Determination of the gas–liquid partition isotherms of the enantiomers of methyl 2-chloropropionate on trichloroacetyl pentyl β-cyclodextrin using the elution by characteristic points method

Daniel U. Staerk[a,1], Aroonsiri Shitangkoon[a], Eileen Winchester[a], Gyula Vigh[a,*],
Attila Felinger[b,c,2], Georges Guiochon[b,c]

[a]*Department of Chemistry, Texas A&M University, College Station, TX 77843-3255, USA*
[b]*Department of Chemistry, University of Tennessee, Knoxville, TN 37996-1600, USA*
[c]*Division of Chemical and Analytical Sciences, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6120, USA*

Abstract

The gas–liquid partition isotherms of the enantiomers of methyl 2-chloropropionate on a trichloroacetyl pentyl β-cyclodextrin stationary phase were determined at three different temperatures using the elution by characteristic points method. The isotherms were described using the single-component and competitive bi-Langmuir isotherm equations. The measured and calculated isotherms as well as the retention factor and separation selectivity data agree, indicating that these isotherms might be suitable for the modeling of the preparative-scale gas chromatographic separation of the enantiomers.

Keywords: Preparative chromatography; Partition isotherms; Elution by characteristic points method; Enantiomer separation; Methyl 2-chloropropionate

1. Introduction

Previously, we demonstrated [1] that the enantiomers of a chiral synthon, methyl 2-chloropropionate (MCP), could be separated by preparative gas chromatography [2,3] using a trichloroacetyl pentyl β-cyclodextrin (AMP5) stationary phase [4] in a 1 m×22.5 mm I.D. packed column. Although this separation was quite successful, the determination of the optimum operating conditions for a maximum

production rate at a specified purity of the products required considerable experimental work. It would be valuable if one could predict these optimum conditions by modeling the separation, similarly to what is now available in preparative-scale liquid chromatography of enantiomers [5,6]. However, any successful modeling attempt depends on an accurate knowledge of the sorption isotherms of the mixture components and on a proper representation of these competitive isotherms [6]. Therefore, the objective of the work reported here was to obtain the sorption isotherms of the enantiomers of MCP on the chiral stationary phase AMP5, as a first step toward the description of their band profiles in overloaded elution-mode preparative gas chromatography (GC).

* Corresponding author.
[1] Present address: Du Pont Experimental Station, P.O. Box 80228, Wilmington, DE 19880-0228 (USA).
[2] On leave from the Department of Analytical Chemistry, University of Veszprém, H-8201 (Hungary).

Although the pioneering work of Rouchon et al. [7,8] was carried out in nonlinear gas chromatography, the thrust of the research effort in this area has moved almost entirely into liquid chromatography (LC). The basic concepts are the same in both methods, except for the major role played in GC by the compressibility of the mobile phase. Furthermore, the considerable difference between the partial molar volume of the components in the mobile and stationary phase causes a sorption effect which can no longer be neglected as is done safely in LC [6]. As a consequence, a mass balance equation must be written for the mobile gas phase [7]. These additional complexities, together with the lesser interest paid so far to preparative GC explain why the field has been left unattended. As shown by the earlier results of Rouchon et al. [8], the approach used in LC [6] could be applied in GC as well.

The method of 'Elution by characteristic points' (ECP), which is often used for the determination of equilibrium isotherms between solutions and stationary phases in LC, had been developed and used in GC very long ago [9–11]. It is more practical to use ECP than frontal analysis in GC because it is difficult to prepare gas mixtures of known composition. Recently, Roles and Guiochon [12–14] have used this method to determine single-component sorption isotherms. They demonstrated the potential advantages associated with the use of a highly permeable, efficient megabore capillary column, the inner wall of which is coated with the stationary phase under study. Such columns can be prepared easily and exhibit efficiencies well in excess of several thousand theoretical plates at pressure drops of less than 0.25 atm [15]. These two particular features are important for the achievement of accurate isotherm determinations. It has always been known that ECP introduces a model error, since it is based on the use of an equation borrowed from the ideal model of chromatography, assuming an infinite column efficiency [11]. It has been demonstrated [16] that this model error introduces a relative error of less than 1% on the coefficients of a Langmuir isotherm if the column efficiency exceeds 5000 theoretical plates. As shown in the next section, a low pneumatic resistance is also important to minimize measurement errors, because of the importance of the James and Martin compressibility correction factor when the pressure drop is high and the necessary assumption of a constant column permeability over its entire length, an assumption which is not always warranted with long packed columns. The preparation of the megabore columns requires only small amounts of material, which is important when chiral stationary phase and pure analyte enantiomers are required for isotherm determinations [15]. However, the weight of stationary phase in the column must be known exactly. Errors made in this measurement limit the accuracy of the extrapolation required for the calculation of the profiles of bands eluted from preparative columns.

2. Theory

2.1. ECP procedure

In GC, the sorption isotherm of an analyte relates the stationary phase concentration of the analyte, q, to its vapor pressure, P:

$$q(P) = \frac{1}{J_3^2 RT} \int_0^P V_N(P)\, dP \qquad (1)$$

where $V_N(P)$ is the specific retention volume of the analyte corrected for the column void volume, V_M, T is the absolute column temperature, R is the molar gas constant (82.056 atm ml/mol K), and J_3^2 is the James and Martin factor:

$$J_3^2 = 1.5 \frac{(P_i/P_o)^2 - 1}{(P_i/P_o)^3 - 1} \qquad (2)$$

with P_i as the inlet pressure and P_o as the outlet pressure.

According to Conder and Young [17], the sorption isotherm can be calculated from the diffuse boundary of an analyte peak expressed as analyte partial pressure vs. specific retention volume. Eq. 1 can be rewritten as:

$$q(P) = \frac{V_M}{J_3^2 RTM_s t_0} \int_0^P (t_R(P) - t_0)\, dP \qquad (3)$$

where t_R is the retention time belonging to an integration slice, t_0 the column hold-up time mea-

sured with methane as unretained compound, and M_S the mass of the stationary phase in the column. The column void volume, V_M, is calculated from the corrected flow-rate, F_0, measured at the column outlet, using:

$$V_M = F_0 t_0 J_3^2 \qquad (4)$$

with

$$F_0 = F_M \left(\frac{T}{T_M}\right)\left(\frac{P_M - P_w}{P_M}\right) \qquad (5)$$

where F_M is the measured outlet flow-rate, T_M the ambient temperature, P_M the ambient pressure, and P_w the vapor pressure of water at temperature T_M. The last term in Eq. 5 corrects for the vapor pressure of water in the bubble-type flowmeter used.

In order to convert the detector signal to analyte partial pressure, the detector response must be determined. The partial pressure of the analyte, P, can be calculated from integration area slices by:

$$P = S_2 \cdot A(t) \cdot \Phi \qquad (6)$$

where S_2 is the sensitivity of the detector, $A(t)$ the area of the integration slice, and Φ the number of data points recorded per minute. S_2 in turn is calculated as:

$$S_2 = \frac{RT}{(1 + S_P)S_1 F_0} \qquad (7)$$

where S_1 is the response factor (the slope of the detector calibration curve) determined from a set of chromatograms, F_0 is the outlet flow-rate and S_P the inlet split ratio, given by the ratio of the corrected molar flow-rates for the column and the split vent:

$$S_P = \frac{F_0^*}{F_{SV}^*} \qquad (8)$$

The molar flow-rate for the column, F_0^*, is calculated by assuming that the carrier gas behaves as an ideal gas:

$$F_0^* = \frac{P_M V_M}{RT J_3^2 t_0} \qquad (9)$$

Likewise, the corrected molar flow-rate from the inlet split vent, F_{SV}^* is calculated by:

$$F_{SV}^* = F_{SV}\frac{(P_M - P_w)}{RT_M} \qquad (10)$$

where F_{SV} is the flow-rate measured at the split vent by a bubble flowmeter.

Once P and $q(P)$ are calculated, the experimental isotherm is obtained as the $q(P)$ vs. P curve, which then can be fitted by the chosen isotherm model. Note that the James and Martin factor (Eq. 2) is an important correction in the handling of the raw chromatographic data. This correction is calculated with the assumption that the permeability is constant all along the column. While this true for open tubular columns, wall-coated or porous layer ones, because the stationary phase layer is very thin, the validity of this assumption has never been demonstrated for packed columns. Measurements done with open tubular columns have the advantages of using an homogeneous column and one with a high permeability, hence of operating with little head pressure and with James and Martin factors close to unity.

2.2. Choice of the isotherm model

Since in a capillary column coated with a cyclodextrin-based chiral stationary phase the number of stereogenic sites is limited, the simple Langmuir isotherm [18] equation can be used to describe the measured sorption isotherm. For the less retained (R)-(+) enantiomer, the isotherm equation reads as:

$$q_{(+)} = \frac{q_{S(+)} b_{(+)} P_{(+)}}{1 + b_{(+)} P_{(+)}} \qquad (11)$$

where $q_{(+)}$ is the number of moles of (R)-(+) analyte in one gram stationary phase, and $P_{(+)}$ is the partial pressure of the analyte in the gas phase, $q_{S(+)}$ is the saturation capacity of the stationary phase. An analogous equation can be written for the (S)-(−) enantiomer.

Considering that in a cyclodextrin-based chiral stationary phase both enantioselective and non-enantioselective molecular interactions can take place between the stationary phase and the components being separated, the bi-Langmuir isotherm model [6], accounting for the effects of two different kinds of interaction sites, might describe the measured iso-

therm better. For the less retained (R)-$(+)$ enantio-mer the isotherm equation reads as:

$$q_{(+)} = \frac{q_{Sn}b_nP_{(+)}}{1 + b_nP_{(+)}} + \frac{q_{Se(+)}b_{e(+)}P_{(+)}}{1 + b_{e(+)}P_{(+)}} \qquad (12)$$

where subscripts n and e distinguish the non-enantioselective and enantioselective sites, respectively, and the two sites for each enantiomer have different saturation capacities. An analogous equation can be written for the (S)-$(-)$ enantiomer. Because the nonselective interactions are the same for both enantiomers, the coefficients, q_{Sn} and b_n, of the first term of the isotherm (Eq. 12) are the same for both enantiomers.

Since both enantiomers can vie for the limited number of stereogenic sites in the stationary phase, the competitive Langmuir isotherm equation [6,19,20] may also be considered, provided that the saturation capacity, q_{Se}, is identical for both enantiomers:

$$q_{(+)} = \frac{q_{Se}b_{(+)}P_{(+)}}{1 + b_{(+)}P_{(+)} + b_{(-)}P_{(-)}} \qquad (13)$$

An analogous equation can be written for the (S)-$(-)$ enantiomer. The denominator depends on the partial pressures of both enantiomers. The competitive Langmuir model yields three parameters for the two enantiomers.

Considering that both enantiomers may vie for both types of sites in the stationary phase, the competitive bi-Langmuir equation [6,19] might be applicable,

$$q_{(+)} = \frac{q_{Sn}b_nP_{(+)}}{1 + b_nP_{(-)} + P_{(-)}}$$
$$+ \frac{q_{Se(+)}b_{e(+)}P_{(+)}}{1 + b_{e(+)}P_{(+)} + b_{e(-)}P_{(-)}} \qquad (14)$$

An analogous equation can be written for the (S)-$(-)$ enantiomer. Since the non-enantioselective interactions of the two enantiomers are identical, the competitive bi-Langmuir model yields only five parameters for the two enantiomers.

Once the sorption isotherms of the pure enantiomers are measured, the parameters in Eqs. 11–14 can be found by nonlinear curve-fitting routines or simplex algorithms. The quality of the fit can be

assessed by comparing the measured and calculated isotherm values, as well as the measured and calculated retention factors (k') and separation selectivities (α). The retention factors can be obtained as the multiples of the phase ratio and the partition coefficients, which in turn can be calculated from the isotherm equations. For infinitely dilute analytes the k' expression becomes:

$$k'_+ = \frac{J_3^2 RTM_s t_0}{V_M} \sum q_s b_{(+)} \qquad (15)$$

Since separation selectivity is the ratio of the two retention factors, α can also be calculated from the isotherms as:

$$\alpha = \frac{\sum q_s b_{(-)}}{\sum q_s b_{(+)}} \qquad (16)$$

As a further test of the applicability of the isotherm model selected, one can compare the measured and calculated k and α values at different temperatures.

3. Experimental

A 30.0 m×540 μm I.D. fused-silica capillary, coated with a 0.15 μm thick film of the AMP5 stationary phase [4] was used to determine the sorption isotherms in the 60–80°C range (the temperature range used in our previous preparative-scale enantiomer separations [3]). The capillary column was installed in an HP 5890 II gas chromatograph, equipped with a split/splitless injector and a flame ionization detector (FID). H_2 was used as carrier gas at 50 cm/s linear velocity. The column head pressure was measured with a mercury manometer and adjusted within ±1 mm Hg, while the split flow-rates were measured with a soap-bubble flowmeter.

Racemic MCP, as well as enantiomerically enriched (R)-$(+)$ and (S)-$(-)$ MCP (about 95% ee) were obtained from Aldrich (Milwaukee, WI, USA). The individual enantiomers were further purified by preparative GC as described in [1–3] yielding products with a minimum purity of 99.8% ee.

New detector response curves were determined daily from five replicate injections of six calibration

samples covering the entire MCP concentration range encountered in the isotherm determinations. In order to find the highest column load that can be applied during the isotherm determination, increasingly larger amounts of MCP were injected onto the capillary column and the rear boundaries of the peaks were compared. At low loads, the rear boundaries follow the same common envelope, but above a certain load both the front and the rear boundaries move outward, indicating that the column load is above the limit within which Eqs. 11–14 might be applicable [17]. The highest load that was free of such distortion was selected for the isotherm determination and the measurements were repeated in triplicate.

The pressure vs. elution time profiles were calculated from the detector signal vs. elution time peak profiles, the operating conditions $(T, T_M, t_0, F_0, P_M, P_W, S_1, S_P)$ and Eqs. 2–10 using the Quattro Pro for Windows v. 5.0 (Borland, Scotts Valley, CA, USA) spreadsheet program (the spreadsheet templates are available from the authors upon request). All intermediate calculations were carried out to eight significant digits. The pressure profiles were smoothed with a Savitsky–Golay 5-point algorithm. Next, the pressure and the retention time axes were exchanged such that t as a function of P could be interpolated to 1000 points using equal logarithmic spacing [12]. This procedure weighs more heavily the initial portion of the isotherm, where most of the curvature occurs. Finally, the t vs. P profile was numerically integrated from 0 to P according to Eq. 3, yielding the $q(P)$ vs. P curve, the measured isotherm.

The isotherm models (Eqs. 11 and 12) were fitted to the measured single-component isotherms using the nonlinear regression routines of the TableCurve 2D and TableCurve 3D software packages (Jandel, San Rafael, CA, USA) yielding the respective q and b parameters for the two enantiomers. Subsequently, the parameters in Eqs. 13 and 14 were obtained by simultaneously fitting the measured isotherms of the (R)-$(+)$ and (S)-$(-)$ MCP enantiomers using a nonlinear simplex algorithm [21] and the parameters determined in the single-component fits as initial values. For the simplex procedures, the points from the three replicate measured isotherms were combined into a single large data set.
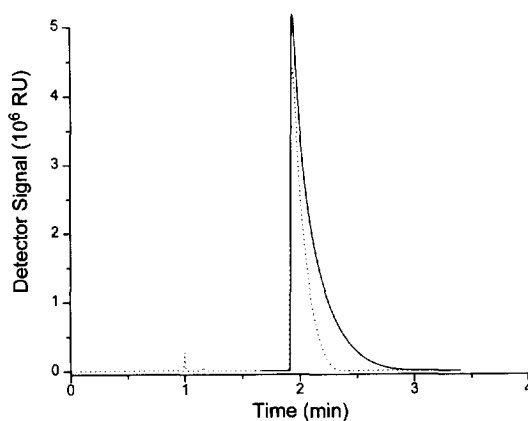

Fig. 1. Overloaded single-component chromatograms of the (R)-$(+)$ enantiomer of MCP (dotted line) and (S)-$(-)$ enantiomer of MCP (solid line) on AMP5 at 60°C.

4. Results and discussion

As an example, the overloaded chromatograms obtained for the individual injection of 20 ng (R)-$(+)$ MCP and 28 ng (S)-$(-)$ MCP at a column temperature of 60°C are shown in Fig. 1. These chromatograms were used to obtain the isotherms plotted in Fig. 2. The isotherms were fitted to the simple and the bi-Langmuir models (Eqs. 11 and 12, respectively); the various model parameter values obtained for the 60, 65 and 80°C isotherms are listed in Tables 1 and 2, for the single-component simple and bi-Langmuir models, respectively.
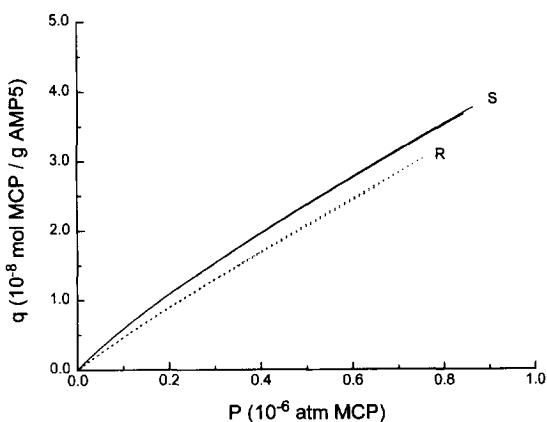

Fig. 2. Isotherm for the (R)-$(+)$ enantiomer of MCP (dotted line) and (S)-$(-)$ enantiomer of MCP (solid line) on AMP5 at 60°C.

Table 1
Isotherm parameters obtained for the simple Langmuir model fits of the measured isotherms of the MCP enantiomers on AMP5 in the 60–80°C range

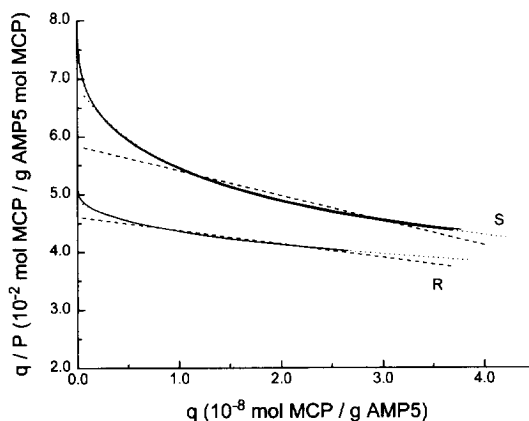| T (°C)	$q_S \pm$ S.D.	$b \pm$ S.D.
(R)-(+) Langmuir parameters:		
60	$(2.00 \pm 0.05) \cdot 10^{-7}$	$(2.32 \pm 0.05) \cdot 10^{5}$
65	$(1.94 \pm 0.04) \cdot 10^{-7}$	$(1.60 \pm 0.03) \cdot 10^{5}$
80	$(9.64 \pm 0.09) \cdot 10^{-7}$	$(1.38 \pm 0.01) \cdot 10^{4}$
(S)-(−) Langmuir parameters:		
60	$(1.37 \pm 0.03) \cdot 10^{-7}$	$(4.27 \pm 0.08) \cdot 10^{5}$
65	$(1.43 \pm 0.14) \cdot 10^{-7}$	$(2.6 \pm 0.3) \cdot 10^{5}$
80	$(9.8 \pm 0.4) \cdot 10^{-7}$	$(1.36 \pm 0.06) \cdot 10^{4}$

Fig. 3. Scatchard plot calculated for the measured (solid line), simple Langmuir model-fitted (dashed line) and bi-Langmuir model-fitted (dotted line) isotherms of the (R)-(+) enantiomer of MCP (below) and (S)-(−) enantiomer of MCP (above) on AMP5 at 60°C.

In order to assess the applicability of the different isotherm equations, the Scatchard plots (q/P vs. q) were obtained [22] and compared for the measured and calculated isotherms. The Scatchard plots calculated for the measured isotherms (solid lines) and their single-component simple Langmuir isotherms (Eq. 11, dashed lines) as well as single-component bi-Langmuir isotherms (Eq. 12, dotted lines) are compared in Fig. 3. The discrepancies are large for the simple Langmuir case, indicating that it does not adequately describe the measured isotherms. Since the competitive simple Langmuir model is based on the same q_S and b coefficients (with the restriction that q_S is the same for both enantiomers), this model need not be considered further, either. If a system follows the bi-Langmuir model, its Scatchard plot is curved [22]. The agreement is better for the bi-Langmuir case, except at very low q values, indicating that the bi-Langmuir model might adequately describe the measured single-component isotherms. Therefore, the competitive bi-Langmuir equation (Eq. 14), which uses these same parameters as the

simple bi-Langmuir equation (with the restriction that q_{Sn} and q_{Se} are the same for both enantiomers), may also provide an adequate description of the measured isotherms.

The parameters of the competitive bi-Langmuir model (Eq. 14) were obtained from the simplex procedure and are listed in Table 3. The measured and calculated isotherms for the two limiting cases (i.e. when $P_+ = 0$ and $P_- = 0$, which are accessible experimentally), are compared in Fig. 4. It can be seen that the agreement is reasonable over the partial pressure range investigated in this work.

The saturation capacities for the non-enantioselective sites are about two orders of magnitude higher than those for the enantioselective sites (Table 3). As expected, the b values are the smallest for the nonselective interactions (b_n), about ten times

Table 2
Isotherm parameters obtained for the bi-Langmuir fits of the measured isotherms of the MCP enantiomers on AMP5, in the 60–80°C range

T (°C)	$q_{Sn} \pm$ S.D.	$b_n \pm$ S.D.	$q_{Se} \pm$ S.D.	$b_e \pm$ S.D.
(R)-(+) Bi-Langmuir parameters:				
60	$(4.3 \pm 0.3) \cdot 10^{-7}$	$(9.6 \pm 0.8) \cdot 10^{5}$	$(1.53 \pm 0.15) \cdot 10^{-9}$	$(5.6 \pm 0.2) \cdot 10^{6}$
65	$(4.8 \pm 0.4) \cdot 10^{-7}$	$(5.7 \pm 0.5) \cdot 10^{5}$	$(1.39 \pm 0.15) \cdot 10^{-9}$	$(4.0 \pm 0.4) \cdot 10^{6}$
80	$(4.8 \pm 1.1) \cdot 10^{-6}$	$(2.6 \pm 0.6) \cdot 10^{3}$	$(1.6 \pm 0.3) \cdot 10^{-9}$	$(8.4 \pm 1.3) \cdot 10^{5}$
(S)-(−) Bi-Langmuir parameters:				
60	$(3.2 \pm 0.2) \cdot 10^{-7}$	$(1.42 \pm 0.9) \cdot 10^{5}$	$(3.4 \pm 0.2) \cdot 10^{-9}$	$(6.6 \pm 0.3) \cdot 10^{6}$
65	$(2.9 \pm 0.4) \cdot 10^{-7}$	$(1.06 \pm 0.16) \cdot 10^{5}$	$(2.31 \pm 0.13) \cdot 10^{-9}$	$(4.6 \pm 0.6) \cdot 10^{6}$
80	$(2 \pm 1) \cdot 10^{-6}$	$(6 \pm 3) \cdot 10^{3}$	$(3.9 \pm 0.6) \cdot 10^{-9}$	$(8.1 \pm 1.0) \cdot 10^{5}$

Table 3

Isotherm parameters obtained for the competitive bi-Langmuir model fits of the measured isotherms of the MCP enantiomers on AMP5, in the 60–80°C range

T (°C)	Nonselective		Selective		
	q_{Sn}	b_n	q_{Se}	$b_{e(+)}$	$b_{e(-)}$
60	$9.66 \cdot 10^{-7}$ [a]	$3.45 \cdot 10^{4}$ [a]	$1.45 \cdot 10^{-8}$	$8.81 \cdot 10^{5}$ [a]	$2.06 \cdot 10^{6}$
65	$6.67 \cdot 10^{-7}$ [a]	$3.17 \cdot 10^{4}$ [a]	$1.91 \cdot 10^{-8}$ [b]	$5.16 \cdot 10^{5}$ [a]	$9.11 \cdot 10^{5}$ [b]
80	$2.51 \cdot 10^{-6}$ [a]	$4.71 \cdot 10^{3}$ [a]	$1.05 \cdot 10^{-8}$ [b]	$1.45 \cdot 10^{5}$ [b]	$3.59 \cdot 10^{5}$ [b]

[a] Parameters varied over an order of magnitude.
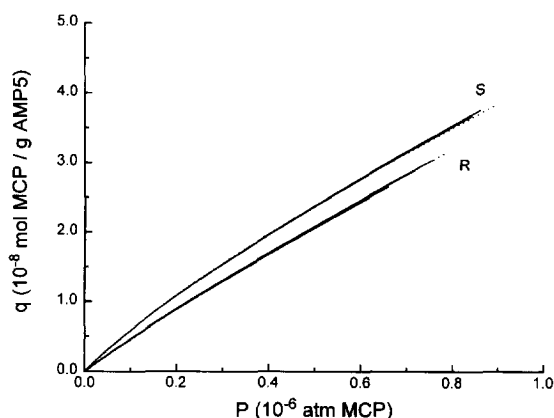[b] Parameters varied over a range of 100%.

Fig. 4. Comparison of the measured (solid line) and competitive bi-Langmuir model-fitted (dotted line) isotherms of the (R)-$(+)$ enantiomer of MCP (below) and (S)-$(-)$ enantiomer of MCP (above) on AMP5 at 60°C.

stronger for the selective interactions of the less retained R-$(+)$ enantiomer, and another several times higher for the more strongly retained S-$(-)$ enantiomer. A similar clear-cut conclusion cannot be made for the saturation capacities, though it can be argued that their value should remain more-or-less constant,

or slightly decrease, as the column temperature is increased.

Finally, in order to further test the applicability of Eq. 14 and the parameters in Table 3, one can compare the measured k' and α values with those calculated at infinite dilution for different temperatures, as shown in Table 4. While the k' values agree reasonably well and there is no systematic bias between the measured and calculated values, the calculated selectivity values are systematically slightly lower than the measured ones underestimating the chiral recognition power of the AMP5 stationary phase.

5. Conclusions

Using the enantiomers of methyl 2-chloropropionate as test analytes on a trichloroacetyl pentyl β-cyclodextrin chiral stationary phase, we demonstrated that the elution by characteristic points method can be applied successfully for the determination of their GC sorption isotherms. The measured isotherms were fitted using the single-component simple

Table 4

Retention factors and separation selectivities, measured at infinite dilution and calculated for the bi-Langmuir and competitive bi-Langmuir models, of the MCP enantiomers on AMP5, in the 60–80°C range

T (°C)	Enantiomer	Chromatographic		Bi-Langmuir		Competitive bi-Langmuir	
		k'	α	k'	α	k'	α
60	(R)-$(+)$	1.00	1.43	1.35	1.39	1.26	1.37
	(S)-$(-)$	1.43		1.88		1.72	
65	(R)-$(+)$	0.755	1.33	0.811	1.32	0.756	1.24
	(S)-$(-)$	1.005		1.007		0.942	
80	(R)-$(+)$	0.369	1.19	0.399	1.16	0.387	1.17
	(S)-$(-)$	0.439		0.462		0.452	

and bi-Langmuir models. Scatchard plots obtained for the measured and fitted isotherms indicate that the bi-Langmuir model provides a better description of the measured single-component isotherms. The parameters of the competitive bi-Langmuir model were determined using a simplex method and the measured and calculated isotherms agreed reasonably well, indicating that the isotherm might be suitable for peak profile modeling.

The fact that a simple isotherm model, such as the bi-Langmuir model, accounts well for the equilibrium data collected for the pair of enantiomers studied should not be a surprise. Interaction of either enantiomer with the chiral selector is highly specific and requires a well defined relative orientation of the two molecules. Hence, adsorption is localized and the adsorption interaction is high, which explains why the sites are saturated at rather low concentrations. The density of the chiral selectors is low and there are no sorbate–sorbate interactions. Thus, all the conventional requirements of the Langmuir isotherm model are met. Furthermore, the term corresponding to the nonselective interactions is sampled only at low concentrations and the activity coefficients of the solutes remain practically constant in that range.

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