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Use of the equilibrium-dispersive model of nonlinear gas chromatography for the modelling of the elution band profiles in the preparative-scale gas chromatographic separation of enantiomers

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Abstract

The equilibrium-dispersive model of chromatography is applied to the study of enantioselective separations of methyl 2-chloropropionate in gas chromatography. The single-component and competitive bi-Langmuir isotherm equations that describe the sorption behavior of single enantiomers and racemates, respectively, are utilized by the equilibrium-dispersive model to predict the elution band profiles of single-component and binary mixture samples. The measured and the calculated band profiles are compared both for the analytical open tubular column used to acquire the isotherm data and for the 1 m×22.5 mm I.D. preparative packed column, followed by the comparison of the enantiomeric purity vs. production curves for both the measured and the simulated systems.

Keywords: Enantiomer separation; Preparative chromatography; Equilibrium dispersive model; Band profiles; Adsorption isotherms; Nonlinear chromatography; Methyl chloropropionate

1. Introduction

In the last decade open tubular gas chromatography (GC) has become a widely used tool in the analysis of enantiomers [1]. The success of these analytical-scale separations led to efforts to extend the scope of the method to preparative-scale separations which utilize less efficient packed columns, but have higher sample capacities. Various cyclodextrin-based stationary phases have been used in the last two years to achieve preparative-scale gas chromatographic enantiomer separations on packed columns [2–5], with production rates varying in the 60 mg/h [5] to 1 g/h [2–4] range. Since optimization of these preparative-scale separations required considerable experimental effort [3,4], it would be valuable if computer modelling could be used to speed up the optimization process, similar to what is now available for the preparative-scale liquid chromatographic separations of enantiomers [6,7]. The

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equilibrium-dispersive model of nonlinear chromatography [7,8] has been extended successfully for the description of the elution band profiles of single component samples in nonlinear adsorption GC [9,10]. The aim of the present study is to use the equilibrium-dispersive model of nonlinear chromatography for the modelling of the separation of binary mixtures.

Modelling efforts in chromatography require the knowledge of the sorption isotherms of the sample components. In a previous paper [11] we determined the individual and competitive sorption isotherms of the enantiomers of a chiral synthon [12], methyl 2-chloropropionate (MCP), on a cyclodextrin-based chiral stationary phase, trichloroacetyl pentyl β-cyclodextrin [13], or AMP5. These isotherms will be used, together with the equilibrium-dispersive model of nonlinear chromatography and the relevant column efficiency data, to model the elution band profiles of the MCP enantiomers in preparative-scale GC, and the calculated profiles will be compared with those obtained experimentally (i) on the analytical, open tubular column used to acquire the isotherm data and (ii) on the 1 m×22.5 mm I.D. preparative column [5].

Success of the modelling efforts also depends on how well some of the implicit and explicit assumptions of the model (column permeability, James–Martin correction factor and parabolic pressure profile invariant along the length of the column) are satisfied. Deviations from these requirements could cause major discrepancies between the calculated and measured band profiles. If, on the other hand, reasonable agreement could be demonstrated between the predicted and experimentally determined peak profiles, computerized optimization studies would become feasible similar to those in HPLC [6,7,14].

2. Theory

The equilibrium-dispersive model of nonlinear chromatography is applicable when the mass transfer kinetics between the mobile phase and the stationary phase is fast, and when all band-broadening effects can be lumped into an apparent dispersion coefficient, D.

In GC, the elution peak profile of a single component can be obtained by solving the following system of partial differential equations [7,10]:

$$\frac{\partial PuX}{\partial z} + P\frac{\partial X}{\partial t} + \frac{RTm_g}{V_g}\frac{\partial q}{\partial t} = D\frac{\partial^2 X}{\partial z^2} \quad (1)$$

$$\frac{\partial Pu(1-X)}{\partial z} - P\frac{\partial X}{\partial t} = -D\frac{\partial^2 X}{\partial z^2} \quad (2)$$

$$q = q(P) \quad (3)$$

$$u = -\frac{1}{\Phi\eta}\frac{\partial P}{\partial z} \quad (4)$$

where P is the local pressure, u the carrier gas velocity, X the mole fraction of the analyte, z the position within the column, t the time, R the universal gas constant, T the column temperature, m_g the mass of stationary phase within the column, V_g the volume occupied by the mobile phase in the column, q the stationary phase concentration of the analyte at an analyte partial pressure of P, D the apparent dispersion coefficient, $1/\Phi$ is the column permeability and η the mobile phase viscosity. In this system of equations, Eq. 1 and Eq. 2 are the mass-balance equations of the analyte and carrier gas, respectively, Eq. 3 is the sorption isotherm and Eq. 4 the Darcy equation relating the mobile phase velocity u and the pressure gradient.

Although analytical solutions cannot be derived for this system of partial differential equations, numerical solutions can be obtained using calculation schemes first suggested by Godunov [15]. Using single-component adsorption isotherms determined for a gas–liquid and a gas–solid adsorption system, respectively, Rouchon et al. [16] and, later, Roles and Guiochon [9,10] found good agreement between the measured band profiles and the ones calculated by solving Eqs. 1–4.

The same model has been applied here to describe competitive, nonlinear GC separations. The numerical solutions for the competitive system were calculated using a first-order difference approach. The finite difference equation for analyte j reads as:

$$(uPX_j)_i^{n+1} = (uPX_j)_i^n - \frac{\Delta z}{\Delta t}\left((PX_j)_i^n + \frac{m_g RT}{V_g}\cdot q(PX_j)_i^n - \left[(PX_j)_{i-1}^n + \frac{m_g RT}{V_g}\cdot q(PX_j)_{i-1}^n \right] \right) \quad (5)$$

and for the carrier gas:

$$(uP)_i^{n+1} = (uP)_i^n - \frac{\Delta z}{\Delta t} \cdot \frac{m_g RT}{V_g} \cdot \sum_{j=1}^{k} \left[q(PX_j)_i^n - q(PX_j)_{i-1}^n \right] \quad (6)$$

where Δz and Δt are the integration increments. These equations assume essentially that the axial dispersion term is zero. To simulate the effect of axial diffusion, the ratio $\Delta z/\Delta t$ is set to $u_z/2$, where u_z, the average velocity, is:

$$u_z = \frac{u}{1+k'} \quad (7)$$

with u as the linear velocity of the carrier gas, k' the retention factor of the analyte at infinite dilution, and Δz the height equivalent of a theoretical plate. It has been demonstrated [7,8] that in such a case the numerical errors caused by the calculation introduce a numerical dispersion which is equivalent to the axial dispersion term in Eq. 1 and Eq. 2 and which was canceled in Eq. 5 and Eq. 6.

The integrated Darcy equation relates the pressure profile as a function of the column length:

$$P(z) = P_0 \cdot \sqrt{\left(\frac{P_i}{P_0}\right)^2 - \frac{z}{L} \cdot \left[\left(\frac{P_i}{P_0}\right)^2 - 1 \right]} \quad (8)$$

where $P(z)$ is the local pressure of the mobile phase, P_i and P_o are inlet and outlet pressures, respectively, and L is column length. This equation is obtained by integrating Eq. 4, following the classical derivation [17], assuming that (i) the column permeability is independent of z and (ii) the gas viscosity is constant and independent of the composition of the mobile phase. The first assumption is certainly valid for open tubular columns, but is more questionable for packed columns. Although not quite rigorous, the second assumption is reasonable because the partial pressure of the analyte does not exceed a few mbar.

Eqs. 5–7, together with the proper choice of initial and boundary conditions and with an isotherm equation, enable the rapid calculation of elution band profiles. The single-component bi-Langmuir isotherm equation:

$$q_{(+)} = \frac{q_{Sn} b_n P_{(+)}}{1 + b_n P_{(+)}} + \frac{q_{Se(+)} b_{e(+)} P_{(+)}}{1 + b_{e(+)} P_{(+)}} \quad (9)$$

and the competitive bi-Langmuir isotherm equation:

$$q_{(-)} = \frac{q_{Sn} b_n P_{(+)}}{1 + b_n (P_{(+)} + P_{(-)})} + \frac{q_{Se} b_{e(+)} P_{(+)}}{1 + b_{e(+)} P_{(+)} + b_{e(-)} P_{(-)}} \quad (10)$$

were used with parameters taken from Ref. [11] and listed here in Table 1 (in the isotherm equations q_{Sn} is the nonselective saturation capacity of the stationary phase, $q_{Se(+)}$ is the enantioselective saturation capacity of the stationary phase, b_n is a nonselective parameter characteristic of both the analyte and the stationary phase, and $b_{e(+)}$ is an enantioselective parameter characteristic of both the analyte and the stationary phase).

3. Experimental

The single-component and the competitive bi-Langmuir isotherms for the enantiomers of methyl 2-chloropropionate (MCP) were determined on the chiral stationary phase trichloroacetyl pentyl β-

Table 1
Isotherm parameters for single component (bi-Langmuir, 8 parameters for the two enantiomers) and racemic (competitive bi-Langmuir, 5 parameters for the two enantiomers) MCP on AMP5 at 60°C

	Enantiomer	$q_{Sn} \pm$S.D.	$b_n \pm$S.D.	$q_{Se} \pm$S.D.	$b_e \pm$S.D.
Single-component (bi-Langmuir)	*(R)*-(+)	$(4.3 \pm 0.3) \cdot 10^{-7}$	$(9.6 \pm 0.8) \cdot 10^{5}$	$(1.53 \pm 0.15) \cdot 10^{-9}$	$(5.6 \pm 0.2) \cdot 10^{6}$
	(S)-(−)	$(3.2 \pm 0.2) \cdot 10^{-7}$	$(1.42 \pm 0.09) \cdot 10^{5}$	$(3.4 \pm 0.2) \cdot 10^{-9}$	$(6.6 \pm 0.3) \cdot 10^{6}$
Two-component (competitive bi-Langmuir)	*(R)*-(+)	$9.66 \cdot 10^{-7}$	$3.45 \cdot 10^{4}$	$1.45 \cdot 10^{-8}$	$8.81 \cdot 10^{5}$
	(S)-(−)	$9.66 \cdot 10^{-7}$	$3.45 \cdot 10^{4}$	$1.45 \cdot 10^{-8}$	$2.06 \cdot 10^{6}$

cyclodextrin (AMP5), coated onto the walls of a megabore open tubular column, using the elution by characteristic points method [11]. The isotherms were used for the modelling of the packed column without modifications. The isotherm parameters are listed in Table 1.

The single-component band profiles used in the first part of this work were also obtained from the prior studies that were completed using the megabore open tubular column [11]. The peak profiles for the competitive case were recorded with a 1 m×22.5 mm I.D. packed column containing the same AMP5 stationary phase and are taken from the preparative-scale studies described in Ref. [4]. Some of the pertinent characteristics of the two columns are listed in Table 2.

In order to study the contributions of the injection step to the recorded peak profiles in the single-component case, a series of measurements were made on the HP 5890 II gas chromatograph (Hewlett-Packard, Avondale, PA, USA), in which the 30 m long megabore open tubular column was replaced with a 50-cm-long section of deactivated, 250 μm I.D. fused-silica tubing (J and W Scientific, Folsom, CA, USA). Since all other conditions were the same as in [11], the recorded signals represent the time histories of analyte transfer during the overloaded elution separations.

The finite difference algorithm of the equilibrium-dispersive model has been implemented in Fortran 77, compiled, and run on either a Vax mainframe (calculation time ca. 10–20 s for a single component, 5000 theoretical plates) or an Intel 80486-DX4 personal computer (calculation time ca. 3–4 min for a single component, 5000 theoretical plates). The input parameters for each simulation are: the column efficiency, the phase ratio, the injected sample amount and the respective sorption isotherms.

4. Results and discussion

4.1. Single-component elution profiles obtained on the megabore open tubular column

The equilibrium-dispersive model of nonlinear GC was used to calculate the elution band profiles for the more retained *S*-(−) enantiomer of MCP using the operating conditions applied with the megabore open tubular column. The elution band profiles were measured and calculated for the same, increasing sample loads: 11.4, 21.8, 64.8, 127, 183, 226 and 287 μg *S*-(−) MCP injected onto the column. Fig. 1 shows both the measured band profiles (above) and the simulated band profiles (below). The isotherm parameters listed in Table 1 were calculated by ECP from the elution band profile of the 287 μg injection.

Though the agreement between the calculated and the measured band profiles for the largest injection is good, it cannot be construed as a validation of the model, since ECP assumes ideal chromatography and the equilibrium-dispersive model merely introduces a minor correction for band spreading due to a finite column efficiency. At lower loads, the shapes of the measured bands and the calculated bands are similar, except that the diffuse portions of the recorded bands do not coincide as they do for the calculated bands. Also, the peak maxima occur sooner in the measured chromatograms than in the simulated chromatograms.

The first phenomenon can be interpreted as an artifact in the measured chromatograms, which is caused by the delayed transfer of the sample from the injector to the capillary. If the sample transfer is delayed, the injection profile does not correspond to a Dirac-pulse, as assumed in the calculation, and the diffuse parts of the chromatograms may no longer coincide. To verify the validity of this explanation, a

Table 2
Column characteristics for the open tubular column and the packed column used in this work

Column format	Column I.D.(mm)	ΔP across column (atm)[a]	Stationary phase amount (g)	Phase ratio	Number of theoretical plates	
					R-(+)	*S*-(−)
Capillary	0.540	0.167	$8.07 \cdot 10^{-3}$	850	5750	4170
Packed	22.5	3.8	44	3.6	600	410

[a] 1 atm = 101 325 Pa.

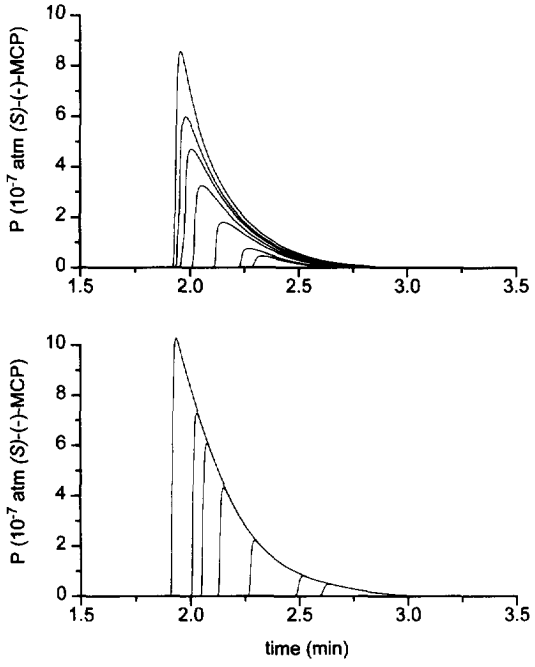

Fig. 1. Comparison of the measured (top) and calculated (bottom) elution band profiles corresponding to the injection of 11.4, 21.8, 64.8, 127, 226 and 287 μg *S*-(−) MCP onto the AMP5-coated megabore open tubular column. Experimental conditions: 30 m× 0.540 mm column, 0.15 μm film thickness; hydrogen carrier gas at 50 cm/s linear velocity; temperature, 60°C, isothermal.

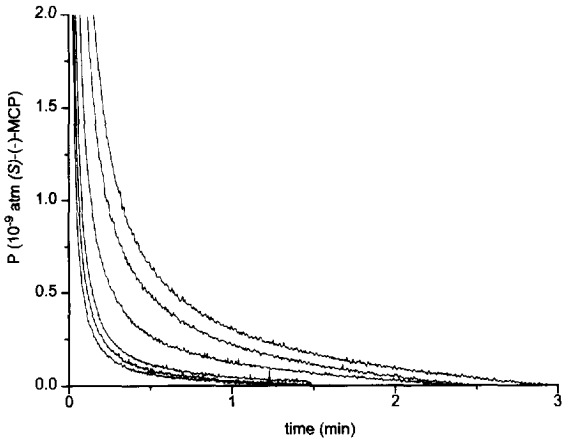

Fig. 2. Comparison of the diffuse portion of the realigned transfer profiles (see text) corresponding to 25, 65, 130, 180, 230 and 290 μg injections. Band mass centers are realigned to t=0. Experimental conditions: 0.50 m×0.250 mm connecting capillary, deactivated but uncoated; hydrogen carrier gas at 50 cm/s linear velocity; temperature, 60°C, isothermal.

series of experiments were made in which the open tubular column was replaced by a short segment (0.5 m) of deactivated 250 μm I.D. capillary tube. Then, a series of injections were made at the 25, 65, 130, 180, 230 and 290 μg levels and the band profiles were again recorded. The bands obtained in the larger injections were much wider, both at the front and at the back, than the ones obtained in the smaller injections. The positions of the mass centers of the bands were calculated and the peaks were realigned so that their mass centers coincided. The diffuse parts of the realigned peaks are shown in Fig. 2. When compared at identical signal levels, these profiles exhibit an almost 2-min-long shift between the diffuse portions of the bands obtained for the smaller injections and the larger injections, validating the proposed explanation.

The second phenomenon can be also interpreted as an error in the calculated chromatograms stemming from a systematic error made in the determination of the adsorption isotherms. Since the isotherm is derived from the largest injection [11], in which the delayed sample transfer leads to a diffuse peak tail that extends far beyond what it should (see Fig. 2), the calculated isotherm over-estimates the stationary phase concentrations (and consequently, the solute retention) that occurs at low concentrations.

Therefore, if exact band profile matching is to be achieved in the future, an experimental procedure has to be designed that ensures that the normalized injection profiles are identical, both in the isotherm determinations and in the band profile comparisons.

4.2. Single-component elution profiles obtained on the 1 m×22.5 mm I.D. packed column

Two drastic changes occur in the experimental conditions when one changes from the megabore open tubular column to the 1 m×22.5 mm I.D. packed column: (i) the phase ratio decreases by about 200-fold, (ii) the column efficiency decreases by about tenfold (Table 2). Therefore, the feasibility of scale-up was tested first by injecting the more retained *S*-(−) MCP enantiomer (about 95% e.e.) alone and recording the elution band profiles at 19,

43, 103, and 212 mg loads. Fig. 3 shows both the measured (top) and the simulated (bottom) chromatograms. As before, the general shapes of the measured and calculated bands agree, but the diffuse parts of the recorded elution band profiles do not coincide and the peak maxima occur at shorter retention times. The same two factors as in the case of the megabore open tubular columns are believed to be the cause of the observed behavior.

4.3. Competitive enantiomer band profiles obtained on the 1 m×22.5 mm I.D. packed column

Finally, the equilibrium-dispersive model of nonlinear GC was used to calculate the elution band profiles for racemic MCP samples and these profiles were compared with those obtained by using the 1 m×22.5 mm I.D. packed column. Since in this case both enantiomers compete for the same sites in the stationary phase, the competitive bi-Langmuir isotherm (bottom part in Table 1) was used for the calculations. Fig. 4 compares the elution band profiles for the injection of 37 mg of racemate, which corresponds to the touching band situation. The calculated band profiles are shown by the solid lines, the measured chromatograms by the dotted traces. The peak tail positions for both the less retained enantiomer, *R*-(+), and the more retained enantiomer, *S*-(−), agree well. However, in agreement with the assumption made earlier that the isotherm would slightly, but systematically, overestimate the extent of analyte sorption in the low-to-medium concentration range, the calculated bands appear to be somewhat more retained than the measured ones, especially for the less strongly binding component.

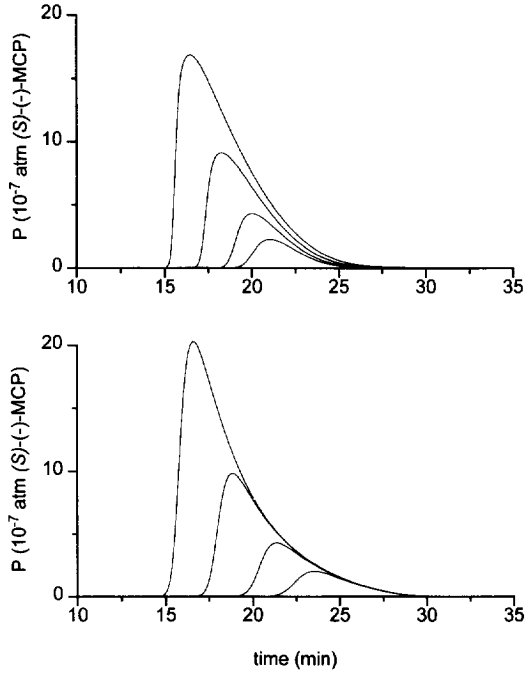

Fig. 3. Comparison of the measured (top) and calculated (bottom) elution band profiles corresponding to the injection of 19, 43, 103 and 212 mg *S*-(−) MCP onto the preparative column. Experimental conditions: 1.0 m×22.5 mm I.D. packed column, 20% (w/w) AMP5; hydrogen carrier gas at 8 cm/s linear velocity; temperature, 60°C, isothermal.

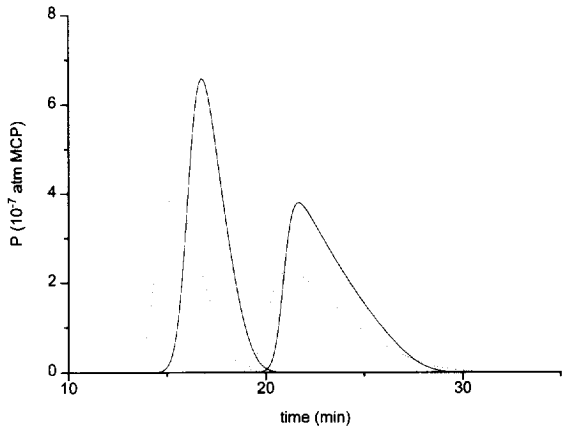

Fig. 4. Comparison of the measured (dotted line) and calculated (solid line) elution band profiles corresponding to the injection of 37 mg racemic MCP onto the AMP5-coated 1 m×22.5 mm I.D. packed column. For conditions, see the legend to Fig. 3.

Fig. 5 compares the elution band profiles for the injection of 205 mg of racemate, which results in analyte partial pressures close to those used in the isotherm determinations. The calculated band profiles (solid lines) agree well with the measured chromatograms (dotted traces). This good agreement between measured and calculated elution profiles indicates that the equilibrium-diffusive model, coupled with sorption isotherms determined with the help of a highly permeable megabore open tubular column, can indeed be used to calculate the band profiles that can be obtained with a packed column of moderate separation efficiency. The agreement suggests that the column permeability is reasonably

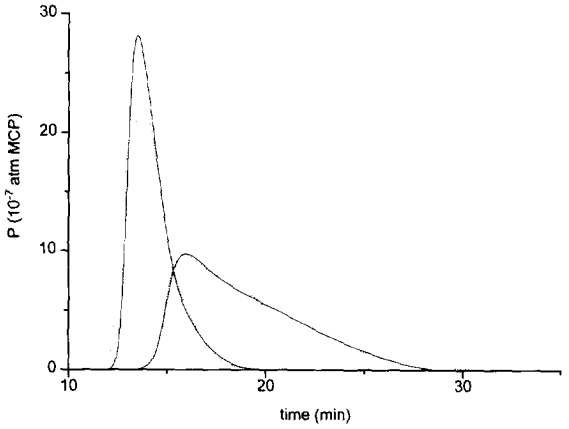

Fig. 5. Comparison of the measured (dotted line) and calculated (solid line) elution band profiles corresponding to the injection of 205 mg racemic MCP onto the AMP5-coated 1 m×22.5 mm I.D. packed column. For conditions, see the legend to Fig. 3.

constant along the column, although local fluctuations of the permeability may explain some of the slight differences between calculated and recorded band profiles.

Not surprisingly, when the purity vs. production curves are calculated from the measured and the calculated band profiles at the 205 mg injection level, the agreement is excellent, as shown in Fig. 6. The slight difference is that in the measured case, the purity of the more retained enantiomer is uniformly slightly lower than the calculated value throughout

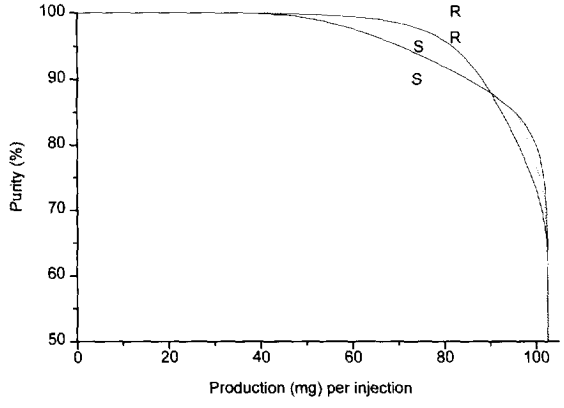

Fig. 6. Comparison of the enantiomeric purity vs. production curves calculated from the measured (dotted line) and simulated (solid line) elution band profiles corresponding to the injection of 205 mg racemic MCP onto the AMP5-coated 1 m×22.5 mm I.D. packed column. For conditions, see the legend to Fig. 3.

the entire range, indicating a slight carry-over (probably by adsorption on parts of the system) of the less retained enantiomer.

5. Conclusions

Elution band profiles corresponding to injections of highly enriched (95% e.e.) single enantiomer as well as racemic samples of methyl 2-chloropropionate onto both open tubular columns and packed columns containing the trichloroacetyl pentyl β-cyclodextrin stationary phase were successfully simulated using the equilibrium-dispersive model of nonlinear gas chromatography and the bi-Langmuir sorption isotherms of the enantiomers.

A systematic error, influencing the retention position of the tail of the measured peaks has been discovered and traced back to problems caused by delayed sample transfer from the injector. The same problem also leads to an overestimation of the stationary phase concentration of the analytes at low-to-medium sample loads. Good agreement was observed between the measured and the calculated band profiles, and between the measured and the calculated purity vs. production curves, when the sample loads were commensurable with the loads used in the isotherm determination. The calculation approach appears to be promising as a tool in the optimization of the preparative-scale GC separation of enantiomers, especially if some of the sample transfer problems and the carry-over problems can be minimized by improved equipment design.

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