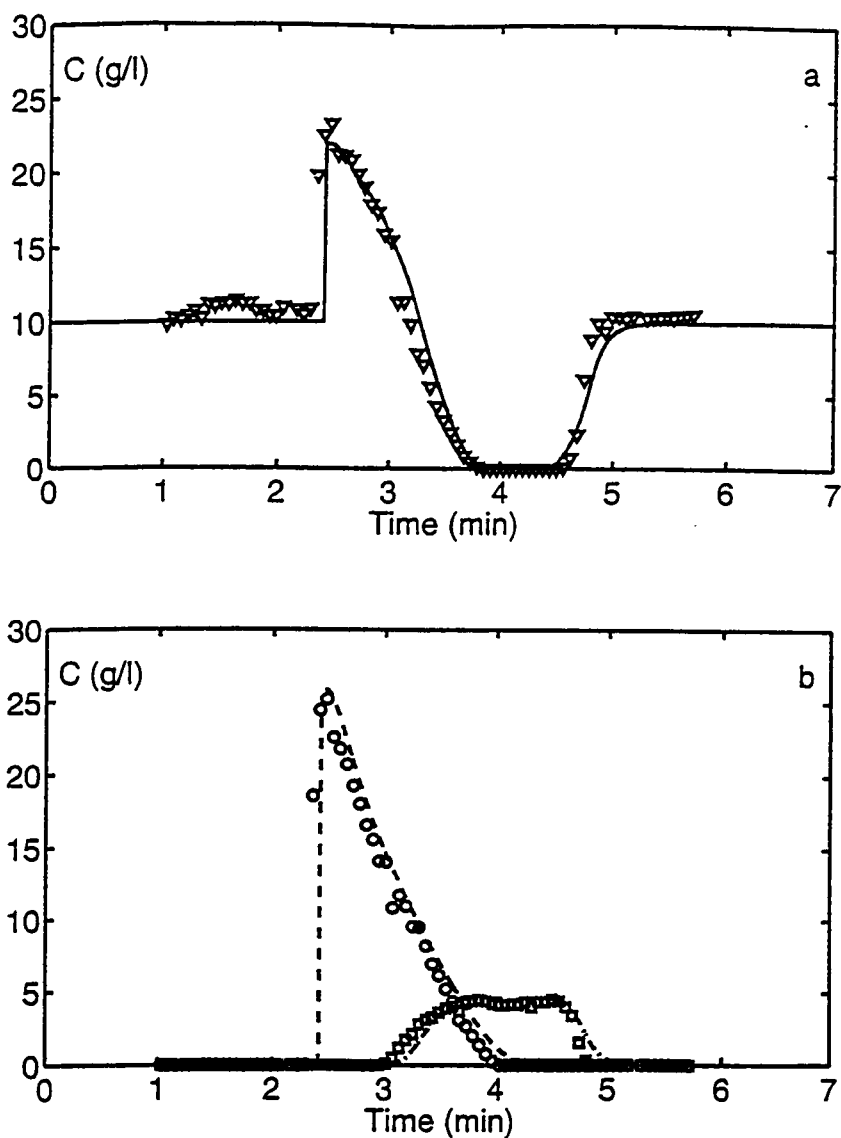


Figure 3.21. Band profiles corresponding to the additive system peaks (a) and solute peaks (b) corresponding to the separation of a binary solute mixture of BA and PE (3:1, w/w) with a total solute concentration of 40 g/l. The mobile phase contains 10 g/l of MBA in a mixture of methanol and water (1:1, v/v). Flow rate is 0.8 ml/min. Volume injected is 0.5 ml. Presented the experimental profiles for BA (circles), PE (squares) and MBA (triangles) along with the calculated profiles for BA (dashed line), PE (dashed-dotted line) and MBA (solid line).

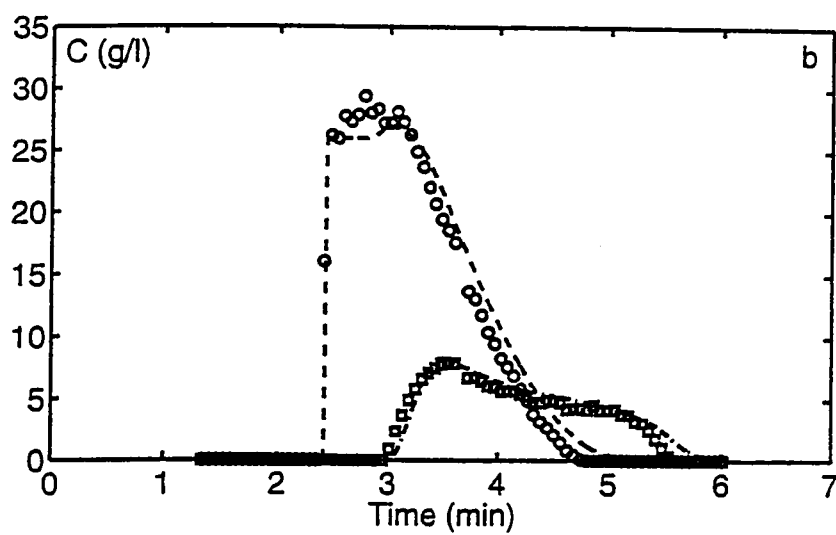
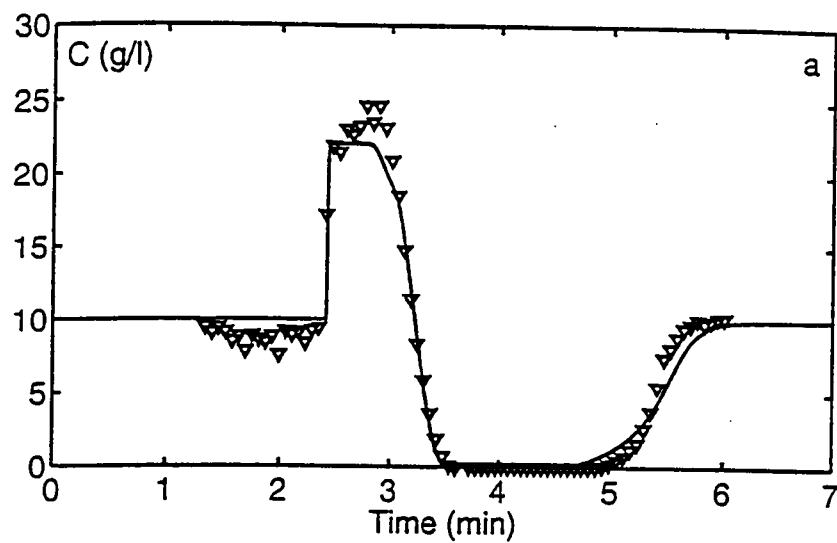


Figure 3.22. Same conditions as in Figure 3.21 but the volume injected was 1.0 ml.

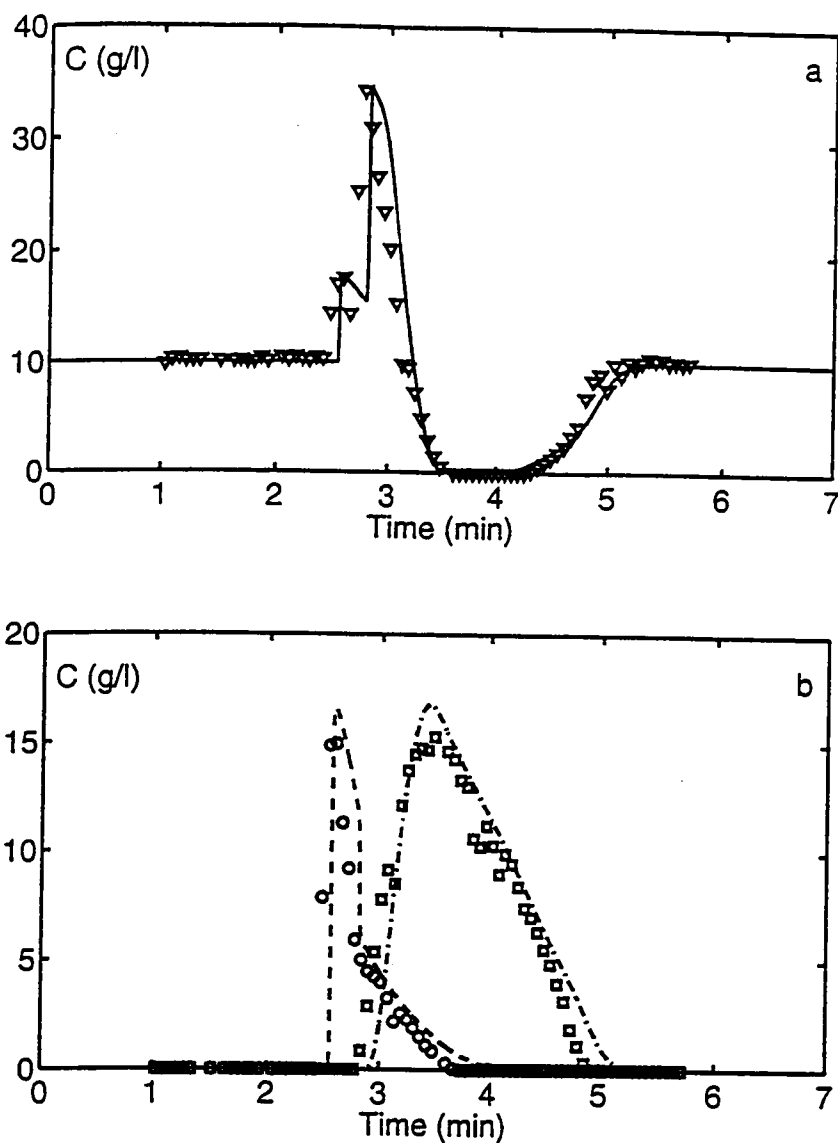


Figure 3.23. Band profiles corresponding to the additive system peaks (a) and solute peaks (b) corresponding to the separation of a binary solute mixture of BA and PE (1:3, w/w) with a total solute concentration of 40 g/l. The mobile phase contains 10 g/l of MBA in a mixture of methanol and water (1:1, v/v). Flow rate is 0.8 ml/min. Volume injected is 0.5 ml. Presented the experimental profiles for BA (circles), PE (squares) and MBA (triangles) along with the calculated profiles for BA (dashed line), PE (dashed-dotted line) and MBA (solid line).

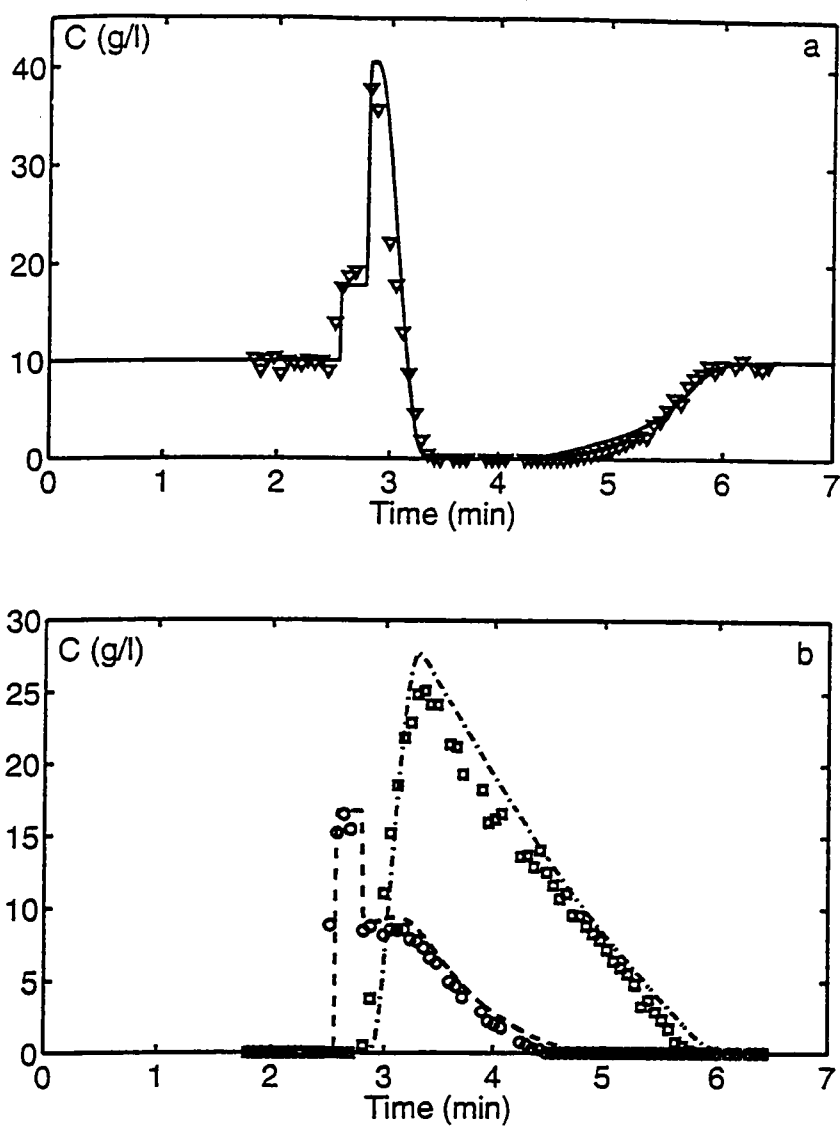


Figure 3.24. Same conditions as in Figure 3.23 but the volume injected was 1.0 ml.

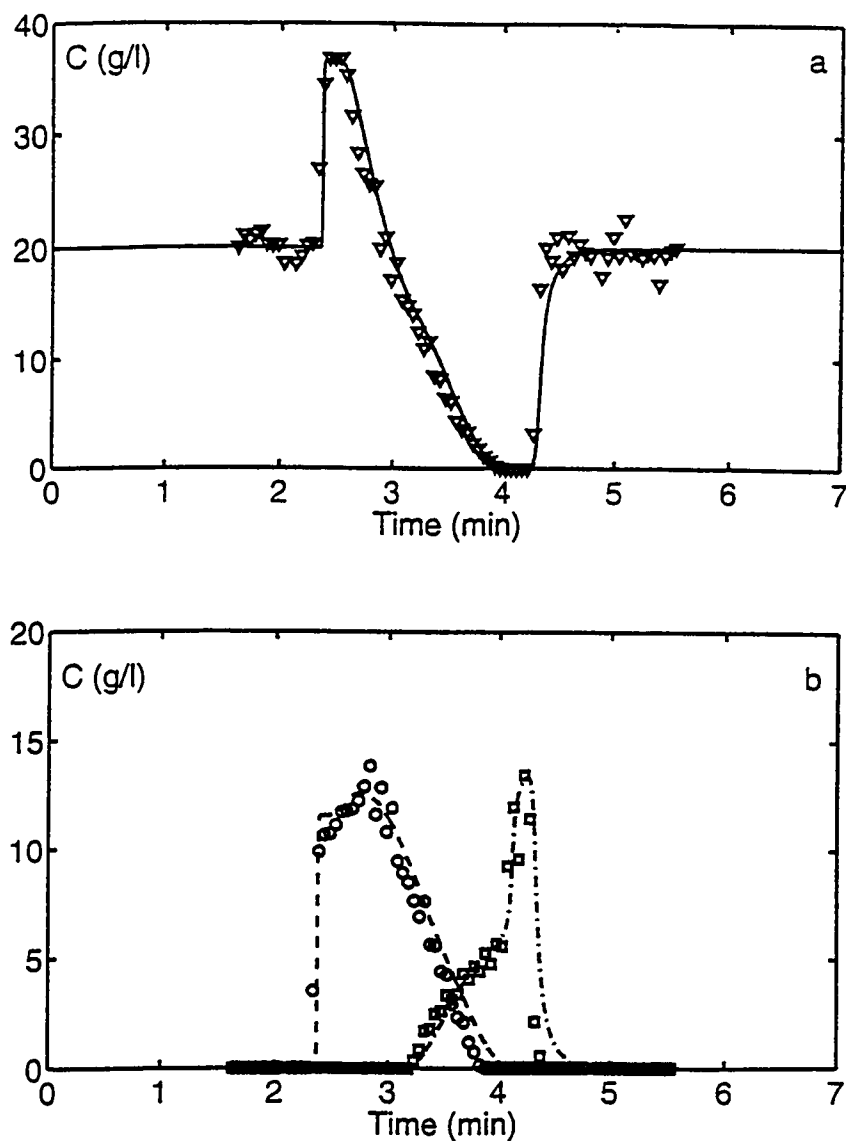


Figure 3.25. Band profiles corresponding to the additive system peaks (a) and solute peaks (b) corresponding to the separation of a binary solute mixture of BA and PE (2:1, w/w) with a total solute concentration of 30 g/l. The mobile phase contains 20 g/l of MBA in a mixture of methanol and water (1:1, v/v). Flow rate is 0.8 ml/min. Volume injected is 0.5 ml. Presented the experimental profiles for BA (circles), PE (squares) and MBA (triangles) along with the calculated profiles for BA (dashed line), PE (dashed-dotted line) and MBA (solid line).

we do know that, in this particular separation, the isotherm of PE is langmuirian. The band profile of PE is the sole result of the competitive interactions among the three solutes in the system under consideration. The band of PE also exhibits two small "hills "with a shallow valley in between. This profile shape was obtained before in theoretical calculations [Golshan-Shirazi and Guiochon, 1989c].

The results obtained with a twice larger injection (1 ml) of the same mixture are shown in Figure 3.22. Although the same features of Figure 3.21 are maintained, there are some striking changes which would not arise in the case of a binary feed sample analyzed with a pure mobile phase, with langmuirian isotherm behavior. The top of the BA band is flat and wide, in sharp contrast of what is observed in the absence of additive and the rear of the band is eluted later and is more diffuse. The small "hill" already observed at the front of the PE band in Figure 3.21 becomes more important and sticks out nearly as a well identified peak (Figure 9b).

The experiment, the results of which are illustrated in Figure 3.23, was carried out under the same experimental conditions as Figure 3.21, except that the mass ratio of BA and PE in the feed sample was reversed. The positive primary additive band became a doublet, in agreement with the experimental evidence. There is also a conspicuous, strong compression of the BA band due to the displacement effect caused by the additive band which intercalates between the bands of BA and PE. The unusual symmetry of the PE band is also noteworthy.

Again, this behavior is not typical of an overloaded langmuirian band.

Figure 3.24 illustrates the same separation as the one in Figure 3.23 but performed with a larger injection volume, 1.0 ml instead of 0.5 ml in Figures 3.21 and 3.23. Note that the doublet associated with the positive primary additive peak became a plateau. In the same time, two plateaus developed at the BA band and a significant tag-along effect, again in agreement with experimental results.

Finally, all the previous experiments were performed with an additive concentration in the mobile phase of 10 g/l. In Figure 3.25, we show the results of a similar separation carried out with a mobile phase concentration increased to 20 g/l. Compared to their profiles determined in the previous experiments, nothing unusual was observed regarding the band shape of BA and MBA. By contrast, the band of PE exhibited a typical anti-langmuirian shape with a diffuse front and a sharp rear. Note also that the band of PE is strongly compressed at the end of the chromatogram and that the mixed band containing both BA and PE is considerably reduced compared to what is seen in Figures 3.20 to 3.24. Similar shapes have been reported [Golshan-Shirazi and Guiochon, 1989d] but no quantitative comparisons with experimental data were carried out.

If properly exploited, the band compression effects underlined above and especially in Figure 3.25 could be very useful when performing preparative separations. Note that a minor component of a binary mixture, *i.e.*, an impurity, can

be compressed, eluted as a narrow band, and recovered at a high purity (and possibly concentrated to a degree, certainly less diluted than under conventional conditions), either in the front or in the rear of the main component, provided that the proper additive be used. Similar manipulations were made under other chromatographic conditions [Katti *et al.*, 1989; Frenz *et al.*, 1990].

Proper manipulations of the mobile phase composition allow the selective concentration of minor components of a binary mixture (and probably of more complex mixtures) into a specific region of the chromatogram. This procedure could facilitate greatly the recovery and purification of important impurities for further analysis. This problem often arises as part of stability studies of pharmaceutical candidates.

3.4 Conclusions on the Separation of Phenylalcohols.

For the first time, experimental adsorption data were measured for a ternary-solute feed mixture in a typical HPLC system. Excellent agreement was found between the single solute adsorption data obtained via FA and FACP. A novel test was developed to check binary solute adsorption data for thermodynamic consistency. According to this test, the data measured in the present study exhibit excellent thermodynamic consistency. Relevant thermodynamic functions derived from these adsorption data at different temperatures indicate that the surface of the octadecylsilica material tested is fairly homogeneous with respect

to the studied solutes.

A nonideal adsorbed solution theory model was developed and applied to the measured multisolute experimental data. The model accounts for the effect of molecular interactions in both phases and provides an excellent prediction of the multisolute adsorption equilibria based on the parameters derived from the single solute adsorption data. The stationary phase exhibits negative deviations from ideality while the mobile phase shows positive deviations, thus both phases actively contribute to the transfer of solutes from the liquid phase to the stationary phase.

Under certain circumstances, the model reduces to a Langmuir type expression. This situation is more likely to be a result of fairly constant values of the activity coefficients in both phases over the studied composition range. Thus, it explains why the Langmuir model has been so successful when fitting single solute data measured in reversed-phase systems, especially for low molecular weight solutes. This fact could explain why the IAS model also produces a correct prediction of the competitive data based on the single solute adsorption data.

Liquid-liquid equilibrium models were also used to describe the experimental data. Although these models provide a good representation of the multisolute equilibria at low concentrations, they fail to represent the curvature of the equilibrium data at higher concentrations and to describe their temperature dependence. These results suggest that liquid chromatography on octadecyl bonded porous

silica more likely belongs to adsorption rather than to partition chromatography.

The excellent agreement between the experimental and the calculated band profiles of sample components and system peaks obtained at high concentrations confirms once more the validity of the theory of nonlinear chromatography and the practical value of the equilibrium-dispersive model. Of particular interest is the demonstration that the simplest adsorption behavior, one following the competitive Langmuir model, may lead to unusual band profiles. Such results are often observed, to be discarded as anomalous and suspect of being irreproducible. The demonstration of their consistency with the fundamentals of adsorption and chromatography should lend them credence and legitimize their systematic investigation.

System peaks are considered as unimportant in conventional reversed phase liquid chromatography (RPLC), which is the most popular preparative process because of the relatively low cost of the mobile phase components. This is because the strong solvents in RPLC, methanol or acetonitrile, act by increasing the mobile phase solubility of the feed components, not by competing with them for access to the stationary phase. Indeed, the retention times observed for BA and PE in the experiments reported in Figures 3.21 to 3.25 exhibit little changes, certainly small ones compared to the changes of the band profiles. Solubility issues often force the chromatographer to consider either nonaqueous reversed-phase or normal-phase chromatography and to use solvent systems in which the

strong solvent acts as a competitor of the feed components. In such a case, the strong solvent and its concentration are selected essentially on the basis of considerations limited to the need to achieve the proper retention and separation under linear conditions, *i.e.*, at low concentrations.

More attention should be paid to nonlinear system peaks and their potential usefulness to design separation methods in which larger throughputs are achieved by concentrating the impurities into certain zones of the chromatograms. Thus, the possibility of adjusting system peaks provides the knowledgeable separation scientist with another degree of flexibility in the development of new methods to enhance production rate, recovery yield, and/or product purity.

Chapter 4

The Separation of Basic Drugs

In this chapter we present the results of the experimental determination of the single solute adsorption equilibria for three basic drugs : buspirone (N - [4 - (4 - [2 - Pyrimidinyl] - 1 - piperazinyl)butyl] - 8 - azaspiro[4,5] - decane - 7,9 - dione), doxepin (11[16H] - [3 - (Dimethylamino) - propylidene]dibenz[b,e]oxepine) and diltiazem (*cis* - (+) -3 - (Acetyloxy) - 5 - [2 - (dimethylamino)ethyl] - 2,3 - dihydro - 2 - (4-methoxyphenyl) - 1,5 - benzothiazepin - 4(5H) - one). The adsorption equilibria was determined in a reversed phase system composed of an octadecylsilica column as the stationary phase and a buffered mixture of water and acetonitrile as the mobile phase. The adsorption data were fitted to the bi-Langmuir model. Within the framework of this model, the adsorption of basic drugs on the octadecylsilica surface is assumed to occur on two different kinds of sites. One low energy site which accounts for the hydrophobic interactions between the solutes and the grafted chains and one high energy site which accounts for the ion exchange interactions between active silanols and the protonated bases.

Multisolute, overloaded band profiles were also measured for the three binaries and for the mixture of the three drugs. Theoretical band profiles were calculated

using the equilibrium dispersive model and the competitive bi-Langmuir model which uses the parameters determined from single solute adsorption isotherm data. Good agreement was found between the experimental and calculated non-linear band profiles.

There are many controversial opinions in the literature regarding the chromatographic behavior of basic solutes. The chromatography of amine bases is extremely important since the overwhelming majority of the known drugs are basic compounds. The chromatography of these solutes is however complex because of the different retention mechanisms which are believed to contribute to the overall outcome of the separations. Among these mechanisms the most important are: (i) hydrophobic interactions; (ii) ion-exchange; (iii) salting-out effects and (iv) hydrogen-bond interactions. As a result, several phenomena are commonly observed when performing separations of basic compounds: (i) severe peak tailing; (ii) irreversible adsorption and (iii) low efficiency [Nawrocki, 1997].

4.1 Experimental.

4.1.1 Equipment.

The adsorption isotherm data and the overloaded band profiles were acquired using the same experimental setup as described in section 3.1.1.

4.1.2 Materials.

A 150 mm $\times$ 3.9 mm i.d. YMC-Basic C₁₈ column (YMC Inc., Wilmington, NC) was used to measure the adsorption data. The particle size was 5 μ m, the average pore size was 120 Å and the void fraction of the column was 0.76. Using a mixture of the three solutes, this column was characterized periodically by elution chromatography. The efficiency and retention data were found essentially unchanged. This column belongs to the so called 'base-deactivated' columns, usually employed in the separation of basic compounds.

In all the experiments the mobile phase was acetonitrile-buffer (35:65, v/v). The buffer was prepared by mixing 0.1 M solutions of H₃PO₄ (Analytical reagent, Mallinckrodt, Paris, KY) and KH₂PO₄ (99.5+ %, Fluka, Ronkonkoma, NY) until pH=3.0 was reached. Acetonitrile and H₂O were HPLC grade, purchased from Fisher Scientific (Pittsburgh, PA, USA).

The solutes employed were three drugs: the anxiolytic buspirone hydrochloride (N - [4 - (4 - [2 - Pyrimidinyl] - 1 - piperazinyl)butyl] - 8 - azaspiro[4,5] - decane - 7,9 - dione), C₂₁H₃₁N₅O₂ $\times$ HCl (99 % by TLC, Sigma, St. Louis, MO); the antidepressant doxepin hydrochloride (11[16H] - [3 - (Dimethylamino) - propylidene]dibenz[b,e]oxepine), C₁₉H₂₁NO $\times$ HCl (98 % by TLC, Sigma, St. Louis, MO) and the Ca²⁺ blocker diltiazem hydrochloride (*cis* - (+) - 3 - (Acetyloxy) - 5 - [2 - (dimethylamino)ethyl] - 2,3 - dihydro - 2 - (4 - methoxyphenyl)

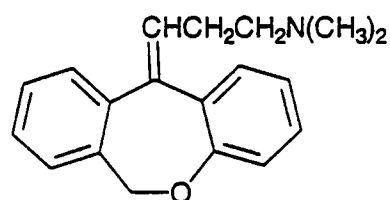
- 1,5 - benzothiazepin - 4(5H) - one), $C_{22}H_{26}N_2O_4S \times HCl$ (99 % by HPLC, Sigma, St. Louis, MO). These are basic drugs whose structures are depicted in figure 4.1.

A similar column was used to analyze the collected fractions. The buffer employed for quantitation was also 0.1 M phosphate but adjusted to pH=6.0 by mixing solutions of KH_2PO_4 (99.5+ %, Fluka, Ronkonkoma, NY) and K_2HPO_4 (99.0+ %, Fluka, Ronkonkoma, NY). In this chapter we will use the indices 4, 5 and 6 when referring to buspirone (BU), doxepin (DO) and diltiazem (DI), respectively.

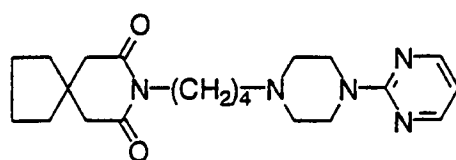
4.1.3 Procedures.

The separation of the three drugs under analytical i.e. linear conditions at pH=3.0 and pH=6.0 is presented in figures 4.2 and 4.3, respectively. The parameters of these separations can be found in Table 4.1.

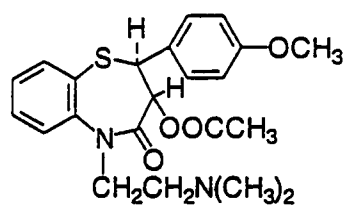
Single-solute adsorption data measured by FA at 25°C as described in section 3.1.3.1 are presented in Table 4.2. The UV signal was recorded at 345 nm, 325 nm and 300 nm for BU, DO and DI respectively. The adsorption data are also represented in figure 4.4 (symbols). Ninety minutes of reequilibration time was needed between injections in order to get reproducible results. Accordingly, only one adsorption data point per composition was measured for this system. No multisolute adsorption data are reported. The adsorption experiments were



a



b



c

Figure 4.1 Structure of doxepin (a), buspirone (b) and diltiazem (c)

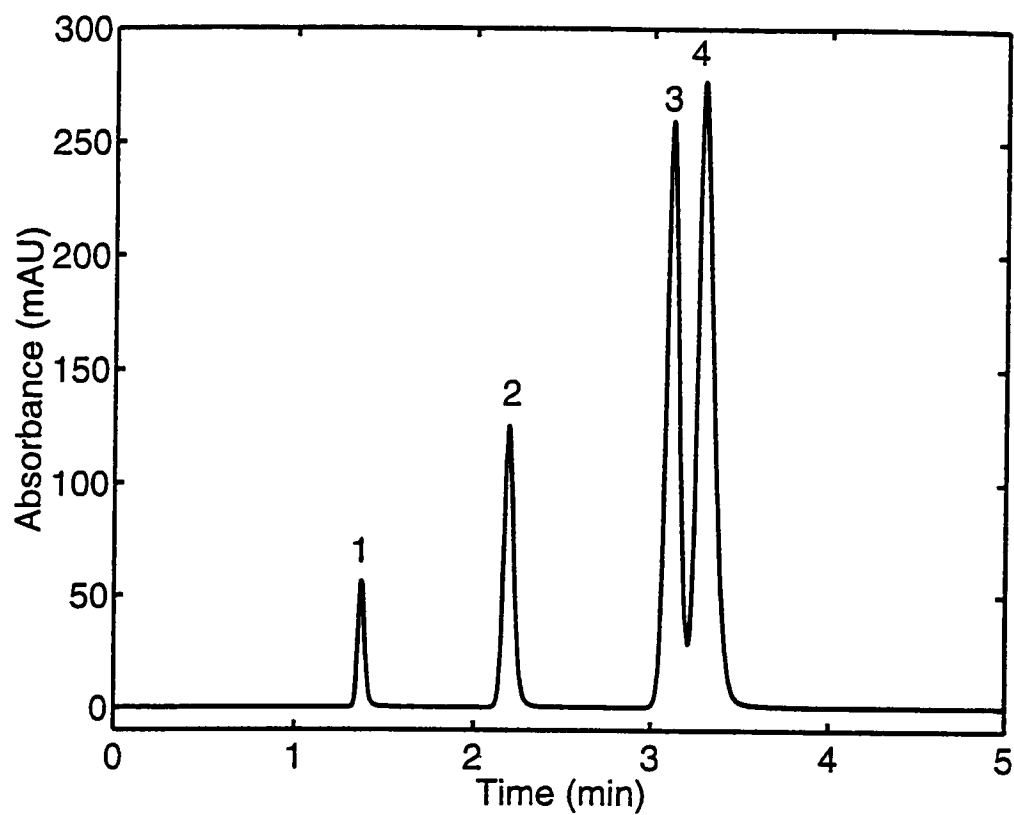


Figure 4.2 Analytical separation of thiourea (1), buspirone (2), diltiazem (3) and doxepin (4). Mobile phase is ACN:Buffer=35:65; Buffer is 0.1 M phosphate, pH = 3.0, T = 25 °C, flow rate is 1 ml/min, injected volume is 20 μ l with a concentration of 0.1 g/l, UV detection at 254 nm.

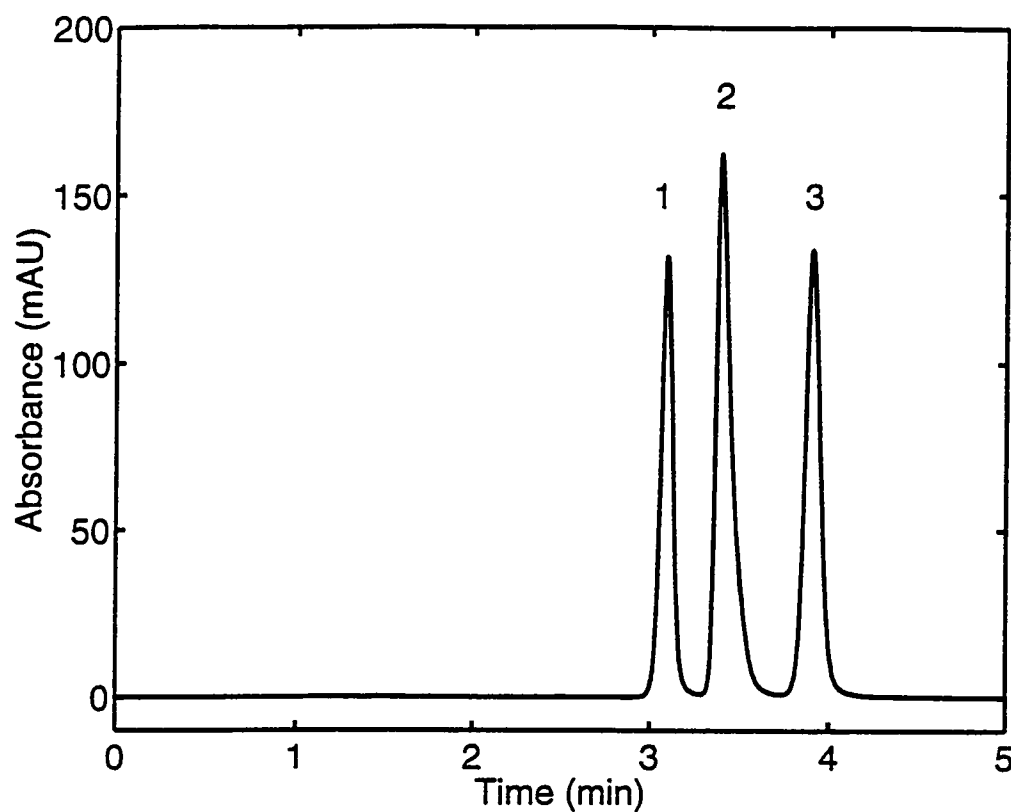


Figure 4.3 Analytical separation of buspirone (1), doxepin (2) and diltiazem (3). Mobile phase is ACN:Buffer=35:65; Buffer is 0.1 M phosphate, pH = 6.0, T = 25 °C, flow rate is 1 ml/min, injected volume is 20 μ l with a concentration of 0.1 g/l, UV detection at 254 nm.

Table 4.1. Parameters of the separation under linear conditions

Parameter	Buspirone	Diltiazem	Doxepin
pH = 3.0			
k'	0.606	1.281	1.411
N	7100	8500	6500
pH = 6.0			
k'	1.256	1.846	1.522
N	8800	9100	7700

Table 4.2. Single-solute equilibrium data measured by FA at 25 °C

C_4	Γ_4	C_5	Γ_5	C_6	Γ_6
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
0.50	0.97	0.50	1.78	0.50	1.76
1.00	1.67	1.00	3.05	1.00	2.98
1.50	2.54	1.50	4.02	1.50	4.22
2.00	2.88	2.00	4.89	2.00	5.15
2.50	3.27	2.50	5.53	2.50	6.17
3.00	3.93	3.00	6.37	3.00	6.82
3.50	4.43	3.50	6.91	3.50	7.59
4.00	4.64	4.00	7.64	4.00	8.24
4.50	5.12	4.50	8.30	4.50	9.27
5.00	5.58	5.00	9.01	5.00	9.44
5.50	5.78	5.50	9.21	5.50	10.15

Table 4.2. (continued)

C_4	Γ_4	C_5	Γ_5	C_6	Γ_6
(g/l)	(g/l)	(g/l)	(g/l)	(g/l)	(g/l)
6.00	6.18	6.00	9.91	6.00	10.69
6.50	6.56	6.50	10.32	6.50	11.30
7.00	7.06	7.00	11.27	7.00	12.02
7.50	7.24	7.50	11.43	7.50	12.39
8.00	7.73	8.00	12.02	8.00	13.05
8.50	7.84	8.50	12.59	8.50	13.50
9.00	7.92	9.00	12.94	9.00	13.91
9.50	8.36	9.50	13.45	9.50	14.47
10.00	8.58	10.00	14.16	10.00	14.38

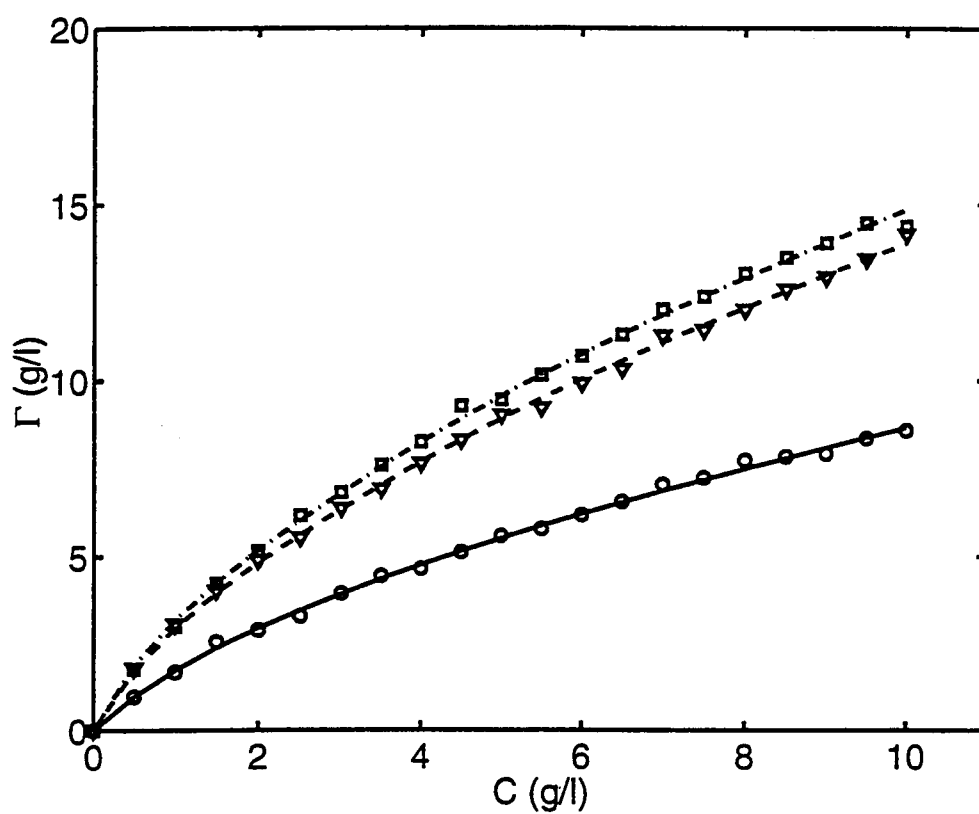


Figure 4.4 Adsorption data of buspirone (circles), doxepin (triangles) and diltiazem (squares). Mobile phase is ACN:Buffer=35:65; Buffer is 0.1 M phosphate, pH = 3.0, $T = 25^\circ \text{C}$.

carried out at low pH with rather concentrated solutions of phosphate buffers. Under these conditions, the stability of the C₁₈ columns is limited since the buffers dissolve the silica [Nawrocki, 1997]. After each experimental session, the columns were flushed initially with a mixture of acetonitrile and water (1:1, v/v). Afterwards, the columns were flushed with acetonitrile.

4.2 Model.

Adsorption data were initially plotted in the form of a Scatchard plot, figure 4.5. Since the experimental data are not linear, the Langmuir model is not likely to provide an adequate fit of the experimental results. Accordingly, we decided to use the bi-Langmuir model to correlate the data under consideration. In this particular case, the model is defined as

$$q_4 = \frac{\Phi \kappa_4 C_4}{1 + \kappa_4 C_4 + \kappa_5 C_5 + \kappa_6 C_6} + \frac{\Psi \lambda_4 C_4}{1 + \lambda_4 C_4 + \lambda_5 C_5 + \lambda_6 C_6} \quad (4.1a)$$

$$q_5 = \frac{\Phi \kappa_5 C_5}{1 + \kappa_4 C_4 + \kappa_5 C_5 + \kappa_6 C_6} + \frac{\Psi \lambda_5 C_5}{1 + \lambda_4 C_4 + \lambda_5 C_5 + \lambda_6 C_6} \quad (4.1b)$$

$$q_6 = \frac{\Phi \kappa_6 C_6}{1 + \kappa_4 C_4 + \kappa_5 C_5 + \kappa_6 C_6} + \frac{\Psi \lambda_6 C_6}{1 + \lambda_4 C_4 + \lambda_5 C_5 + \lambda_6 C_6} \quad (4.1c)$$

The parameters of the model, identified by regression of the joint set of single solute adsorption data are presented in Table 4.3. As shown in figure 4.4 (lines), the model provides an excellent correlation of the experimental adsorption data.

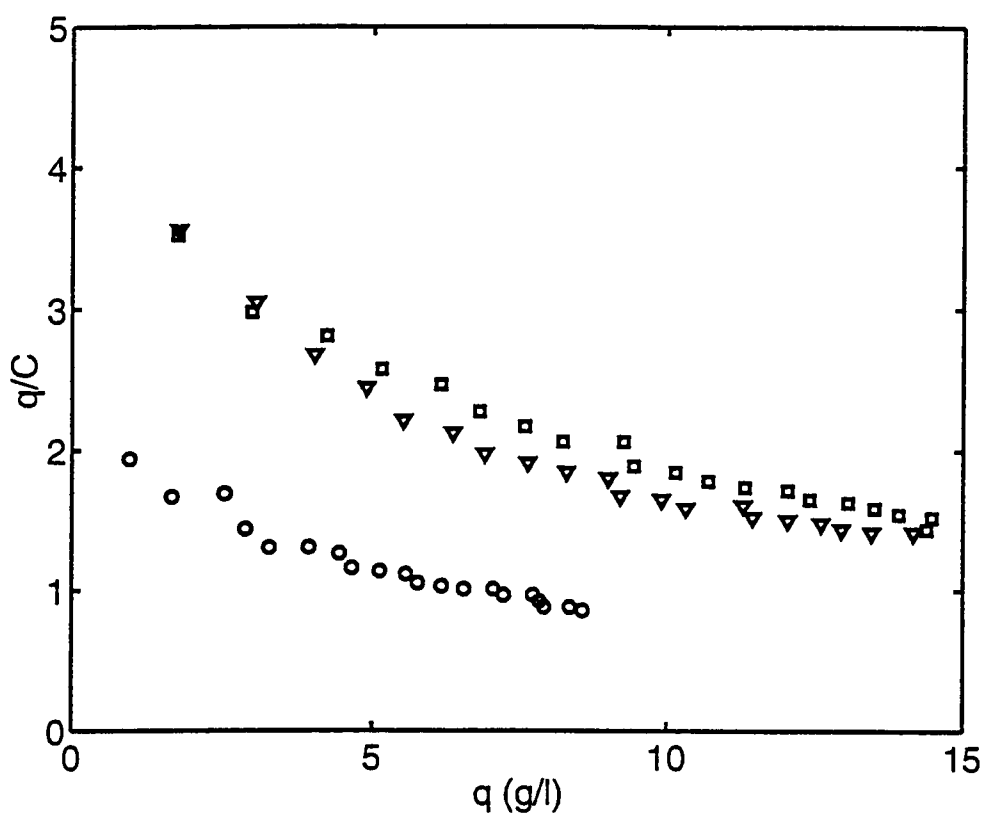


Figure 4.5 Scatchard plot of the adsorption data of buspirone (circles), doxepin (triangles) and diltiazem (squares). Mobile phase is ACN : Buffer = 35 : 65; Buffer is 0.1 M phosphate, pH = 3.0, T = 25 °C.

Table 4.3. Parameters of the bi-Langmuir model

Parameter	Buspirone	Doxepin	Diltiazem
Φ (g/l)		3.6	
κ (l/g)	0.42	0.78	0.86
Ψ (g/l)		47.6	
$\lambda \times 10^2$ (l/g)	1.36	2.89	3.22

Overloaded band profiles were calculated using the equilibrium-dispersive model represented by equation (2.42). The parameters reported in Table 4.1 were used in the calculations.

4.3 Discussion.

The nature of the experimental system studied in this chapter is more complex than the one analyzed in Chapter 3. As shown in figure 4.1 the structures of the drugs are more complicated than the rather simple structures of the light aromatic alcohols treated before. At pH=3.0 these drugs are protonated, thus they exist in solution as cations. The nature of the mobile phase is also more complex since it contains significant amounts of several inorganic ions (H^+ , K^+ , Cl^- and PO_4^{3-}).

It is striking the similarity between the adsorption isotherms of DO and DI, considering the marked differences between the two structures. However, both structures possess a similar aminoalkyl chain which could be responsible for the adsorbate-adsorbent interactions.

In addition, note that the adsorption isotherm data of DO and DI cross at low concentrations. As shown in Table 4.1 and in figure 4.2, doxepin is more retained than diltiazem. On the other hand, in figure 4.4 it is clear that the isotherm of diltiazem is placed over the one for doxepin. The bi-Langmuir model is unable to predict the selectivity reversal at low concentrations. Note in Table 4.3 that

$\kappa_6 > \kappa_5$ and $\lambda_6 > \lambda_5$. Since the saturation capacities on each site are the same for all the solutes, it follows that the model produces a Henry constant for diltiazem which is bigger than the one for doxepin. In practice, the Henry constant for doxepin is higher (see Table 4.1 and figure 4.2). The problem is not critical, however, since (i) the retention factors of DO and DI are very close, equal to 1.4 and 1.3, respectively and (ii) the bi-Langmuir model properly correlates the measured adsorption data at concentrations higher than 0.5 g/l. As a result, the applied isotherm model properly predicts the overloaded single and multisolute band profiles (see below).

A switch in retention order also occurs for these two compounds with changes in the pH of the mobile phase. Note in figure 4.3 that diltiazem elutes the last at pH = 6.0 while doxepin is the most retained at pH = 3.0 (see figure 4.2). These changes in retention as a result of changes in the pH of the mobile phase is one of the key factors commonly employed for the optimization of analytical separations of organic cations [Snyder, 1997].

Note in figure 4.4 that the dual site Langmuir model provides an excellent correlation of the single solute adsorption data. As shown in Table 4.3 the site with the lower value of the saturation capacity has the bigger value of the equilibrium constant. Thus, stronger adsorbate-adsorbent interactions occur in this site. The ratio between the saturation capacities of the two sites is roughly 13. In previous studies, this ratio has been found as large as 60 [Eble et al., 1987].

It is believed [Nawrocki, 1997] that two main mechanisms govern the adsorption behavior of basic compounds on C_{18} phases: hydrophobic interactions (with both hydrocarbon and siloxane moieties) and ion-exchange with a subfraction of extremely acidic silanols.

As stated before, several types of silanol exist. They could exist as isolated, geminal or bonded vicinal species. It is estimated that only 1-6 % of the silanols are isolated, free silanols. These silanols are the ones responsible for the strong interactions. Bonded silanols have a lower adsorption energy (50-65 kcal/mol) while isolated silanols are much stronger sites (ca 90 kcal/mol) [Nawrocki, 1997]. Recall that the isosteric heats determined for the phenylalcohols studied in chapter 3 (see Table 3.10) were only about 2.4 kcal/mol. Of course, the phenylalcohols are just neutral species without the ability "to sample" the high energy sites present on the silica surface. Note that the ratio of unreacted silanols to grafted chains in a typical octadecylsilica surface is roughly equal to 1. Accordingly, only a limited fraction of the unreacted silanols can be considered as the strongly interacting sites. It is believed that these strongly acidic silanol sites are generated by metal traces buried in the silica matrix [Nawrocki, 1997].

At pH=3.0 the ionization of the majority of the silanols is suppressed (pK_a of silanols is about 7.1-7.2) and only the most acidic sites remain dissociated, thus retaining the ability for cation exchange. Moreover, in this study we have used a rather concentrated buffer (0.1 M) and a more retained buffer cation (K^+). These

two factors should suppress further silanol ionization. Another important fact is that we employed acetonitrile as the organic modifier in the mobile phase. The peaks of basic compounds are usually more asymmetrical when using acetonitrile-based mobile phases. Acetonitrile is unable to form hydrogen bonds with residual silanols, in contrast to methanol and tetrahydrofuran. Thus, acetonitrile cannot mask the silanols. It interacts mainly with the alkyl chains. It is worth noting that at pH=3.0 the drugs should be protonated, so they will be able to interact with the acidic silanols via the cation exchange mechanism.

Another factor affecting the process is the degree of protonation of the solutes. The pH of organic solvent/buffer solutions is usually higher than the measured pH of the buffer alone. On the other hand, the pK_a of the solutes is usually lower than those determined in aqueous solutions. Several published data summarize a consistent pattern of about -0.3 pK_a units per 10 % addition of organic [Nawrocki, 1997]. The higher the pK_a , the stronger will be the interactions of the solute with the highly acidic silanols and the greater will be the degree of asymmetry of the bands. The pK_a of buspirone, doxepin and diltiazem in aqueous, dilute solutions are about 8.0-9.0 [CompuDrug Chemistry; 1992], respectively. Accordingly, they will interact strongly with the silanols.

Note that the tailing of the BU band presented in figure 4.6 is less pronounced than the tailing of the DO and DI bands presented in figures 4.7 and 4.8, respectively. It is possible that the steric hindrance around the nitrogen atoms in BU

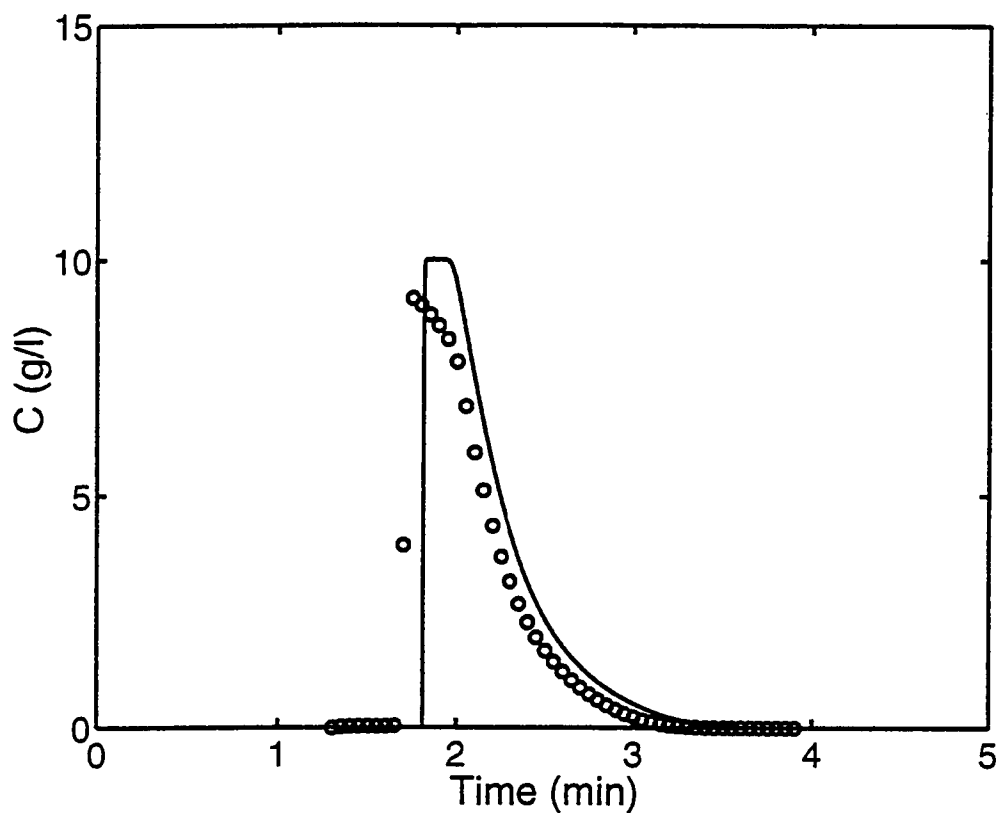


Figure 4.6 Experimental (circles) and calculated (line) band profile of buspirone. Mobile phase is ACN : Buffer = 35 : 65; Buffer is 0.1 M phosphate, pH = 3.0, T = 25 °C, flow rate is 1 ml/min, injected volume is 500 μ l with a concentration of 10 g/l, UV detection at 345 nm.

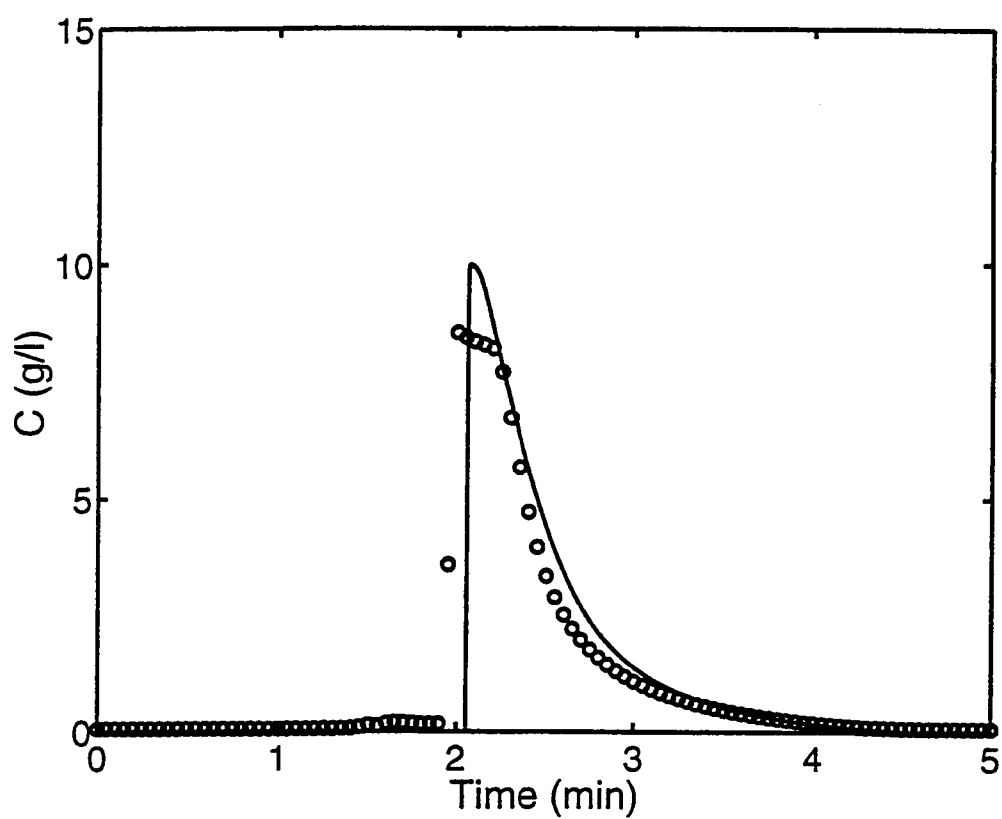


Figure 4.7 Experimental (circles) and calculated (line) band profile of doxepin. Mobile phase is ACN : Buffer = 35 : 65; Buffer is 0.1 M phosphate, pH = 3.0, T = 25 °C, flow rate is 1 ml/min, injected volume is 500 μ l with a concentration of 10 g/l, UV detection at 325 nm.

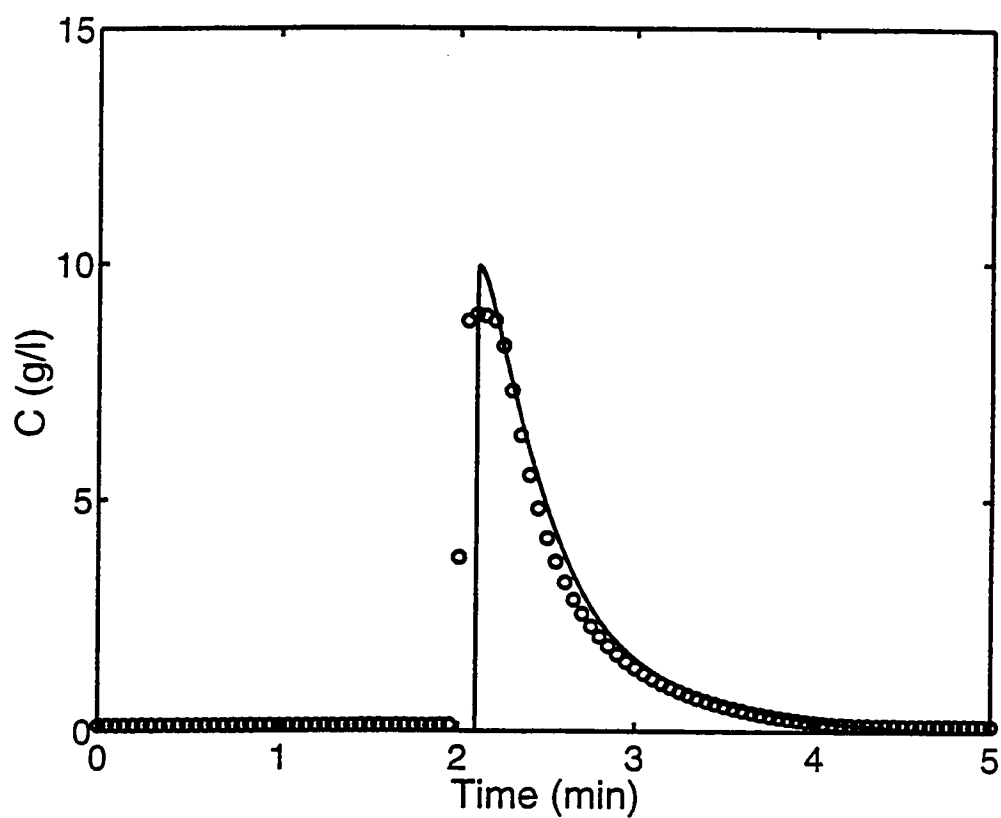


Figure 4.8 Experimental (circles) and calculated (line) band profile of diltiazem. Mobile phase is ACN : Buffer = 35 : 65; Buffer is 0.1 M phosphate, pH = 3.0, T = 25 °C, flow rate is 1 ml/min, injected volume is 500 μ l with a concentration of 10 g/l, UV detection at 300 nm.

(located in the rings) is greater than in the other two cases, where a nitrogen atom is located at the end of a lateral chain.

The long peak tailing observed in figures 4.7 and 4.8 has been observed quite often in the chromatography of basic compounds [Nawrocki, 1997]. It is considered to be a result of the presence of a subfraction of the surface silanols with enhanced acidity which interact strongly with the protonated organic bases.

The prediction of the single component profiles based on the equilibrium-dispersive model is quite good. The situation is a logical outcome of the fact the column is quite efficient for the studied solutes (see Table 4.1). There are still some deviations at the top of the peaks. The calculated profiles are somewhat taller.

Multisolute profiles corresponding to the three possible binaries and the ternary mixture of the drugs are also well predicted, as shown in figures 4.9 to 4.12. The good agreement between calculated and experimental profiles constitutes an indirect confirmation that the competitive equilibria should follow the bi-Langmuir model. Note in figure 4.11 that the shocks of DO and DI coincide, which is a result of the fact that the isotherms of these two species are very close (see figure 4.4). The spike of DI seen in this figure and also in figure 4.12 for the ternary mixture is a displacement effect produced by DO. In figure 4.13, a single solute system peak is presented for the injection of BU in a stream of DI. Note that also in this case the model is able to provide a good approximation of the

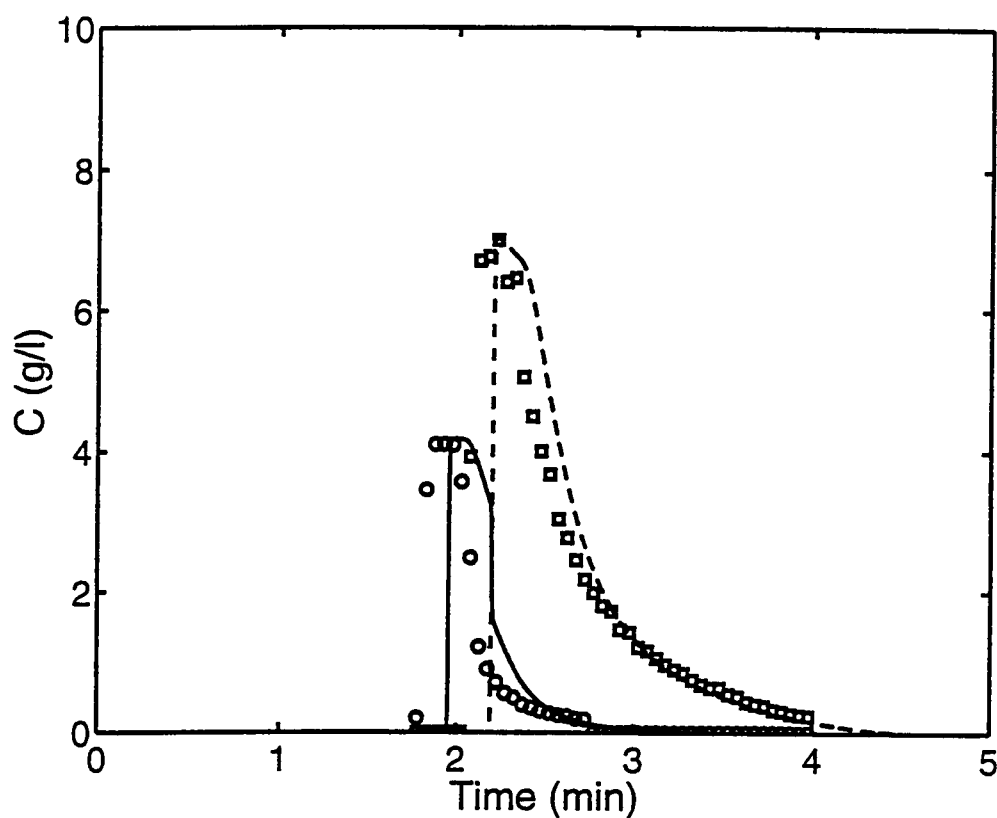


Figure 4.9 Experimental (symbols) and calculated (lines) band profiles of buspirone (circles and solid line) and diltiazem (squares and dashed line). Mobile phase is ACN : Buffer = 35 : 65; Buffer is 0.1 M phosphate, pH = 3.0, T = 25 ° C, flow rate is 1 ml/min, injected volume is 500 μ l with a total solute concentration of 10 g/l, the mass ratio of BU : DI = 1 : 3 (w/w), UV detection at 300 nm.

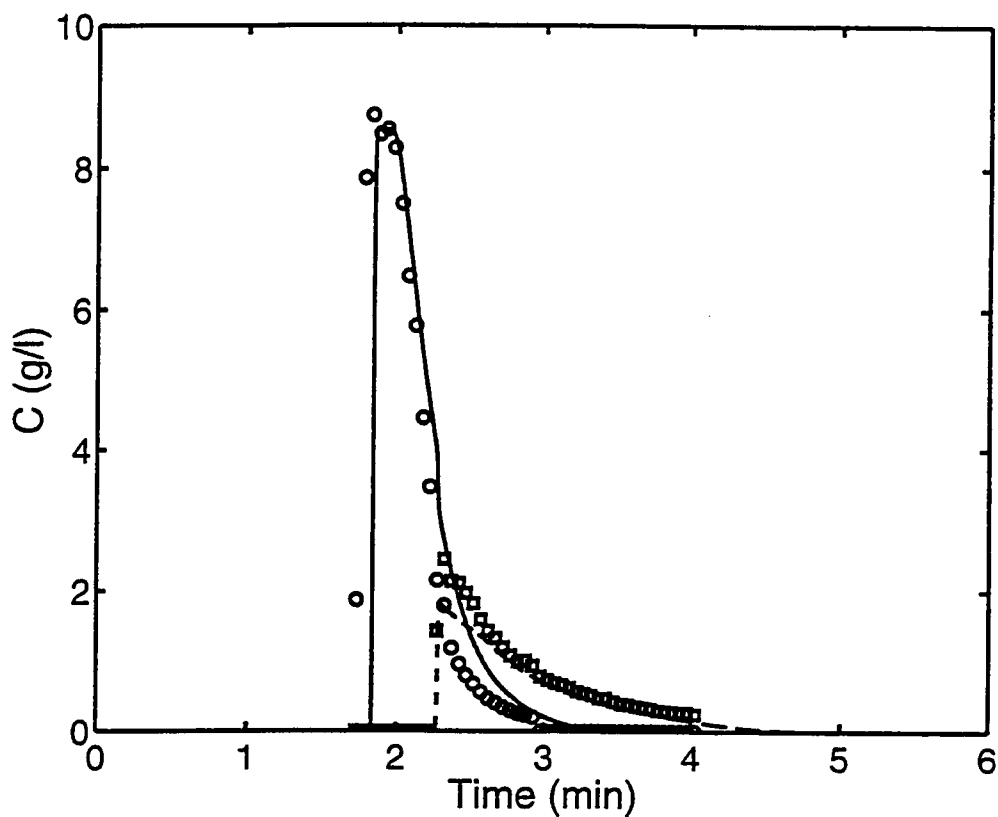


Figure 4.10 Experimental (symbols) and calculated (lines) band profiles of buspirone (circles and solid line) and doxepin (squares and dashed line). Mobile phase is ACN : Buffer = 35 : 65; Buffer is 0.1 M phosphate, pH = 3.0, T = 25 °C, flow rate is 1 ml/min, injected volume is 500 μ l with a total solute concentration of 10 g/l, the mass ratio of BU : DO = 3 : 1 (w/w), UV detection at 300 nm.

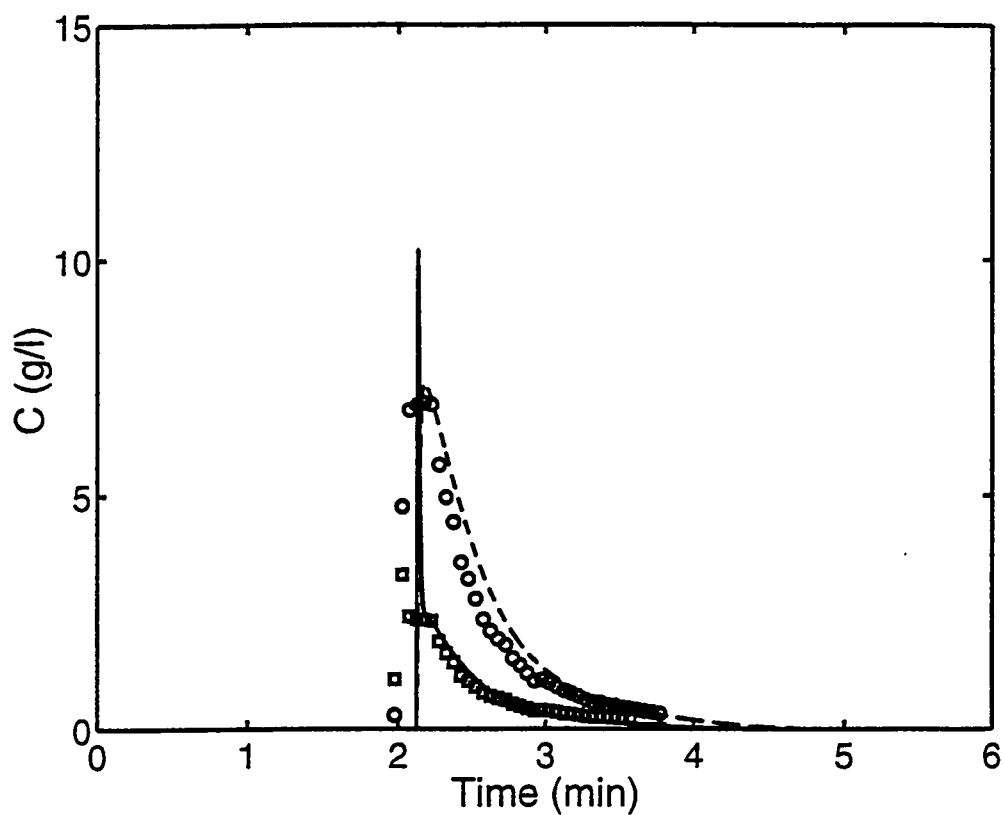


Figure 4.11 Experimental (symbols) and calculated (lines) band profiles of diltiazem (squares and solid line) and doxepin (circles and dashed line). Mobile phase is ACN : Buffer = 35 : 65; Buffer is 0.1 M phosphate, pH = 3.0, T = 25 °C, flow rate is 1 ml/min, injected volume is 500 μ l with a total solute concentration of 10 g/l, the mass ratio of DI : DO = 1 : 3 (w/w), UV detection at 300 nm.

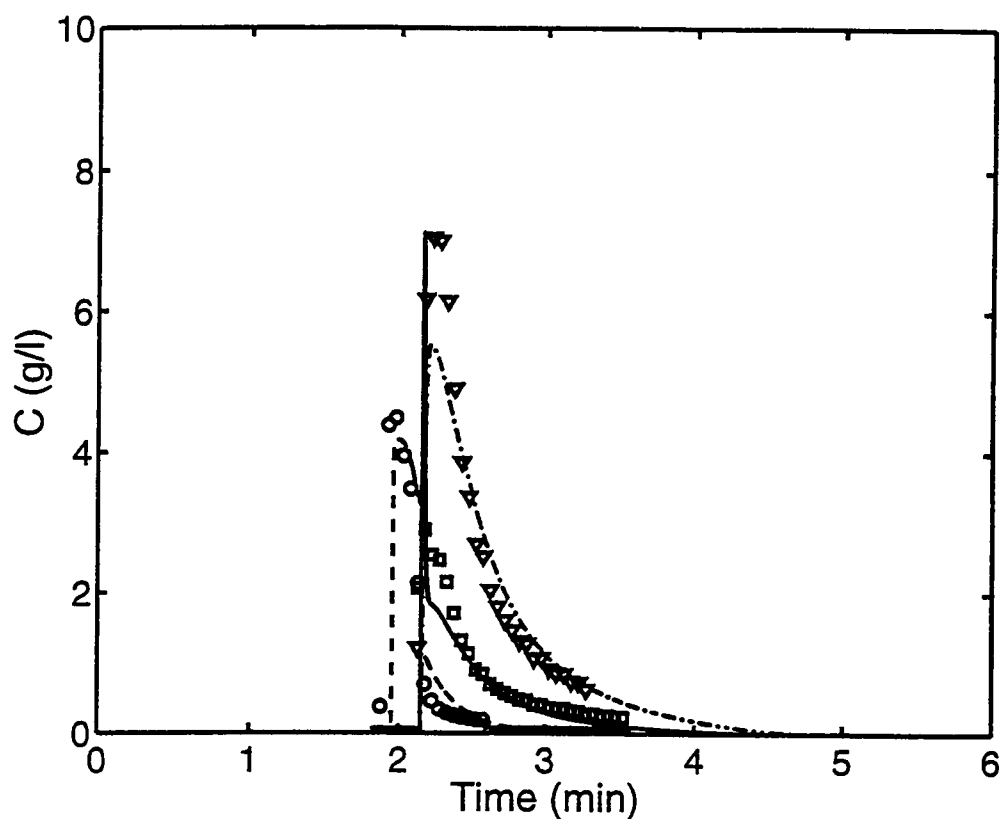


Figure 4.12 Experimental (symbols) and calculated (lines) band profiles of buspirone (circles and dashed line), diltiazem (squares and solid line) and doxepin (triangles and dashed-dotted line). Mobile phase is ACN : Buffer = 35 : 65; Buffer is 0.1 M phosphate, pH = 3.0, T = 25 °C, flow rate is 1 ml/min, injected volume is 500 μ l with a total solute concentration of 10 g/l, the mass ratio of BU : DI : DO = 1 : 1 : 3 (w/w), UV detection at 300 nm.

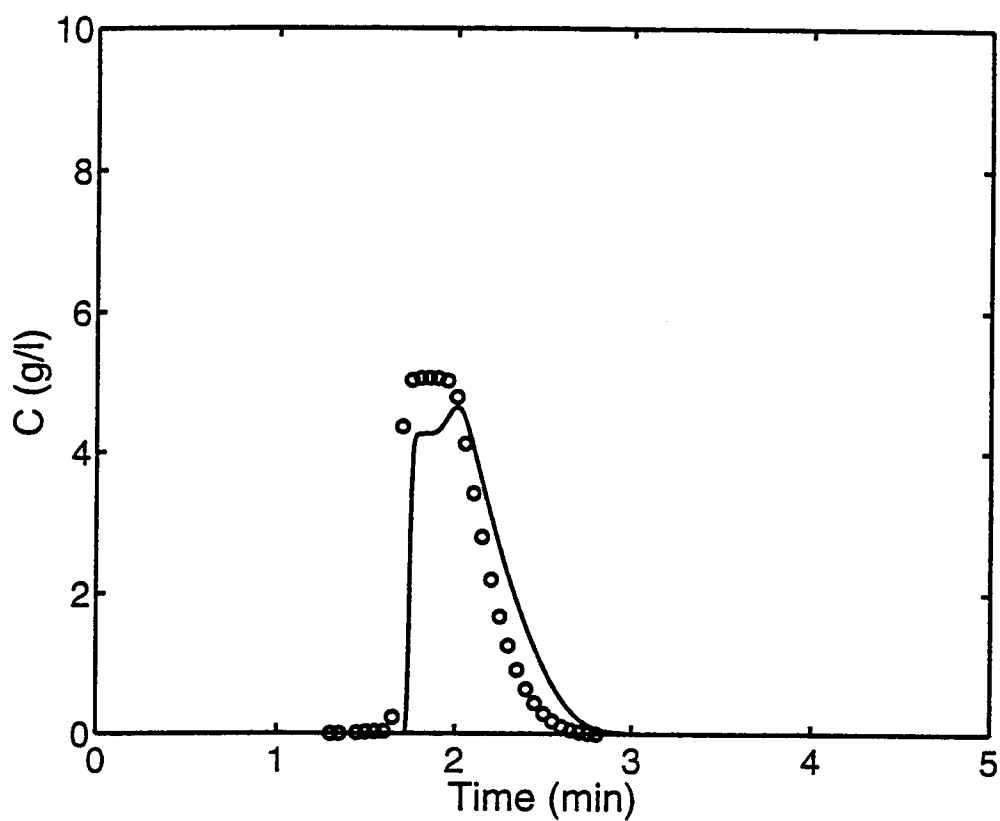


Figure 4.13 Experimental (circles) and calculated (solid line) system peak of buspirone. The mobile phase contains 4 g/l of diltiazem in a mixture of ACN and buffer (35:65, v/v). The buffer is 0.1 M phosphate, pH = 3.0. $T = 25^\circ\text{C}$, flow rate is 1 ml/min, injected volume is 500 μl with a buspirone concentration of 5 g/l, UV detection at 345 nm.

experimental profile of BU.

4.4 Conclusion on The Separation of Basic Drugs.

The multisolute phase equilibria in a complex experimental system of three ionized drugs adsorbing on a C₁₈ column from a buffered mobile phase can be well described using the competitive bi-Langmuir model. According to this model, the adsorption takes place on two different types of sites by two different mechanisms. Hydrophobic interactions take place on a low energy site (alkyl chains) and ion-exchange interactions occur on a high energy site (highly acidic silanols). These results confirm previous findings [Nawrocki, 1997]. The application of this isotherm model and the equilibrium dispersive model provides an accurate representation of the overloaded band profiles measured in the system under consideration.

Chapter 5

The Separation of a Racemic Pharmaceutical Intermediate

Recycling has been regarded for a long time as a way of improving the quality of the preparative chromatography separations. It could be particularly useful for the separation of racemic mixtures [Seidel-Morgenstern and Guiochon, 1993c; Charton et al., 1994; Grill, 1998; Grill and Miller, 1998]. The technique usually improves recovery yield, decreases pressure drop and solvent consumption and increases production rate [Martin et al., 1976; Charton et al., 1994].

Recycling can be implemented in different ways. The most popular modes are (i) closed loop, (ii) alternate pumping, (iii) recycling of an intermediate cut and (iii) recycling of the second peak tail [Seidel-Morgenstern and Guiochon, 1993c; Charton et al., 1994]. Some techniques introduce fresh sample on each cycle after the recycled fractions have been reinjected [Charton et al., 1994]. Combinations of these techniques are of course possible.

Mathematical models have been developed for the description of specific recycling techniques [Martin et al., 1976; Seidel-Morgenstern and Guiochon, 1993c; Charton et al., 1994]. Accurate predictions of the associated band profiles have been obtained via the equilibrium-dispersive model and relevant equilibrium data [Charton et al., 1994]. In other cases, only experimental studies have been con-

ducted [Grill, 1998; Grill and Miller, 1998].

In this chapter we present the results of the experimental determination of the single and binary solute adsorption equilibria for a racemic pharmaceutical intermediate (RPI). The adsorption equilibria was determined by frontal analysis in a system composed of a chiral HPLC column as the stationary phase and acetonitrile as the mobile phase. The adsorption data were well correlated by the Langmuir model.

The adsorption equilibrium data were used to calculate overloaded band profiles corresponding to the separation of racemic mixtures at both analytical and preparative scales. Theoretical band profiles were calculated using the equilibrium dispersive model and the competitive Langmuir model which uses the parameters determined from single solute adsorption isotherm data. Good agreement was found between the experimental and calculated nonlinear band profiles.

The separation at the preparative scale corresponds to a new recycling technique which has been developed for the separation of racemic mixtures. In this process, the fresh sample is injected periodically into the interior of a circulating chromatographic profile. Simultaneously, fractions of the purified enantiomers are collected periodically from both ends of the binary profile [Grill, 1998; Grill and Miller, 1998]. Experimental results and theoretical calculations demonstrate that a pseudo steady state develops after the completion of a finite number of cycles.

5.1 Experimental.

5.1.1 Equipment.

5.1.1.1 Analytical Scale.

The adsorption isotherm data and the overloaded band profiles at the analytical scale were acquired using the same experimental setup described in section 3.1.1.

5.1.1.2 Preparative Scale.

The recycling experiments were performed at R&S Technology using a Steady CycleTM system. The instrument is composed of a NovaPrep 200 mobile phase pump with a maximum flow rate of 200 ml/min and a maximum pressure of 2500 psi (R&S Technology, Wakefield, RI); a variable wavelength UV detector equipped with a high pressure flow cell (Hitachi, Japan); a six-port, air-actuated injection valve (Rheodyne, Cotati, CA) with 5.0 ml injection loop; several air actuated collection valves (Mace, Upland, CA) and an injection metering pump Model BBB-4 (Eldex Labs, San Carlos, CA). TurboPrep[©] software (Merck, Darmstadt, Germany) was used to control the instrumentation.

To analyze the fractions collected for the last cycle, a Varian Vista 550 HPLC system (Varian, Walnut Creek, CA) equipped with a 9090 autosampler, a Knauer

variable-wavelength UV detector and a Spectra-Physics SP4290 integrator was used.

5.1.2 Materials.

A 250 mm $\times$ 4.6 mm i.d. Chiralpak AS column (Chiral Technologies, Exton, PA) was used to measure the adsorption data and the overloaded band profiles at the analytical scale. The adsorbent is amylose tris[(S)- α -methylbenzyl carbamate] coated on silica gel. The particle size was 10 μ m and the void fraction of the column was 0.77. A 250 mm $\times$ 20 mm i.d. Chiralpak AS column (Chiral Technologies, Exton, PA) was used to measure the overloaded band profiles under recycling conditions at the preparative scale. The particle size was 10 μ m and the void fraction of the column was 0.72.

In all the experiments the mobile phase was acetonitrile. Acetonitrile was HPLC grade, purchased from Fisher Scientific (Pittsburgh, PA, USA). The solutes employed are proprietary compounds belonging to Searle (Searle, Skokie, IL). In this chapter we will use the indices 7 and 8 when referring to the first enantiomer (E1) and second enantiomer (E2), respectively.

5.1.3 Procedures.

5.1.3.1 Analytical scale.

The separation of the racemate under linear conditions is presented in figure

5.1. The parameters of the separation under linear conditions can be found in Table 5.1. Single-solute adsorption data measured by FA at 22°C as described in section 3.1.3.1 are presented in Table 5.2. Binary-solute adsorption data measured by FA at 22°C as described in section 3.1.3.2 are presented in Table 5.3. The UV signal was recorded at 254 nm. The adsorption data are also represented in figures 5.2 and 5.3 (symbols). Due to the limited quantities of pure enantiomers and racemate available, only one adsorption data point per composition was measured for this system. The total absorption signal corresponding to two overloaded injections of the racemate were also measured. They are presented in figures 5.4 and 5.5.

5.1.3.2 Preparative scale.

Figure 5.6 shows a schematic diagram of the recycling setup. At the beginning of a run the injection loop (IL) is filled with sample by the injection pump (IP). The sample is drawn from the sample reservoir (SR). To accomplish this operation the injection valve (IV) is placed in the load position (dashed line flow path). Any excess of sample go to waste through the port LW. At the same time, the mobile phase pump (MPP) draws mobile phase from the mobile phase reservoir (MPR), through the mobile phase valve (MPV) and pumps it through the column (C), through the detector (D), through the IV (dashed line flow path), through the collection valve manifold (CVM) and goes to waste through

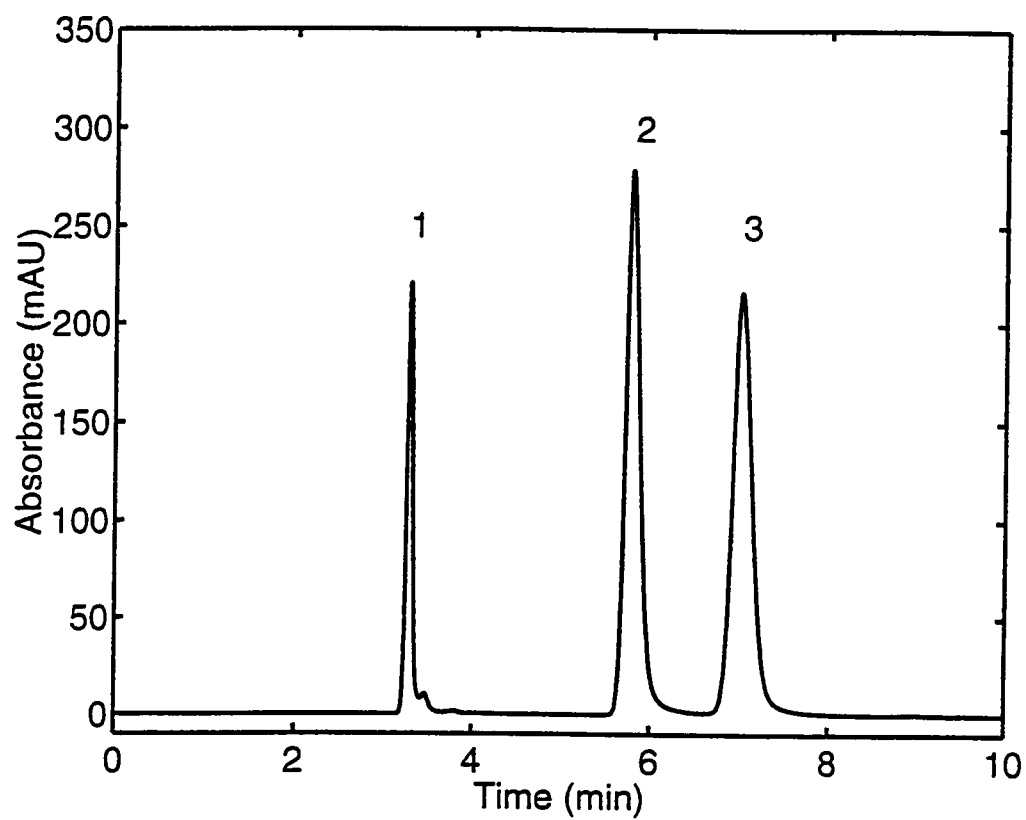


Figure 5.1 Analytical separation of tri-*tert.*-butylbenzene (1), E1 (2) and E2 (3). Mobile phase is ACN; $T = 22\text{ }^{\circ}\text{C}$, flow rate is 1 ml/min, injected volume is 20 μl with a concentration of 0.5 g/l, UV detection at 225 nm.

Table 5.1. Parameters of the separation under linear conditions

Parameter	First Enantiomer	Second Enantiomer
Analytical column (4.6x250 mm)		
k'	0.785	1.16
N	6600	5400
Preparative column (20x250 mm)		
k'	0.79	1.186
N	3721	3270

Table 5.2. Single-solute equilibrium data measured by FA at 22 °C

C_7	Γ_7	C_8	Γ_8
(g/l)	(g/l)	(g/l)	(g/l)
1.00	2.31	1.00	3.44
2.00	4.19	2.00	6.27
3.00	5.87	3.00	8.72
3.50	6.71	3.50	9.87
4.00	7.28	4.00	10.95
5.00	8.68	5.00	12.95
6.00	9.92	6.00	14.72
7.00	11.05	7.00	16.36
8.00	12.29	8.00	17.94
9.00	13.17	9.00	19.52
10.00	13.58	10.00	20.21

Table 5.3. Binary-solute equilibrium data of
the two enantiomers

C_7	C_8	Γ_7	Γ_8
(g/l)	(g/l)	(g/l)	(g/l)
0.50	0.50	1.11	1.75
0.75	0.75	1.67	2.54
1.00	1.00	2.18	3.26
1.25	1.25	2.58	3.93
1.50	1.50	3.01	4.56
1.75	1.75	3.35	5.18
2.00	2.00	3.76	5.75
2.50	2.50	4.39	6.79
2.75	2.75	4.70	7.27
3.00	3.00	5.00	7.77
3.50	3.50	5.56	8.66
4.00	4.00	6.04	9.52
4.50	4.50	6.61	10.37
5.00	5.00	6.92	11.05

Table 5.3. (continued)

C_7	C_8	Γ_7	Γ_8
(g/l)	(g/l)	(g/l)	(g/l)
0.75	0.25	1.70	0.85
1.50	0.50	3.22	1.65
2.25	0.75	4.53	2.32
3.00	1.00	5.58	2.93
3.75	1.25	6.63	3.49
4.50	1.50	7.67	4.01
5.25	1.75	8.53	4.48
6.00	2.00	9.07	4.86
6.38	2.13	9.57	5.08
6.75	2.25	9.77	5.28
7.50	2.50	10.53	5.66

Table 5.3. (continued)

C_7	C_8	Γ_7	Γ_8
(g/l)	(g/l)	(g/l)	(g/l)
0.25	0.75	0.57	2.67
0.50	1.50	1.04	4.85
0.75	2.25	1.44	6.73
1.00	3.00	1.81	8.40
1.25	3.75	2.12	9.99
1.50	4.50	2.41	11.46
1.75	5.25	2.67	12.88
2.00	6.00	2.91	14.08
2.25	6.75	3.10	15.13
2.50	7.50	3.41	16.11

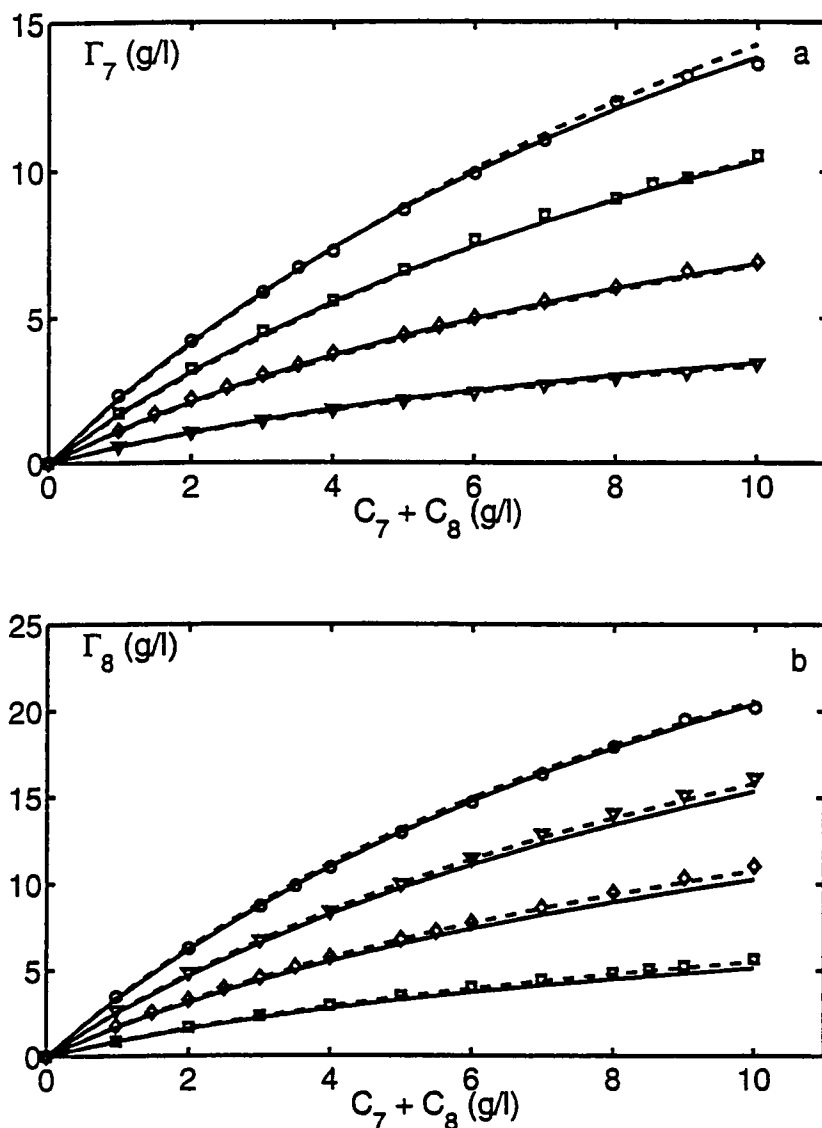


Figure 5.2. Adsorbed amount of E1 (a) and E2 (b) determined via FA in their mixtures. Identical convention as in figure 3.9. The solid lines are the calculated amounts via eq.(5.2) when using the parameters determined from single solute data. The dashed lines are the calculated amounts via eq.(5.2) when using the parameters determined from the joint set of single and binary solute data.

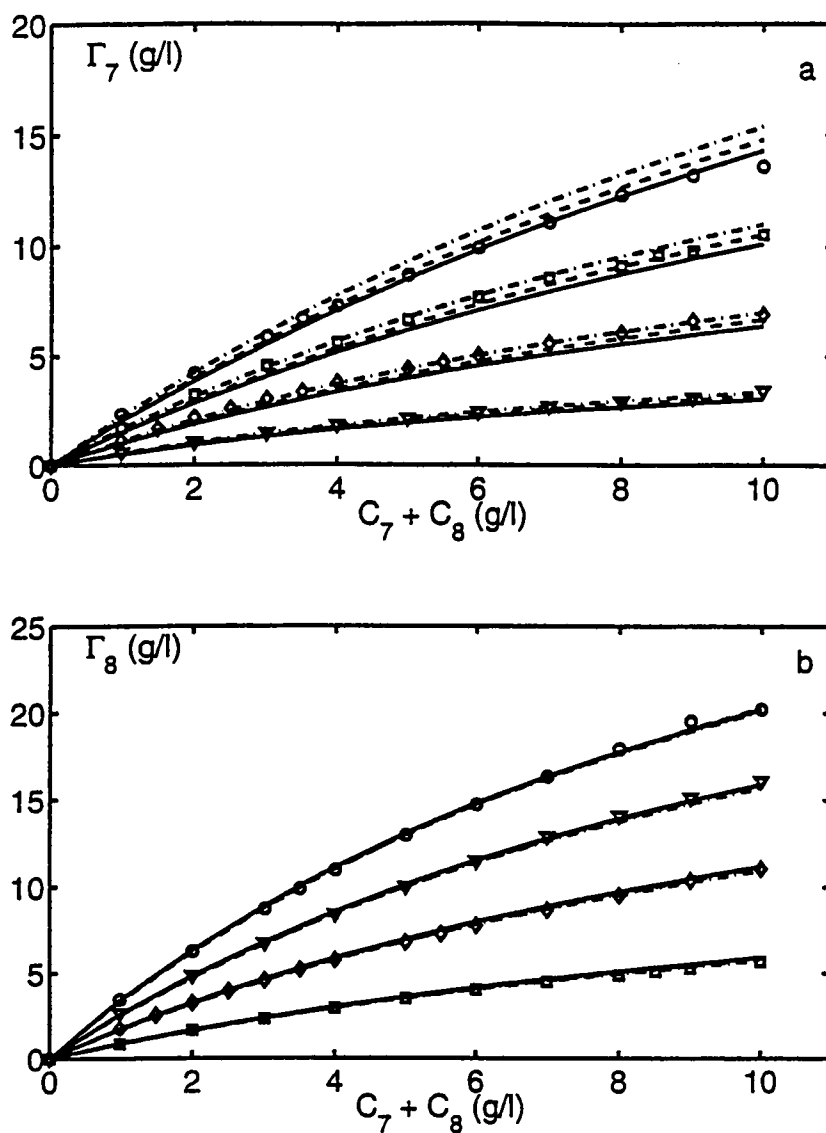


Figure 5.3 Identical convention as in figure 5.2. The solid lines are the calculated amounts via eq.(5.3) when using the parameters determined from single solute data. The dashed lines are the calculated amounts via eq.(5.3) when using the parameters determined from the joint set of single and binary solute data. The dashed-dotted lines are the calculated amounts via eq.(5.3) when using the parameters determined from racemate data.

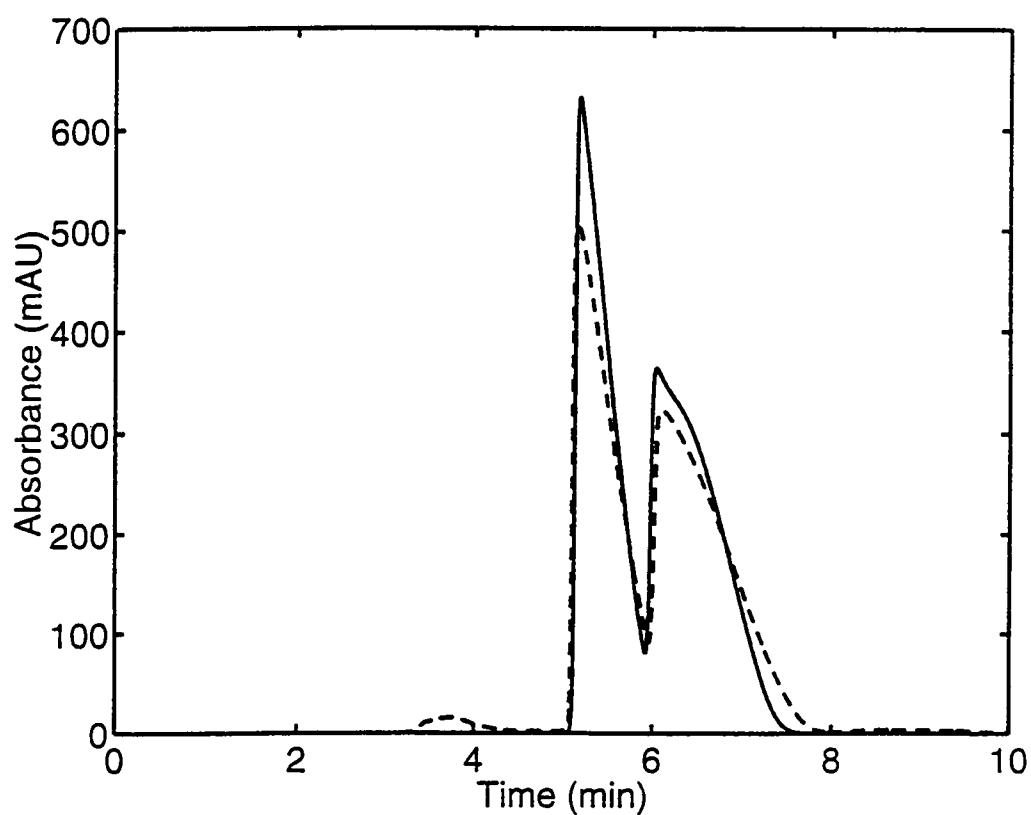


Figure 5.4 Experimental (dashed line) and calculated (solid line) band profile of the racemate. Mobile phase is ACN; $T = 22^{\circ}\text{C}$, flow rate is 1 ml/min, injected volume is 500 μl with a concentration of 5 g/l, UV detection at 254 nm.

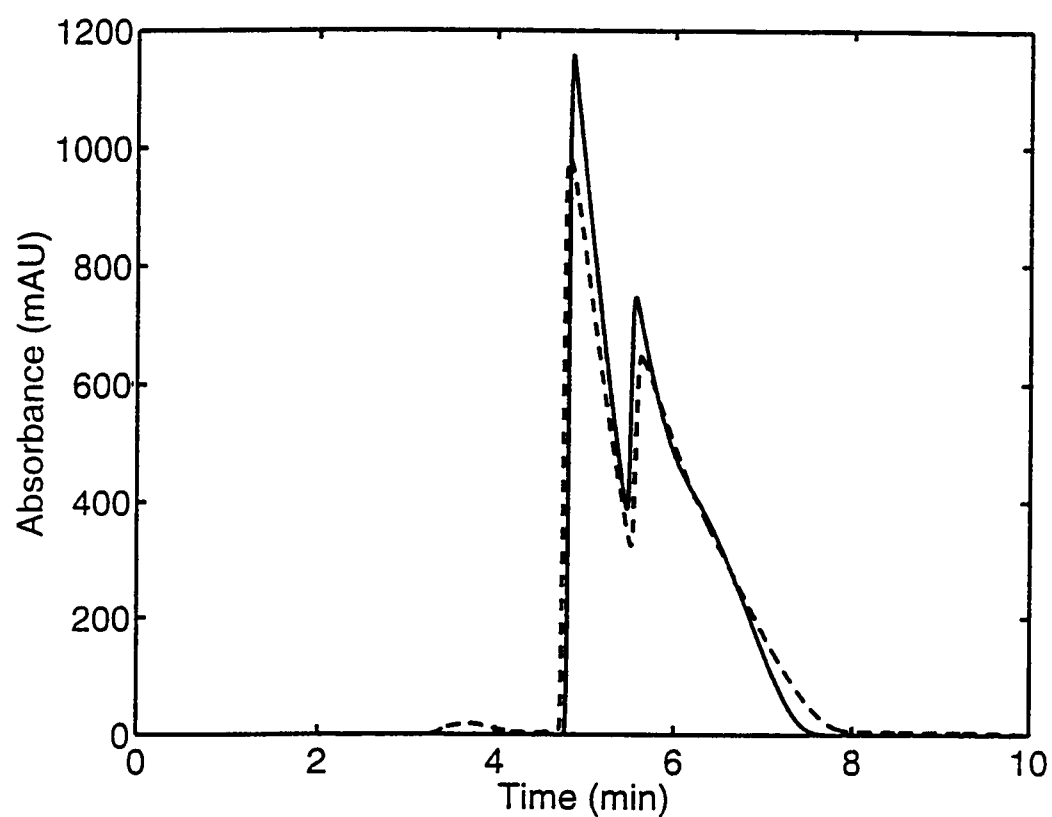


Figure 5.5 Experimental (dashed line) and calculated (solid line) band profile of the racemate. Mobile phase is ACN; $T = 22^{\circ}\text{C}$, flow rate is 1 ml/min, injected volume is 500 μl with a concentration of 10 g/l, UV detection at 254 nm.

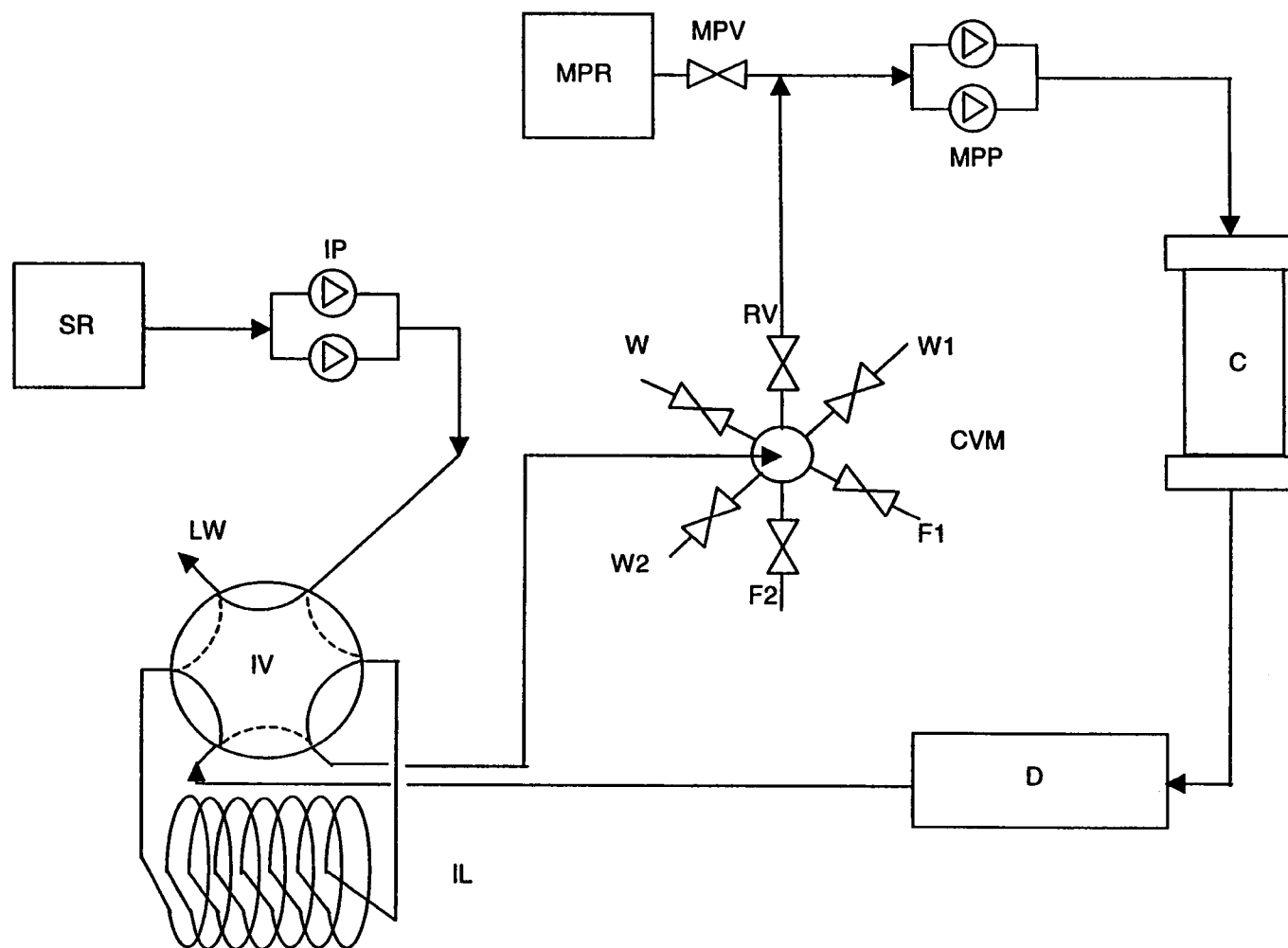


Figure 5.6 Schematic diagram of the recycling setup. See text for details of operation.

the waste valve (W).

The run starts by simultaneously placing the IV in the inject position (solid line flow path), opening the recycling valve (RV) and closing the MPV and W. The sample in the IL is therefore transported by the mobile phase through the RV and the MPP onto the column. Once all the sample has been injected into the column, the IV is switched back to the load position (dashed line flow path), the RV is closed and the MPV and W1 are opened, thus directing the effluent to waste. The IL is then filled again as described before.

When the leading edge of the profile is detected, valve F1 is opened and valve W1 is closed. Mobile phase is continued to be drawn from the MPR. At the appropriate time, valves F1 and MPV close and the RV opens. The collection of fraction one is complete. Simultaneously, the first part of the circulating profile is directed to the column through the RV and the MPP.

At the appropriate time, as the central part of the profile elutes from the column, the IV is switched to the inject position (solid line flow path). This action diverts the effluent from the detector through the IL and fresh sample is injected into the interior of the profile.

At some specific time, valves MPV and F2 open and the RV closes. This action starts the collection of fraction 2 which lasts for some time until valve F2 is closed and valve W2 opens. In a simultaneous fashion, the collection of fraction 2 is concluded and the effluent is directed to waste. Then the cycle starts

again with the detection of the profile leading edge. A detailed explanation of the process can be found elsewhere [Grill, 1998]

In the experiments reported here, a relative time method was employed to control the operation of the instrument like valve switching, pump operation, etc. Within this procedure, the leading front of the circulating UV signal is determined using the ascending slope method. When the setpoint value is met, the collection valve of fraction 1 is opened and the remaining time events are defined relative to the opening of the aforementioned valve. The setup was operated at a flow rate of 21.8 ml/min. The fresh sample of racemate had a concentration of 10 g/l. The results of the experiments corresponding to the initial injection and cycles 1 through 10 are presented in figures 5.7 to 5.19. The graphs show the UV absorption signal detected at 235 nm as a function of the relative cycle time. The absorption signal was normalized (I_{norm}) according to

$$I_{norm} = \frac{I}{I_{max}} \quad (5.1)$$

where I is the value of the UV absorbance and I_{max} is the maximum value of the UV signal for the given profile.

Fractions were collected for the last cycle (cycle 20). The fractions were analyzed by HPLC using acetonitrile as the mobile phase pumped at a rate of 1 ml/min. A 250 mm $\times$ 4.6 mm i.d. Chiralpak AS, 10 μ m column (Chiral Technologies, Exton, PA) was used to analyze the fractions. The injection volume was

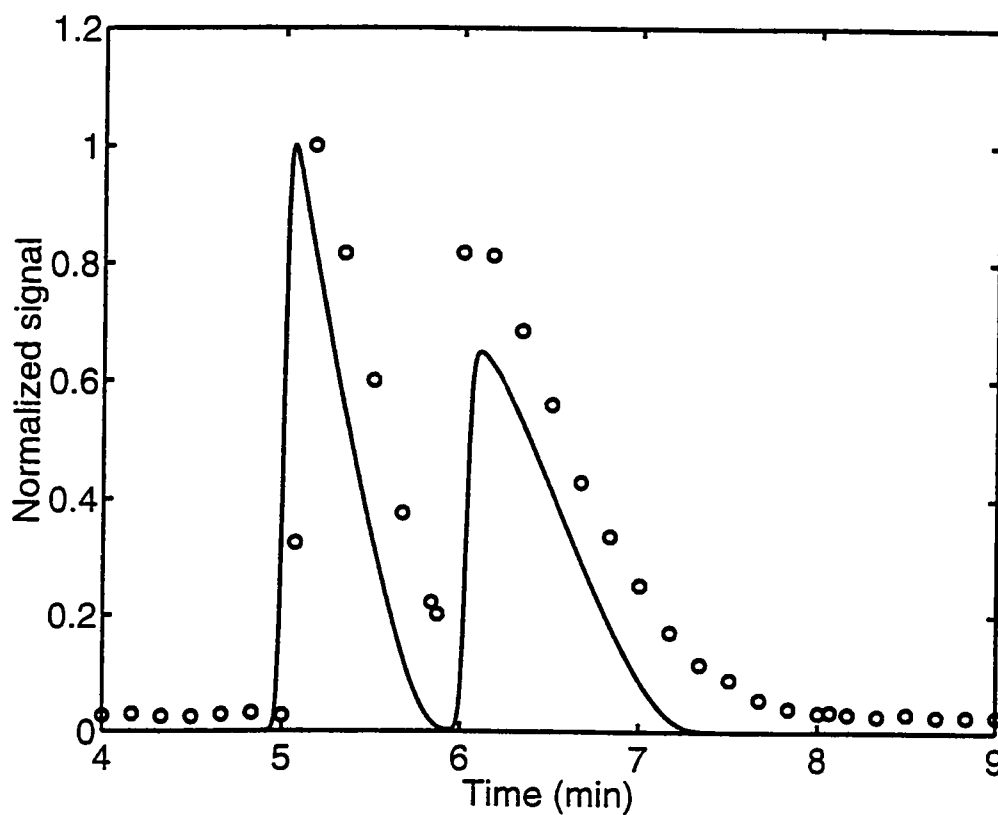


Figure 5.7 Experimental (circles) and calculated (solid line) band profile for the initial pass of the racemate in the recycling setup. No extracolumn dispersion included in the model. Mobile phase is ACN; $T = 22\text{ }^{\circ}\text{C}$, flow rate is 21.8 ml/min, injected volume is 5 ml with a concentration of 10 g/l, UV detection at 235 nm.

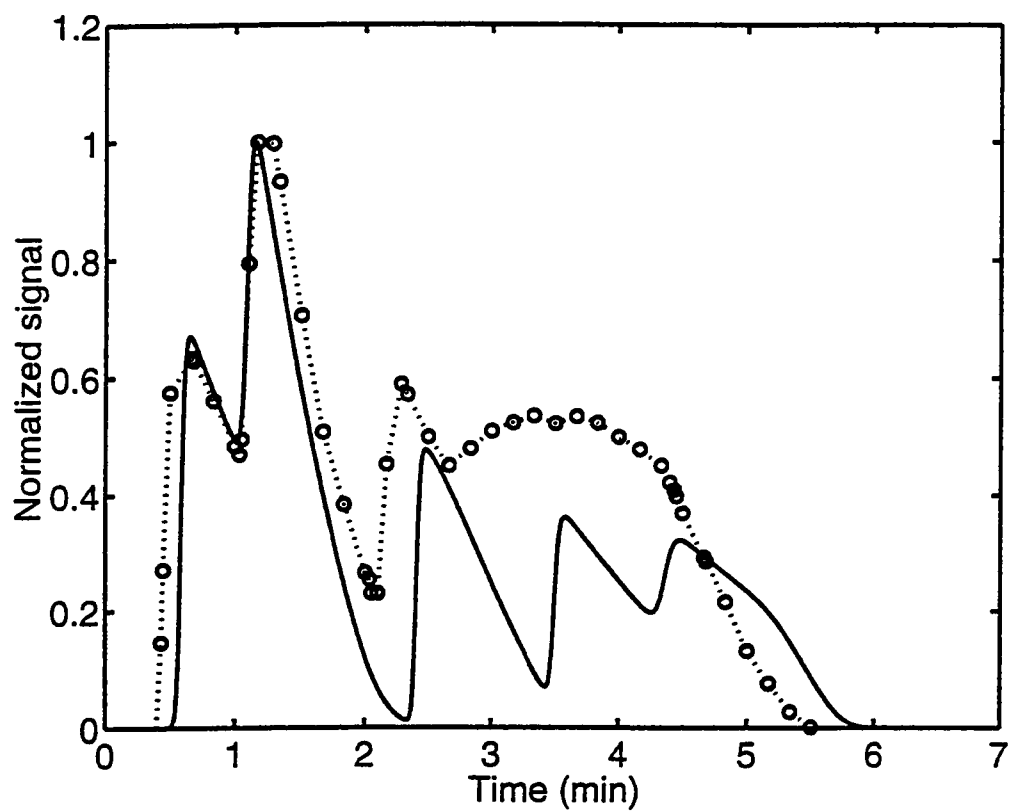


Figure 5.8 Identical conditions as in figure 5.7 but results provided for cycle 5.

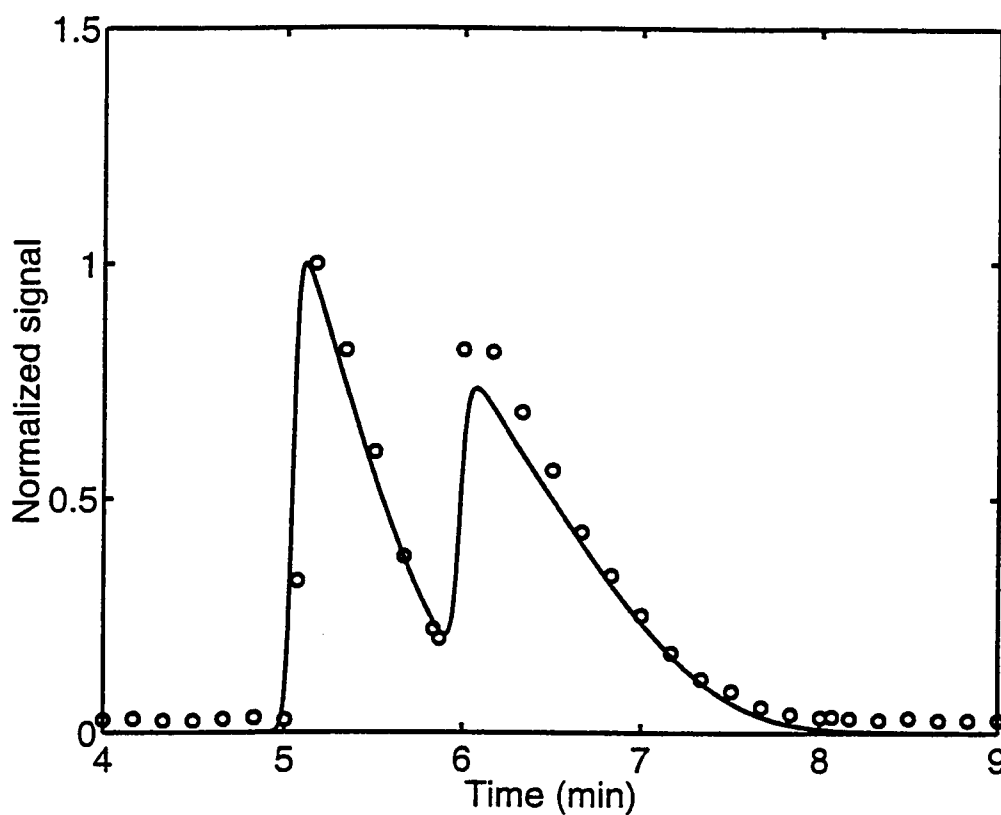


Figure 5.9 Experimental (circles) and calculated (solid line) band profile for the initial pass of the racemate in the recycling setup. Extracolumn dispersion included in the model. Mobile phase is ACN; $T = 22\text{ }^{\circ}\text{C}$, flow rate is 21.8 ml/min, injected volume is 5 ml with a concentration of 10 g/l, UV detection at 235 nm.

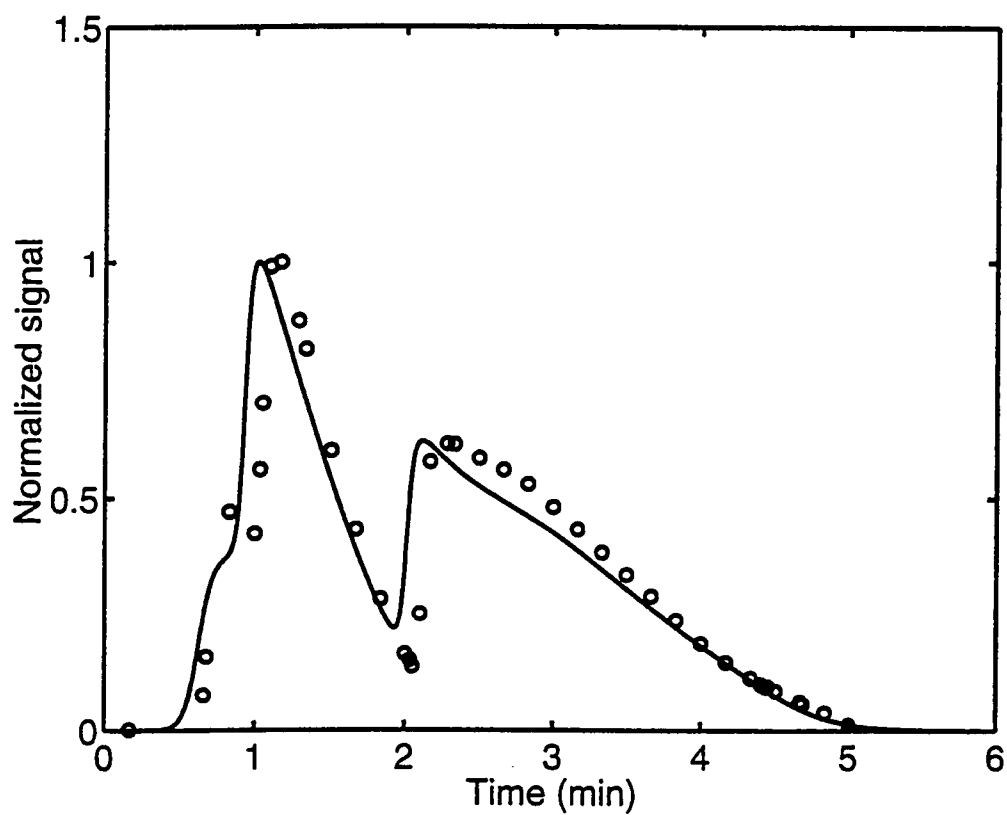


Figure 5.10 Identical conditions as in figure 5.9 but results provided for cycle 1.

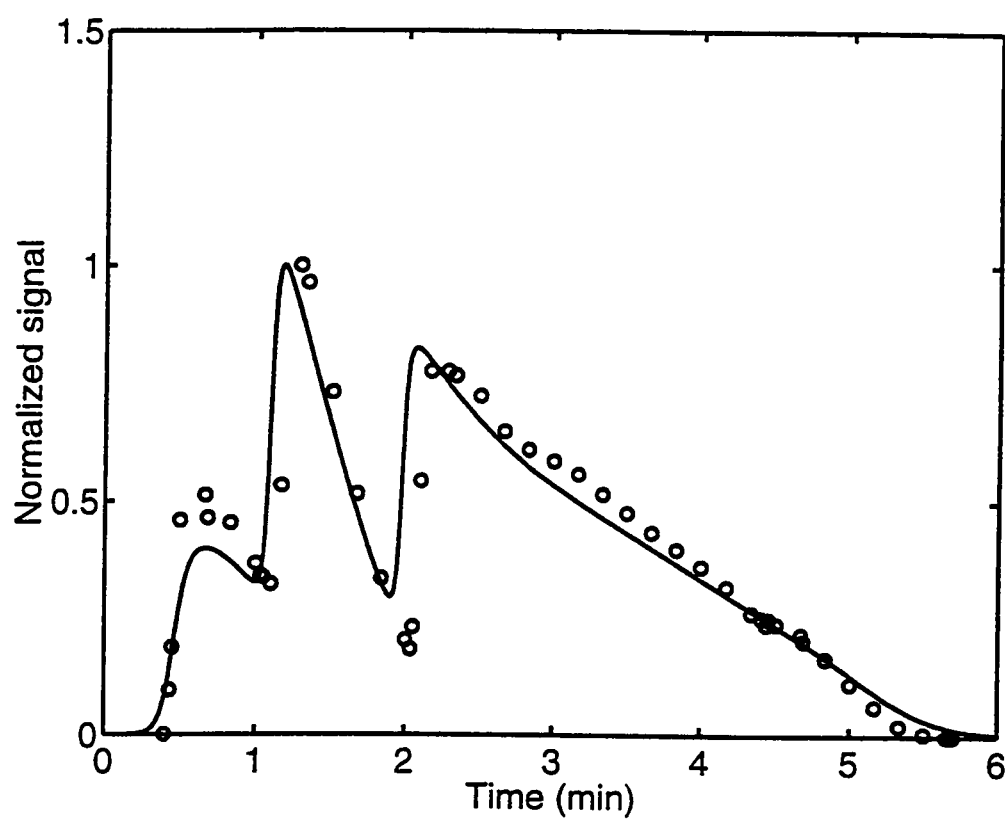


Figure 5.11 Identical conditions as in figure 5.9 but results provided for cycle 2.

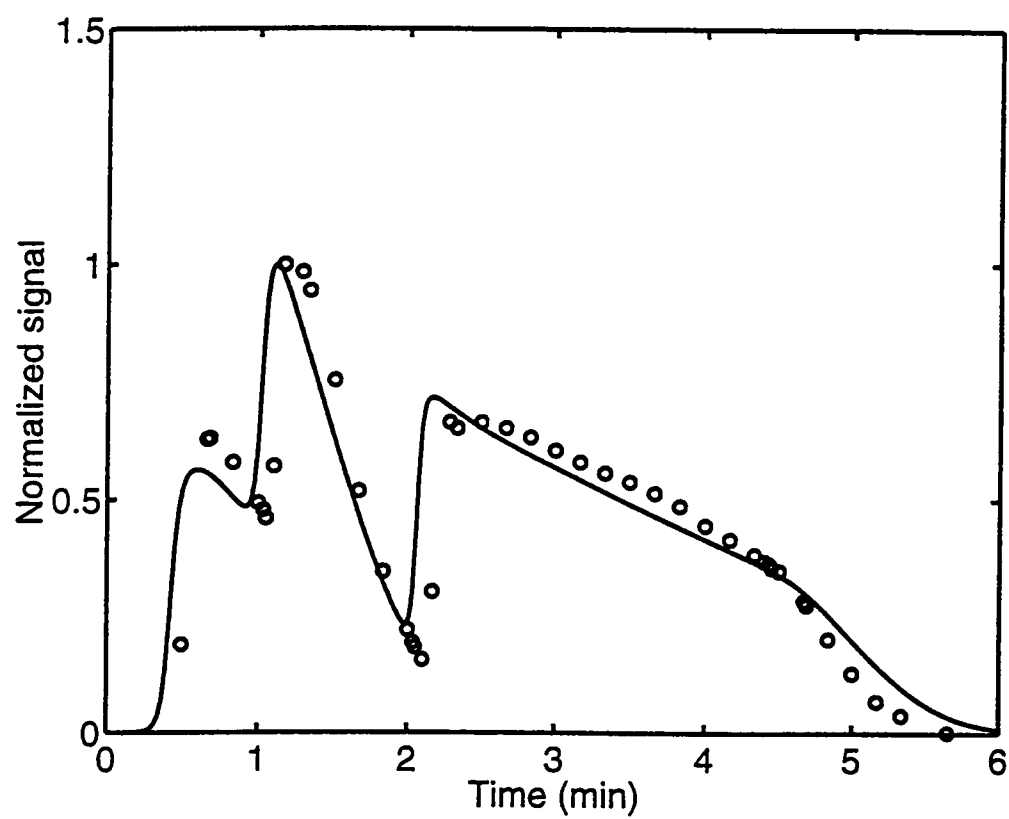


Figure 5.12 Identical conditions as in figure 5.9 but results provided for cycle 3.

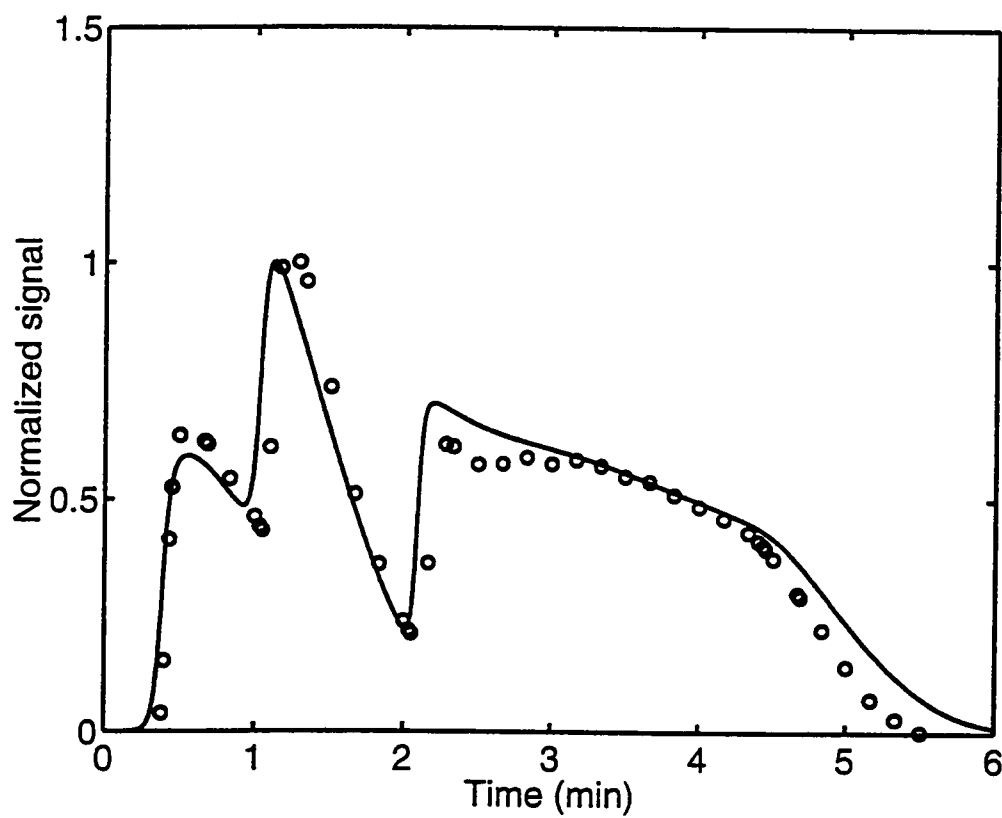


Figure 5.13 Identical conditions as in figure 5.9 but results provided for cycle 4.

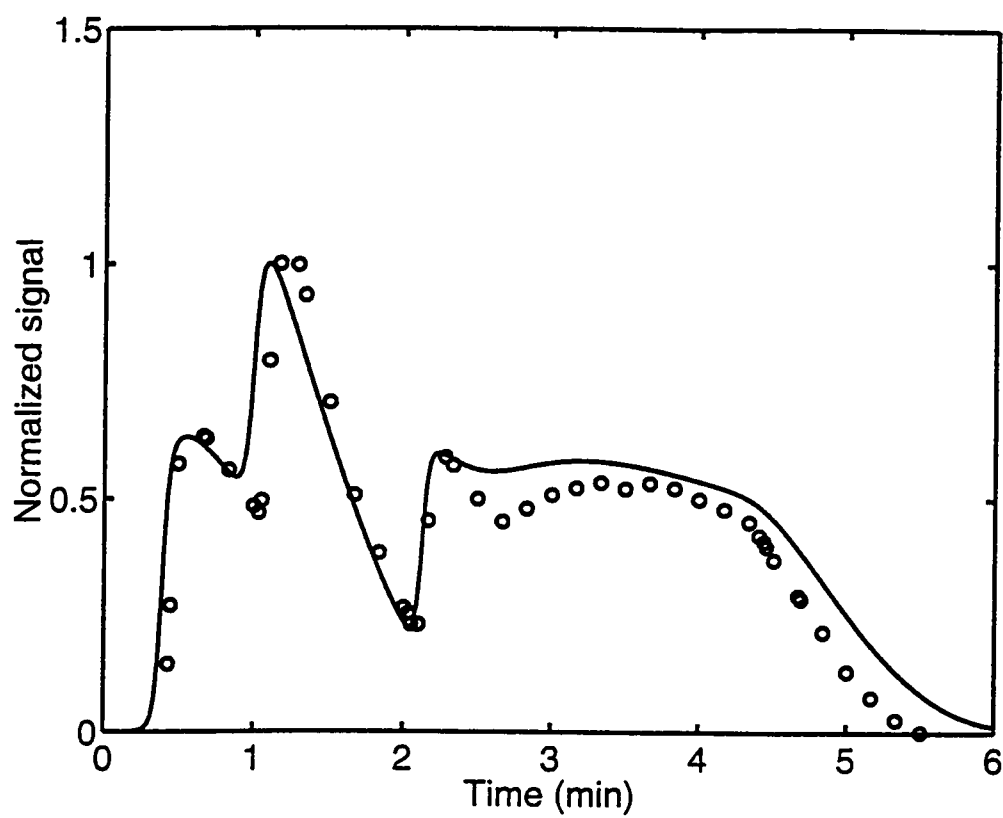


Figure 5.14 Identical conditions as in figure 5.9 but results provided for cycle 5.

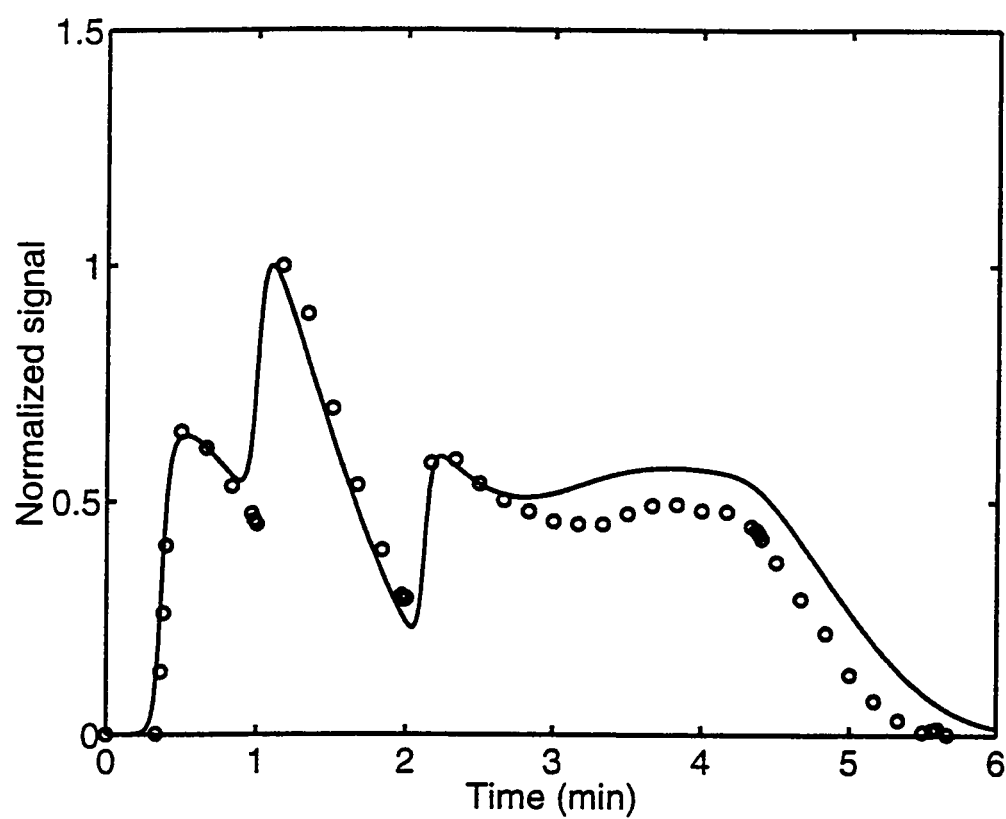


Figure 5.15 Identical conditions as in figure 5.9 but results provided for cycle 6.

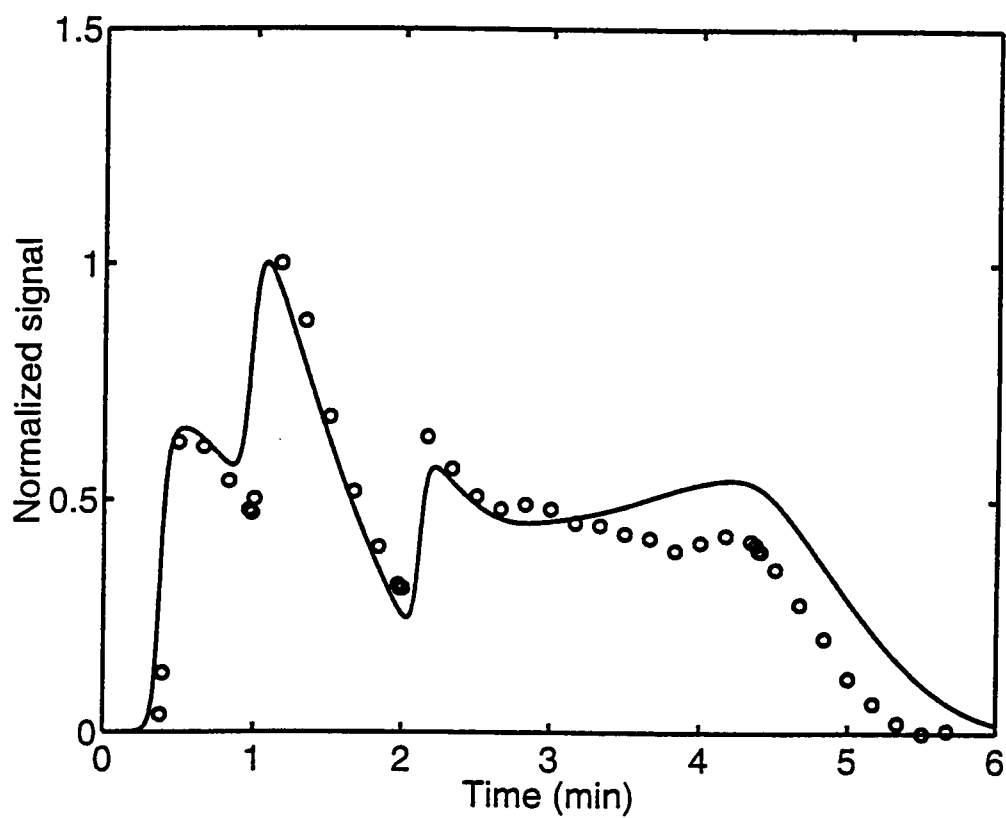


Figure 5.16 Identical conditions as in figure 5.9 but results provided for cycle 7.

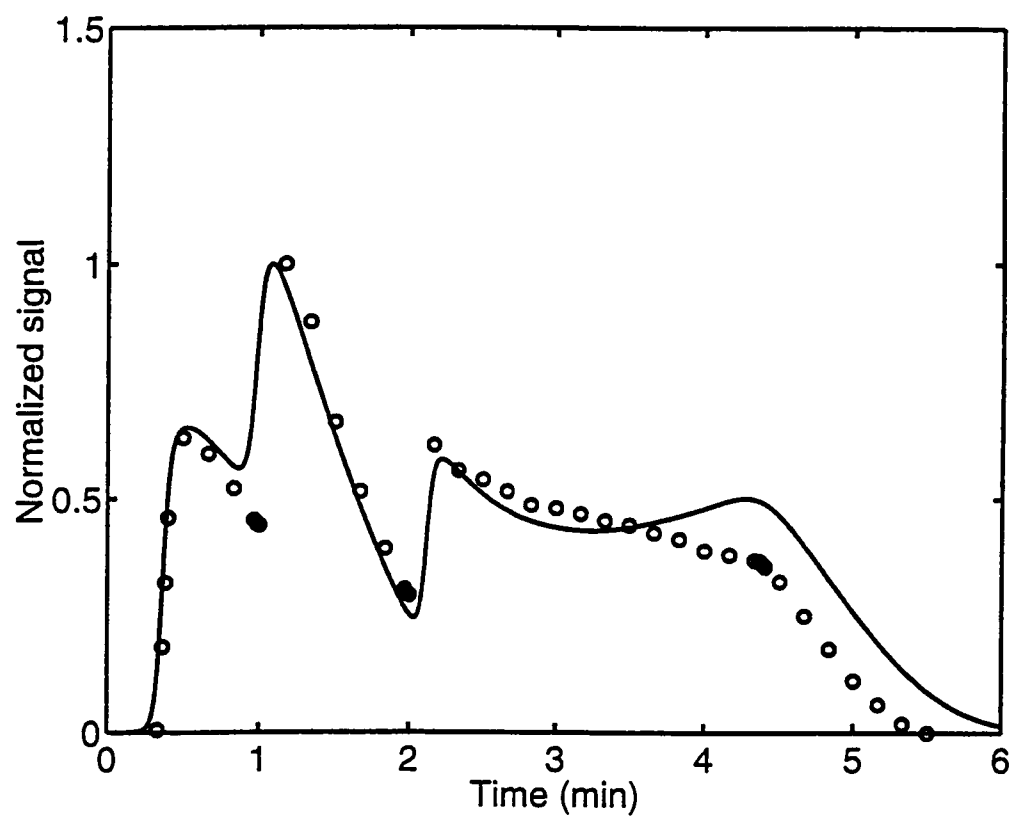


Figure 5.17 Identical conditions as in figure 5.9 but results provided for cycle 8.

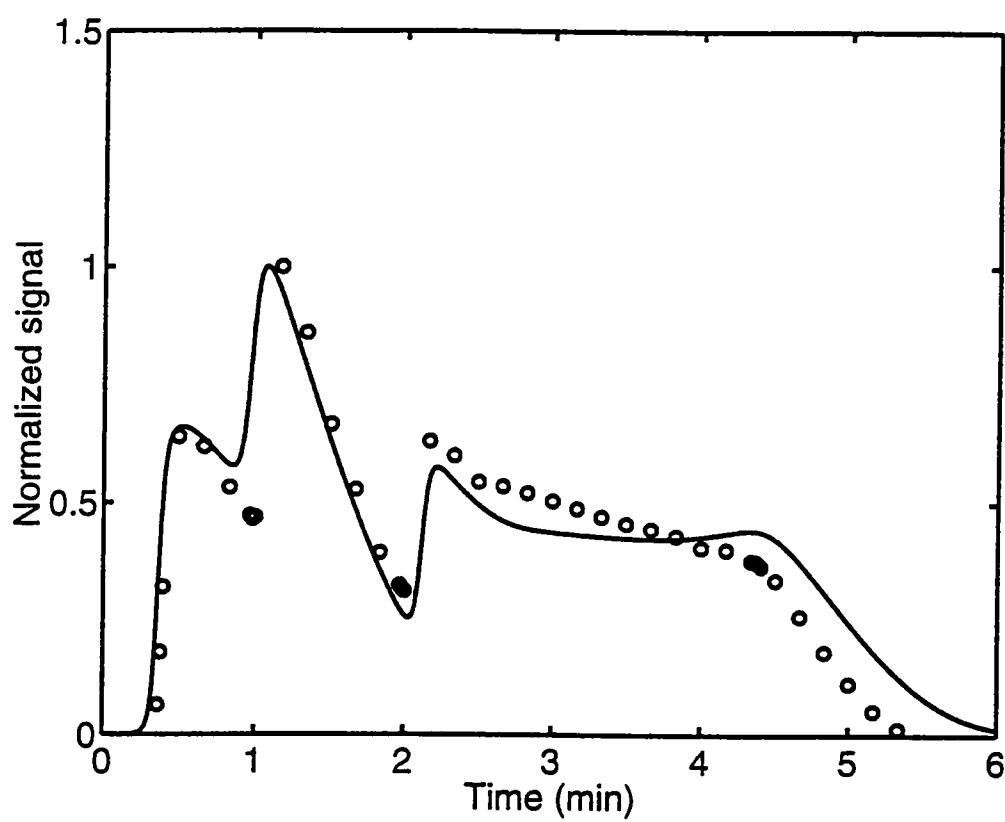


Figure 5.18 Identical conditions as in figure 5.9 but results provided for cycle 9.

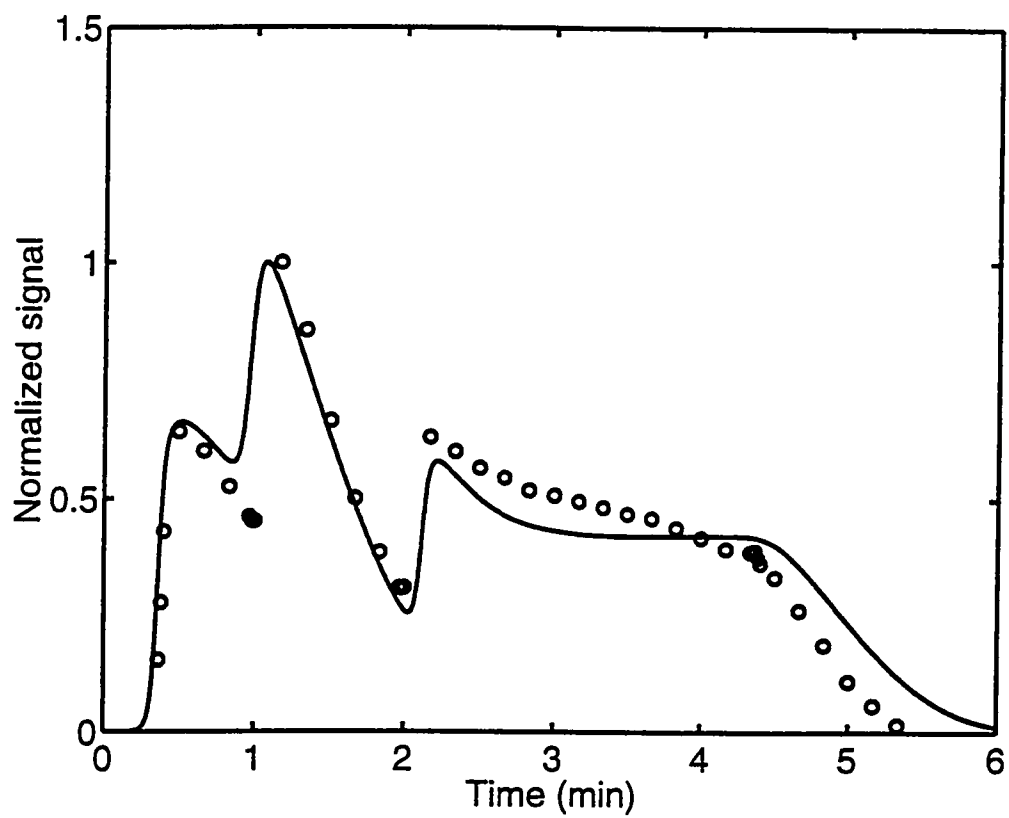


Figure 5.19 Identical conditions as in figure 5.9 but results provided for cycle 10.

20 μl and the detector wavelength was set 220 nm. The results of the analysis are presented in figure 5.20.

5.2 Model.

The single solute and binary adsorption data were analyzed in terms of the Langmuir model. The model was applied in two ways. In the first case, different adsorption capacities were assumed for each enantiomer. In the second case, a common value of the saturation capacity was assumed.

When different adsorption capacities are assumed for each enantiomer the isotherm model is defined as

$$q_7 = \frac{n_7^\infty K_7^L C_7}{1 + K_7^L C_7 + K_8^L C_8} \quad (5.2a)$$

$$q_8 = \frac{n_8^\infty K_8^L C_8}{1 + K_7^L C_7 + K_8^L C_8} \quad (5.2b)$$

When the single solute adsorption data were fitted to eqs. (5.2) , the parameters presented in the third row of Table 5.4 are obtained. On the other hand, when the combined set of both single solute and binary adsorption data are fitted, the results shown in the last row of table 5.4 are obtained.

When a common saturation capacity is assumed for both enantiomers, the isotherm model is defined as

$$q_7 = \frac{n_{7,8}^\infty K_7^L C_7}{1 + K_7^L C_7 + K_8^L C_8} \quad (5.3a)$$

$$q_8 = \frac{n_{7,8}^\infty K_8^L C_8}{1 + K_7^L C_7 + K_8^L C_8} \quad (5.3b)$$

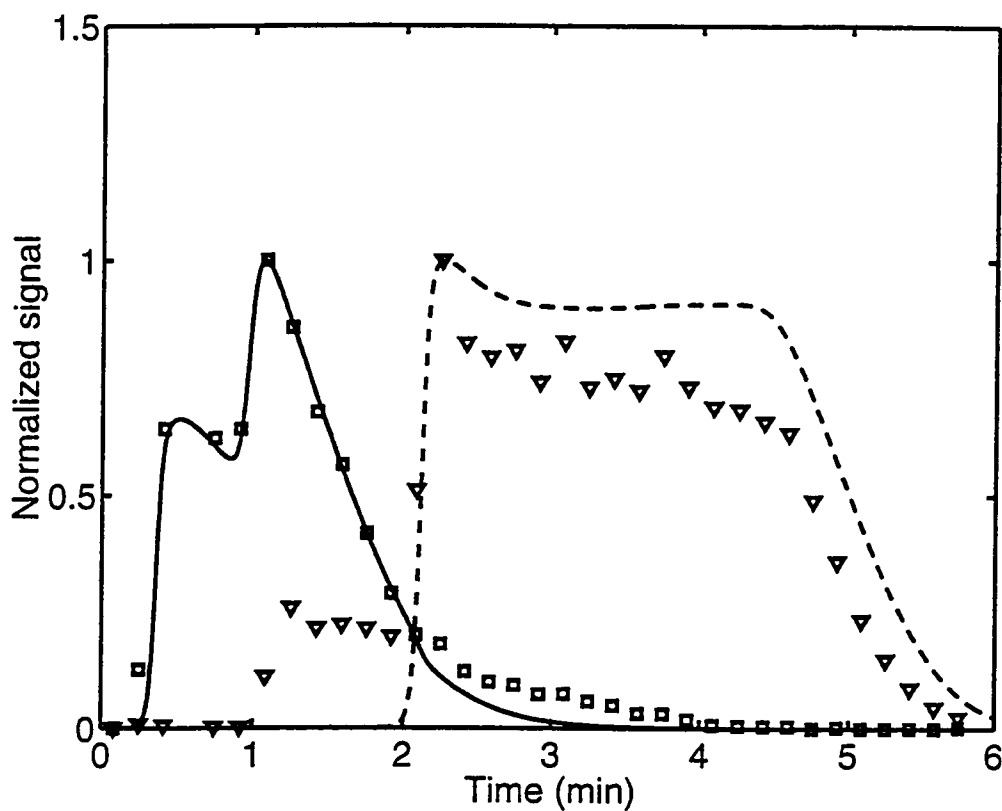


Figure 5.20 Experimental (symbols) and calculated (lines) band profiles of E1 (squares and solid line) and E2 (triangles and dashed line) as obtained at the end of cycle 20. Extracolumn dispersion included in the model. Mobile phase is ACN; $T = 22^{\circ}\text{C}$, flow rate is 21.8 ml/min, injected volume is 5 ml with a concentration of 10 g/l.

Table 5.4. Fit of the experimental adsorption data to Eq. (5.2)

Data	n_7^{∞}	$K_7^L \times 10^2$	n_8^{∞}	$K_8^L \times 10^2$	F	RSS
	(g/l)	(l/g)	(g/l)	(l/g)		(g/l) ²
Single	32.8	7.28	47.9	7.45	1308.58	5.86
All	37.3	6.18	47.2	7.74	846.43	2.15

In this latter case the model is thermodynamically consistent [LeVan and Vermeulen; 1981]. Table 5.5 presents the parameters obtained when a unified value of the saturation capacity is assumed for both enantiomers. Three sets of parameters corresponding to three different situations were identified. In the first case the parameters were derived from the fit of the single solute data (third row). In the second case they were estimated from the fit of the combined set of single solute and competitive adsorption data (second row). In the third case they were determined from the fit of the adsorption data obtained with the racemic mixture alone (last row).

In previous chapters we have shown how important is to account for the extracolumn, nonideal flow behavior in order to achieve a good prediction of the overloaded band profiles. The flow nonidealities were mainly represented by the diffuse injection profiles like the ones represented in figure 3.18.

In a recycling setup like the one represented in figure 5.6, the extracolumn, nonideal flow behavior should be a major factor affecting the overall outcome of the process. Two aspects of the problem are important. First, the bands leaving the column in cycle $i-1$ have to travel for some time before reentering the column in cycle i , so there is a delay. Second, the bands receive additional dispersion when traveling through the tubing, valves, loop, pump and other devices. In order to estimate this effects, we removed the column from the setup presented in figure 5.6 and injected a tracer. From this experiment, we determined a delay

Table 5.5. Fit of the experimental adsorption data to Eq. (5.3)

Data	$n_{7,8}^{\infty}$	$K_7^L \times 10^2$	$K_8^L \times 10^2$	F	RSS
	(g/l)	(l/g)	(l/g)		(g/l) ²
Single	44.6	4.73	8.31	339.78	7.24
All	46.4	4.68	7.78	412.89	4.46
Racemate	44.5	5.29	8.26	1954.69	9.66

time of 0.77 min.

Afterwards, the overloaded band profiles were calculated using the equilibrium-dispersive model represented by equation (2.42). The parameters reported in Table 5.1 were used in the calculations and the delay time was accounted for. The results of the calculations for the initial pass and for cycle 10 are presented in figures 5.7 and 5.8, respectively .

In order to include in the model not only the delay time but also the extra-column dispersion, we decided to represent the recycling setup depicted in figure 5.6 as shown in figure 5.21. In this representation, we keep the chromatographic column with its parameters as it is in the real setup. On the other hand we replace the remaining elements of the system by a dispersion column which creates a degree of dispersion equivalent to the one originated in the real system.

We adopted for the dispersion column a one-parameter dispersion model defined by [Fogler; 1992]

$$\frac{\partial C_i}{\partial \omega} + \frac{\partial C_i}{\partial y} = \frac{1}{Pe_d} \frac{\partial^2 C_i}{\partial y^2} \quad (5.4)$$

In the above equation, the Peclet number is defined by

$$Pe_d = \frac{u_d L_d}{D_d} \quad (5.5)$$

where u_d , L_d and D_d are the superficial velocity, the length and the axial dispersion coefficient in the dispersion column, respectively.

In eq. (5.4), y is the dimensionless position variable defined as $y = l/L_d$, where

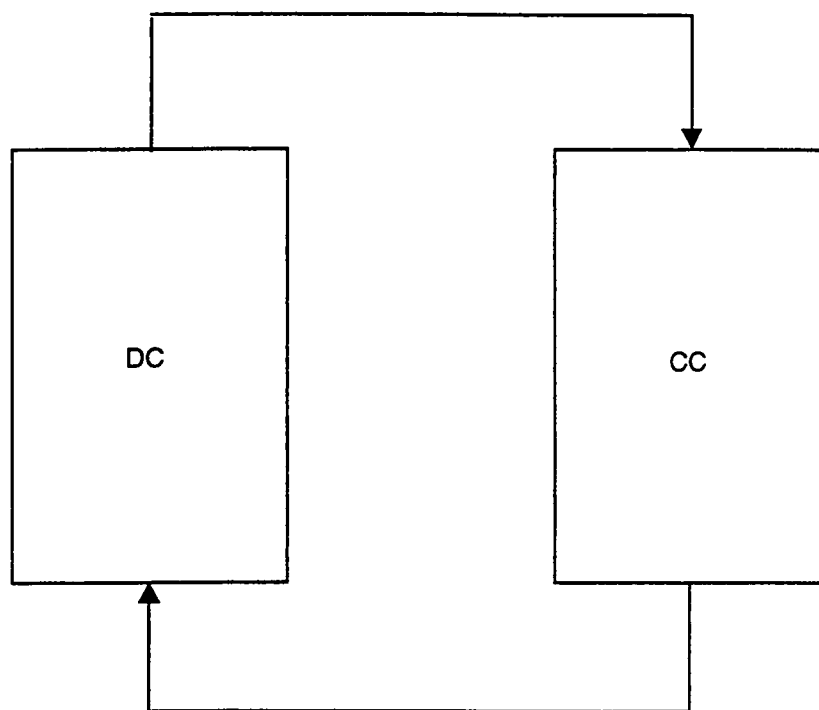


Figure 5.21 Schematic diagram of the recycling setup within the context of the model including the chromatographic column (CC) and the dispersion column (DC).

l defines the axial position taken in the direction of the flow. The dimensionless time variable ω is defined as $\omega = \frac{u_d t}{L_d}$. In order to get a good approximation of the experimental, overloaded band profiles we employed a dispersion column with a diameter of 1.0 cm, a length of 18.0 cm and characterized by a Peclet number equal to 10.0.

Equation (5.4) was solved using a reported numerical scheme of integration based on finite differences [Rhee et al., 1971]. The discretization leads to a system of linear equations which was solved using the routine F04FAF from the NAG library [NAG, 1993]. The stability conditions proposed by Rhee et al. were also used. The initial condition employed in all the calculations were the one corresponding to a column not containing any solute. The boundary condition at the column inlet is defined by the profile leaving the chromatographic column and the changes it undergoes as a result of the collected fractions and the fresh sample injected. The results of the calculations for the initial pass and cycles 1 through 10 are presented in figures 5.9 to 5.20.

5.3 Discussion.

The retention factors presented in Table 5.1 for the analytical and preparative columns are basically the same. This is a logical result since both columns were packed with the same batch of packing material. Thus, the adsorption isotherm data determined with the analytical column should be useful for the prediction

of overloaded band profiles in the preparative column.

When different adsorption capacities are assumed for each enantiomer, the values of the two sets of parameters are very close for the second enantiomer (see Table 5.4). Note in figure 5.2b that the correlation of the single solute data of E2 provided by the two sets of parameters is basically the same. On the other hand, the parameters differ somehow for the first enantiomer, specially the value of the saturation capacity. The situation is clear in Figure 5.2a, where the correlation of the single solute data given by the parameters obtained from the whole set of adsorption data deviates slightly at higher values of the concentration.

The adsorbed amounts corresponding to the competitive data of the second enantiomer calculated on the basis of the single solute parameters are also slightly underpredicted, as shown in figure 5.2b. Note in Table 5.4 that the value of the residual sum of squares (RSS) between the model estimates and the experimental data is higher when the model uses the single solute parameters. However, despite the slight deviations observed, both sets of parameters provide an adequate description of the adsorption data, as seen in figure 5.2.

When the same value of the adsorption capacity is assumed for each enantiomer, the values of the same parameter are close among the three sets (see Table 5.5). Also, the prediction of the data corresponding to the second enantiomer (see figure 5.3b) is excellent and basically independent of the particular set of parameters employed. On the other hand, the deviations between the model

predictions and the experimental data are greater in the case of the first enantiomer as shown in figure 5.3a. The smallest deviations are of course produced by the parameters obtained from the correlation of the whole set of adsorption data. The parameters obtained from the fit of the single solute data slightly underpredict the experimental adsorbed amounts for the binary mixtures. On the other hand the parameters obtained from the fit of the racemate data slightly overpredict them, specially the single solute data at higher concentrations.

It is understandable that the parameters obtained from the fit of the racemate data should deviate at higher concentrations. Recall that these correlations are basically interpolations valid within the range of concentrations studied. In the case of the racemate, the maximum experimental concentration employed for each enantiomer was 5 g/l. Thus, predictions of data beyond this value are likely to deviate. However, the fact that a reasonably good prediction of the adsorption surface can be obtained from the fit of the sole racemate data is extremely important from the practical point of view.

In practice, pure enantiomers are usually not available at the initial stages of the development of a particular separation. Accordingly, if the adsorption equilibria can be reasonably well approximated on the sole basis of the racemate adsorption data, the simulation of the separation can be performed in a straightforward fashion. The model can then be used in the scale-up or optimization procedures. As a result, the time devoted to method development can

be significantly reduced.

Initially, we decided to calculate the overloaded band profiles measured with the analytical column. We employed the equilibrium dispersive model using the experimental injection profile as the boundary condition and the competitive Langmuir isotherm, eq. (5.2) with the parameters presented in Tables 5.1 and 5.4. Since we measured the total absorption signal rather than the individual band profiles we converted the calculated total solute concentration into UV absorbance via a correlation polynomial. This second order polynomial was derived from the correlation of the absorption signal associated with the FA plateaus and the corresponding total solute concentrations. Recall that the UV absorbance is the same for both enantiomers. The calculated profiles are presented in figures 5.4 and 5.5. Note the good description of the experimental data achieved by the model.

Later we performed the calculations associated with the operation of the recycling setup. The results obtained with the model which does not include any extracolumn dispersion are presented for the initial pass and cycle 5 in figures 5.7 and 5.8, respectively. Although the position of the shocks on the time axis are properly predicted, the experimental band profiles show more dispersion, as expected.

Accordingly, the extracolumn dispersion should be included in the model in order to better predict the experimental results. The results of these calculations

are presented in figures 5.9 to 5.20. Note the significant improvement achieved. However, as shown in figure 5.20, there are still some features of the individual profiles which are not properly accounted by the model. The 'tag along ledge' of the second enantiomer which protrudes into the region of the first enantiomer is not predicted by the model. As a result, the calculated individual profile of the second enantiomer overpredicts the experimental observations since an amount of the second enantiomer was not diverted to the region of the 'tag along ledge'.

The intrusion of the first enantiomer into the region of the second enantiomer, although predicted by the model, is less pronounced than the one observed in practice. It seems that there is a need for more dispersion in the central region of the profile. The situation is important since the leading edge of the individual profile of E2 and the rear edge of the individual profile of E1 are critical to determine the windows for the collection of fractions. Still, the model as it is gives insight into the matter. Additional safety factors can be assumed in order to recover fractions enriched in E1 and E2. On the other hand, the prediction of the position of the shocks is excellent. The rear part of the profiles are also reasonably well predicted.

5.4 Conclusion on The Separation of the RPI.

The binary solute phase equilibria studied in this chapter can be well represented by the competitive Langmuir model. The parameters of the model,

derived either from the single solute, multisolute or racemate adsorption data are reasonably close. This fact is extremely important from the practical point of view. It means that a reasonable approximation of the phase equilibria can be obtained from racemate adsorption data alone. So, the process of method development, scale up and optimization can be started even before pure enantiomers are available.

The competitive Langmuir model and the equilibrium dispersive model provide an accurate representation of the experimental, overloaded band profiles obtained at the analytical scale. At the preparative scale, reasonably good estimations of the profiles were achieved. It has been shown how important is to take into account in the model the extracolumn band broadening, which ultimately determines the final outcome of the separations.

Chapter 6

Summary and Conclusions

Unique multisolute adsorption equilibrium data are presented in this study for very different experimental systems. These systems include both relatively simple stationary phases like octadecylsilica packings and more complex adsorbents like amylose derivatives coated on silica gel. The nature of the solutes also varies from rather simple structures like the ones corresponding to the light aromatic alcohols to more complicated structures like the ones corresponding to the basic drugs. The nature of the mobile phase also has a different degree of complexity. In one case it is a pure solvent like acetonitrile while in another case is a mixture of water, acetonitrile and significant amounts of inorganic ions. On the other hand, the unifying features of these systems are (i) the low molecular weight of the studied solutes, less than 2000 Da and (ii) the high efficiency of the columns employed.

It is remarkable that the multisolute adsorption data for all the systems studied follow either the IAS or the HIAS formalism. We believe that this situation is a result of the fact that in the range of low concentrations usually employed in preparative chromatography, the activity coefficients of the species involved are roughly constant in both phases at equilibrium.

The study also confirms that once the multisolute adsorption equilibria are well characterized, the equilibrium-dispersive model is an extremely useful tool which permits accurate predictions of the multisolute band profiles and system peaks for highly efficient columns. One additional factor is important, however, in order to obtain accurate predictions of the band profiles. The model of the process should account for the extracolumn dispersion of the bands in loops, pumps and other devices always used in the chromatographic instrumentation.

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Vita

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