

# General model for the achiral chromatography of enantiomers forming dimers: application to binaphthol

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## Abstract

This work deals with the development of a model for the description of the chromatographic behavior of enantiomers forming dimers on achiral stationary phases. The model describes the formation of both homochiral and heterochiral dimers by introducing two equilibrium constants,  $K_{\text{homo}}$  and  $K_{\text{hetero}}$ , which have to be independently estimated. The adsorption of both monomeric and dimeric species is described by a bi-Langmuir isotherm. Both adsorption and dimerization equilibrium models are implemented in a standard equilibrium-dispersive model of the chromatographic column. The isotherm parameters are determined by fitting of pulses constituted either of the pure enantiomers or of non racemic mixtures of both enantiomers. The validity of the model is then assessed by application to the binaphthol case.

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## 1. Introduction

The possibility of obtaining the enantiomeric enrichment of non-racemic mixtures of specific chiral compounds by chromatography on achiral stationary phases has been assessed experimentally for several systems [1–8]. Namely, 100% enantiomeric enrichment was obtained for binaphthol on an aminopropylsilica stationary phase [9]. The occurrence of this behavior is attributed to the formation of homochiral and heterochiral dimers by association of the single enantiomers present in solution. Being diastereomers with different chemical and physical properties, these dimers can be separated also without the need of a chiral selector.

In a recent paper, we developed a model for the description of the chromatographic behavior of these systems [9]. This was obtained by coupling the description of the dimerization and adsorption equilibria to a standard equilibrium dispersive model of the chromatographic column. Such a model was based on the underlying assumption that the homochiral and heterochiral dimerization constants were not indepen-

dent, namely that  $K_{\text{hetero}} = 2K_{\text{homo}}$ . This implies that the model can be applied only to those systems for which the enthalpies of formation of the homochiral and of the heterochiral dimers are the same, whereas their absolute molar entropies differ by a factor  $R \ln 2$  as it can be demonstrated through statistical arguments.

In this work, the above model is extended to the more general case, where this assumption is relaxed, i.e.  $K_{\text{hetero}} \neq 2K_{\text{homo}}$ . This is obtained by exploiting new results where it was shown how to treat this general case, and a method was developed for the determination of both homochiral and heterochiral dimerization constants from optical rotation measurements [10]. Such a general model will be then applied to the binaphthol case, whose dimerization equilibrium constants are  $K_{\text{homo}} = 1.31/\text{mol}$  and  $K_{\text{hetero}} = 3.11/\text{mol}$ .

## 2. Theory and model equations

In this section, we present the model that describes a chromatographic column where two enantiomers  $R$  and  $S$  that can form dimers according to the following reactions are present:



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For the sake of brevity, in the following only the relevant equations are given while we rely on the detailed discussion and comments reported elsewhere [9]. In the presence of the above reactions, the following relationships give the overall enantiomer concentrations in terms of monomers and dimers concentrations at every position in the column and every time (see Section 5 for the explanation of the symbols):

$$r = m_R + 2d_{RR} + d_{RS}; \quad (4)$$

$$s = m_S + 2d_{SS} + d_{RS}. \quad (5)$$

Assuming equilibrium of the dimerization reactions and ideal behavior of the liquid phase, i.e.  $d_{RR} = K_{\text{homo}}m_R^2$ ,  $d_{SS} = K_{\text{homo}}m_S^2$ , and  $d_{RS} = K_{\text{hetero}}m_Rm_S$ , these equations can be recast as a one-to-one mapping between overall concentrations and monomer concentrations:

$$r = m_R + 2K_{\text{homo}}m_R^2 + K_{\text{hetero}}m_Rm_S; \quad (6)$$

$$s = m_S + 2K_{\text{homo}}m_S^2 + K_{\text{hetero}}m_Rm_S. \quad (7)$$

The overall enantiomer concentrations in the adsorbed phase are given by the following equations:

$$\bar{r} = \overline{m_R} + 2\overline{d_{RR}} + \overline{d_{RS}}; \quad (8)$$

$$\bar{s} = \overline{m_S} + 2\overline{d_{SS}} + \overline{d_{RS}}. \quad (9)$$

The quantities on the right hand side are obtained using the adsorption isotherms of both monomeric and dimeric species, that are assumed to obey the multicomponent bi-Langmuir model:

$$\overline{m_R} = \frac{h_1m_R}{G} + \frac{a_1m_R}{B}; \quad (10)$$

$$\overline{m_S} = \frac{h_1m_S}{G} + \frac{a_1m_S}{B}; \quad (11)$$

$$\overline{d_{RR}} = \frac{h_2d_{RR}}{G} + \frac{a_2d_{RR}}{B} = \frac{h_2K_{\text{homo}}m_R^2}{G} + \frac{a_2K_{\text{homo}}m_R^2}{B}; \quad (12)$$

$$\overline{d_{SS}} = \frac{h_2d_{SS}}{G} + \frac{a_2d_{SS}}{B} = \frac{h_2K_{\text{homo}}m_S^2}{G} + \frac{a_2K_{\text{homo}}m_S^2}{B}; \quad (13)$$

$$\begin{aligned} \overline{d_{RS}} &= \frac{h_3d_{RS}}{G} + \frac{a_3d_{RS}}{B} \\ &= \frac{h_3K_{\text{hetero}}m_Rm_S}{G} + \frac{a_3K_{\text{hetero}}m_Rm_S}{B}; \end{aligned} \quad (14)$$

where the denominators  $G$  and  $B$  are:

$$\begin{aligned} G &= 1 + g_1(m_R + m_S) + g_2K_{\text{homo}}(m_R^2 + m_S^2) \\ &\quad + g_3K_{\text{hetero}}m_Rm_S, \end{aligned} \quad (15)$$

$$\begin{aligned} B &= 1 + b_1(m_R + m_S) + b_2K_{\text{homo}}(m_R^2 + m_S^2) \\ &\quad + b_3K_{\text{hetero}}m_Rm_S. \end{aligned} \quad (16)$$

This allows expressing also  $\bar{r}$  and  $\bar{s}$  in terms of the two fluid phase monomer concentrations  $m_R$  and  $m_S$ :

$$\begin{aligned} \bar{r} &= \frac{h_1m_R + 2h_2K_{\text{homo}}m_R^2 + h_3K_{\text{hetero}}m_Rm_S}{G} \\ &\quad + \frac{a_1m_R + 2a_2K_{\text{homo}}m_R^2 + a_3K_{\text{hetero}}m_Rm_S}{B} \end{aligned} \quad (17)$$

$$\begin{aligned} \bar{s} &= \frac{h_1m_S + 2h_2K_{\text{homo}}m_S^2 + h_3K_{\text{hetero}}m_Rm_S}{G} \\ &\quad + \frac{a_1m_S + 2a_2K_{\text{homo}}m_S^2 + a_3K_{\text{hetero}}m_Rm_S}{B} \end{aligned} \quad (18)$$

The chromatographic column is described using the equilibrium dispersive model, i.e. by lumping axial dispersion and mass transfer into an apparent axial dispersion coefficient. Two independent material balances can be written, most conveniently in terms of the overall enantiomer concentration, i.e.  $r$ ,  $s$ ,  $\bar{r}$  and  $\bar{s}$ :

$$\varepsilon \frac{\partial r}{\partial t} + (1 - \varepsilon) \frac{\partial \bar{r}}{\partial t} + u \frac{\partial r}{\partial z} = \varepsilon D_{ap} \frac{\partial^2 r}{\partial z^2}; \quad (19)$$

$$\varepsilon \frac{\partial s}{\partial t} + (1 - \varepsilon) \frac{\partial \bar{s}}{\partial t} + u \frac{\partial s}{\partial z} = \varepsilon D_{ap} \frac{\partial^2 s}{\partial z^2}. \quad (20)$$

The adsorbed phase concentrations  $\bar{r}$  and  $\bar{s}$  are given in terms of the fluid phase ones  $r$  and  $s$ , implicitly through Eqs. (6), (7), (17) and (18). In fact Eqs. (6) and (7) can be inverted yielding a single pair of positive values for  $m_r$  and  $m_s$ ; these are function of the concentrations  $r$  and  $s$ , and of the dimerization equilibrium constants:

$$m_R = m_R(r, s, K_{\text{homo}}, K_{\text{hetero}}); \quad (21)$$

$$m_S = m_S(r, s, K_{\text{homo}}, K_{\text{hetero}}). \quad (22)$$

Substituting the last equations into Eqs. (17) and (18), and then the resulting equations into the partial differential Eqs. (19) and (20), yields a system of two PDEs in the unknowns  $r$  and  $s$ . Once this is solved and  $r$  and  $s$  are obtained as functions of time and space, Eqs. (21) and (22) are used once more to calculate the concentrations  $m_R$  and  $m_S$ , through which the detailed fluid and solid phase compositions can be calculated. More details about this variable transformation are provided in Appendix A of [9], where the equations (A.7)–(A.11) should be replaced by:

$$\frac{\partial m_R}{\partial r} = \frac{1}{J} \frac{\partial s}{\partial m_S} = \frac{1 + 4K_{\text{homo}}m_S + K_{\text{hetero}}m_R}{J}, \quad (23)$$

$$\frac{\partial m_R}{\partial s} = -\frac{1}{J} \frac{\partial r}{\partial m_S} = -\frac{K_{\text{hetero}}m_R}{J}, \quad (24)$$

$$\frac{\partial m_S}{\partial r} = -\frac{1}{J} \frac{\partial s}{\partial m_R} = -\frac{K_{\text{hetero}}m_S}{J}, \quad (25)$$

$$\frac{\partial m_S}{\partial s} = \frac{1}{J} \frac{\partial r}{\partial m_R} = \frac{1 + 4K_{\text{homo}}m_R + K_{\text{hetero}}m_S}{J} \quad (26)$$

In these equations the parameter  $J$  is the determinant of the jacobian of the transformation  $(m_R, m_S) \mapsto (r, s)$ , defined by Eqs. (6) and (7), and it is given as:

$$\begin{aligned} J &= \frac{\partial r}{\partial m_R} \frac{\partial s}{\partial m_S} - \frac{\partial s}{\partial m_R} \frac{\partial r}{\partial m_S} \\ &= (1 + 4K_{\text{homo}}m_R + K_{\text{hetero}}m_S) \\ &\quad \times (1 + 4K_{\text{homo}}m_S + K_{\text{hetero}}m_R) - K_{\text{hetero}}^2 m_R m_S \end{aligned} \quad (27)$$

### 3. Application: binaphthol enantiomers

The general model presented above has been applied to the description of the achiral chromatography of binaphthol enantiomers. Apart from those parameters obtained by independent measurements, i.e. the homochiral and heterochiral dimerization constants and the column void fraction,  $\varepsilon = 0.73$ , the evaluation of the model parameters ( $a$ ,  $b$ ,  $h$  and  $g$ ) required the application of a fitting procedure based on chromatographic pulse experiments. These experiments were reported previously in a paper, which the reader is referred to for a detailed description of material and methods [9]. It is worth pointing out that the on-line concentration of the two enantiomers was evaluated from optical rotation,  $\alpha$ , and UV absorbance data,  $A$ , following the approach presented in [10], i.e. by solving the following system of two non-linear equations:

$$\begin{aligned} \alpha &= \mu(m_R - m_S) + \delta(m_R^2 - m_S^2) \\ &= \alpha(r, s; K_{\text{homo}}, K_{\text{hetero}}, \mu, \delta); \end{aligned} \quad (28)$$

$$\begin{aligned} A &= M(m_R + m_S) + D(d_{RR} + d_{SS}) + Ed_{RS} \\ &= A(r, s; K_{\text{homo}}, K_{\text{hetero}}, M, D, E). \end{aligned} \quad (29)$$

The values of the response parameters for optical rotation ( $\mu = 2190 \pm 130$  mdeg l/mol,  $\delta = -11000 \pm 200$  mdeg l/mol) and for UV absorbance ( $M = 32.8 \pm 0.6$  V l/mol,  $D = 71 \pm 5$  V l/mol and  $E = 156 \pm 11$  V l/mol) have also been determined previously [10]. It is worth noting that the other two parameters in the model Eqs. (19) and (20) are the superficial velocity,  $u$ , which is given, and the axial dispersion coefficient, which is accounted for through numerical dispersion using five thousand grid points in our simulations [11].

#### 3.1. Adsorption isotherms

Among the parameters appearing in the adsorption isotherms, i.e. in Eqs. (10) to Eqs. (14), the dimerization equilibrium constants are determined independently and their value is:  $K_{\text{homo}} = 1.3$  l/mol and  $K_{\text{hetero}} = 3.1$  l/mol.

The number of parameters to be estimated through the pulse fitting procedure can be reduced by imposing a few physical constraints. In particular, the molar loading capacity of the adsorption sites for monomers and dimers can be assumed to be one twice as big as the other [9]. This assumption leads to the following four relationship:

$$g_i = \frac{2g_1 h_i}{h_1} \quad (i = 2, 3); \quad (30)$$

$$b_i = \frac{2b_1 a_i}{a_1} \quad (i = 2, 3). \quad (31)$$

The above constraints reduce the number of independent parameters to be estimated to eight, i.e.:  $a_1$ ,  $a_2$ ,  $a_3$ ,  $h_1$ ,  $h_2$ ,  $h_3$ ,  $b_1$  and  $g_1$ .

#### 3.2. Monomers and homochiral dimers

The values for the adsorption isotherm parameters, i.e.  $a_1$ ,  $a_2$ ,  $b_1$ ,  $h_1$ ,  $h_2$  and  $g_1$ , corresponding to monomers and homochiral dimers have been determined by fitting the retention times of pulses constituting of a single enantiomer [9]. The best-fit values, which allowed for a rather good agreement between experimental data and model results, are:  $h_1 = h_2 = 32$ ,  $a_1 = a_2 = 38$ ,  $g_1 = g_2/2 = 74$  l/mmol, and  $b_1 = b_2/2 = 0.5$  l/mmol. It is worth noting that these values are exactly the same as those obtained previously [9], where a slightly different value for the homochiral dimerization constant had been used. In fact, it was observed that the values of the ratios  $h_2/h_1$  and  $a_2/a_1$  in the range 0.001–20 does not significantly affect the calculated retention time in the investigated range. This is an evidence that the selectivity of the stationary phase between homochiral dimers and monomers cannot be determined from our chromatographic data; this results in assuming that the infinite dilution coefficients of the two terms of the bi-Langmuir isotherm for monomers and dimers are the same, i.e. that:  $h_1 = h_2$  and  $a_1 = a_2$ . Therefore, under this assumption the value of the homochiral dimerization constant has a minor effect on the calculated retention time of the pure enantiomer.

#### 3.3. Heterochiral dimers

The values for the parameters  $h_3$  and  $a_3$ , which control the behavior of the model when simulating pulse chromatograms of mixtures of enantiomers, particularly of non-racemic mixtures, have also been estimated. This was done by repeating the fitting procedure using the equilibrium dispersive model and experimental retention times of pulses constituted of both enantiomers. As shown in Fig. 1 for pulses of different compositions solutions at 30 g/l overall concentration, a rather good qualitative and quantitative agreement was obtained. This is confirmed when the calculated elution profiles of the two enantiomers are compared with the experimental chro-

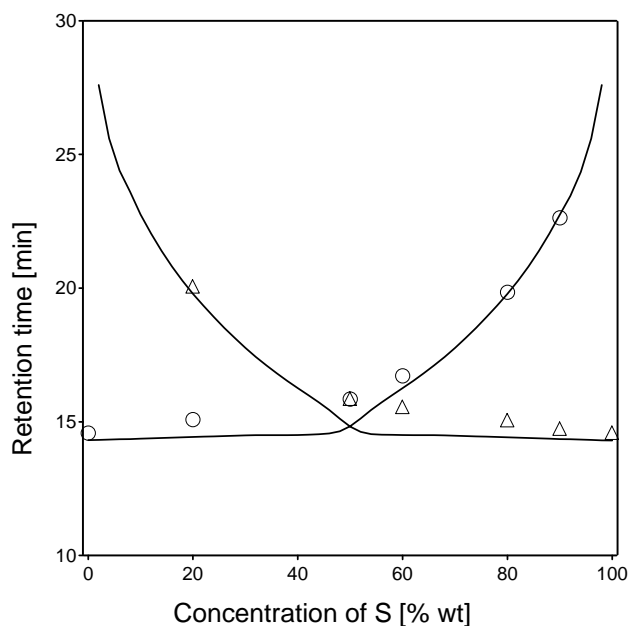
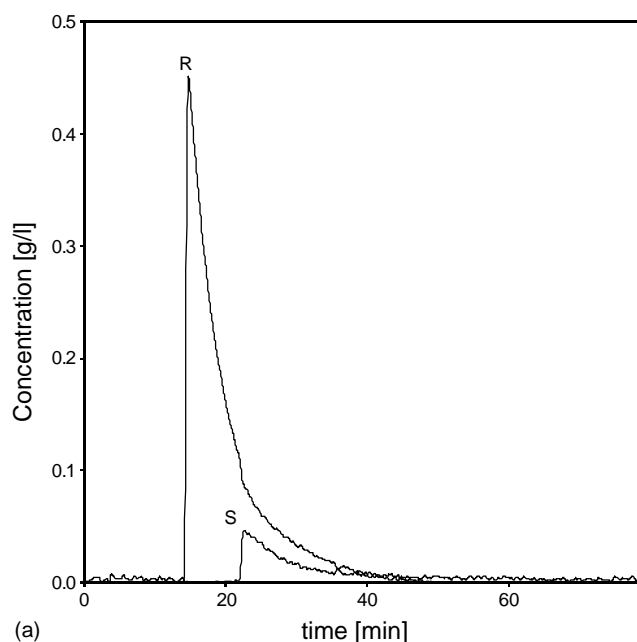


Fig. 1. Experimental (symbols) and calculated (solid line) retention times of the peak maxima of the two enantiomers for 100  $\mu$ l pulses of 30 g/l solutions at different relative compositions.

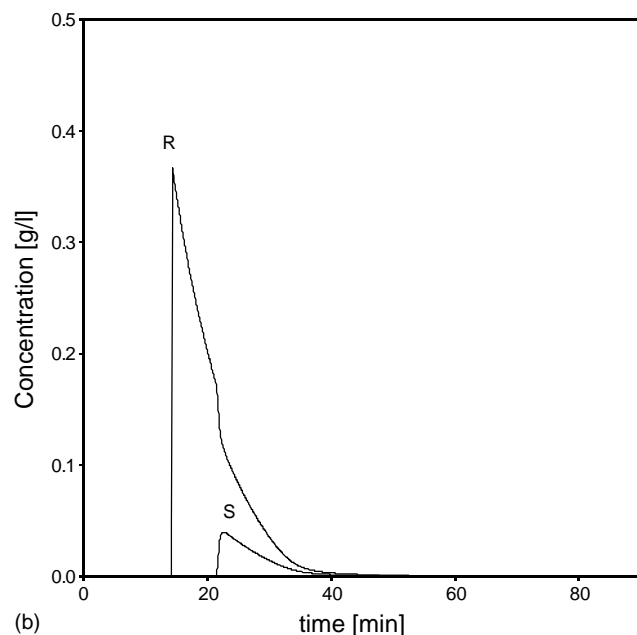
matograms. For the sake of brevity, the results of two simulation runs at different compositions are compared with the corresponding experimental chromatograms in Figs. 2 and 3. These results were obtained with the following values of the parameters:  $h_3 = 3000h_1$ , and  $a_3 = 460$ , and therefore with  $g_3 = 444 \times 10^3$  l/mmol, and  $b_3 = 12.10$  l/mmol according to Eqs. (30) and (31). It is worth noting that these selectivity values are both larger than those determined in our previous paper, where it was assumed that  $K_{\text{hetero}} = 2K_{\text{homo}}$  [9]. This is understandable, since the extent of dimerization achieved with the new dimerization constants ( $K_{\text{homo}} = 1.3$  l/mol and  $K_{\text{hetero}} = 3.1$  l/mol) is clearly smaller than that achieved with the old parameter values ( $K_{\text{homo}} = 2.4$  l/mol and  $K_{\text{hetero}} = 2K_{\text{homo}} = 4.8$  l/mol), thus requiring larger selectivity values in order to achieve the same separation factor.

#### 4. Concluding remarks

In this work, a general mathematical model for the description of the achiral chromatography of enantiomers forming dimers has been developed. With respect to previous works, the underlying assumption, which leads to a proportionality relationship relating the homochiral and heterochiral dimerization constants, has been relaxed. The validity of the model has been assessed by application to the binaphthol case. Namely, the pulse chromatograms consisting of single enantiomer and of non-racemic mixtures of both enantiomers were fitted to the model simulations,



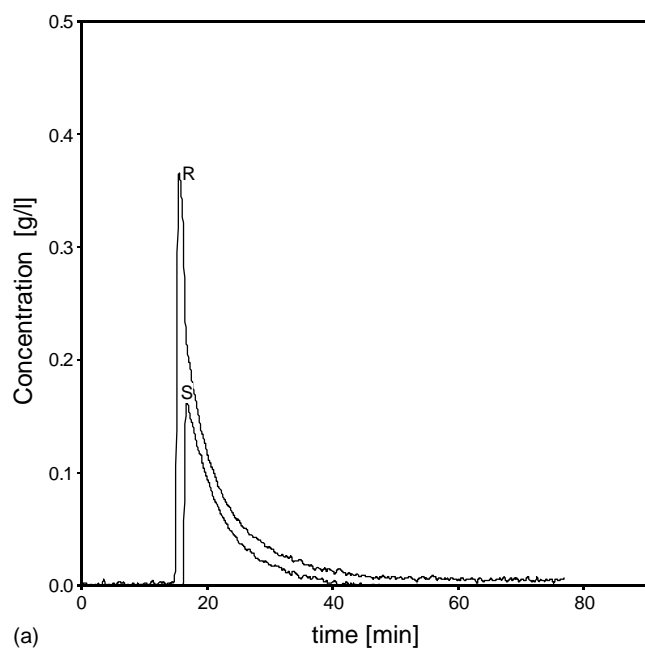
(a)



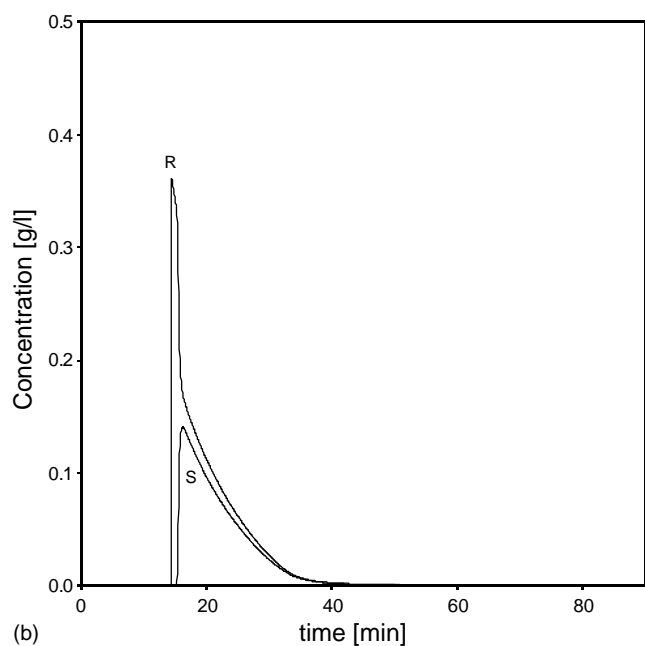
(b)

Fig. 2. Elution of a 100  $\mu$ l pulse of a 30 g/l 10/90 solution of S(–) and R(+)-1-1'-bi-2-naphthol: (a) experimental concentration profiles of the two enantiomers; (b) calculated elution profiles of the two enantiomers.

thus allowing for the estimation of the parameters of the adsorption isotherms. The resulting agreement between experiments and model results is fairly good. The developed procedure is of general validity and can be applied to any experimental system where enantiomers form dimers, provided that adsorption equilibrium occurs, that the fluid phase is diluted enough to be described as thermodynamically ideal, and that the homochiral and heterochiral dimerization constants are measured independently.



(a)



(b)

Fig. 3. Elution of a 100  $\mu$ l pulse of a 30 g/l 40/60 solution of *S*(–) and *R*(+)-1-1'-bi-2-naphthol: (a) experimental concentration profiles of the two enantiomers; (b) calculated elution profiles of the two enantiomers.

## 5. Nomenclature

$a_1, a_2, a_3$	bi-Langmuir isotherm parameters
$A$	UV absorbance (V)
$b_1, b_2, b_3$	bi-Langmuir isotherm parameters (l/mmol)
$B$	denominator in the bi-Langmuir isotherm
$c$	overall fluid concentration, $c = r + s$ (M)
$d_{ii}$	fluid concentration of dimers ( $ii = RR, SS, RS$ ) (M)

$\bar{d}_{ii}$	adsorbed concentration of dimers ( $ii = RR, SS, RS$ ) (M)
$D$	UV absorbance coefficient for homochiral dimers (V l/mol)
e.e.	enantiomeric excess
$E$	UV absorbance coefficient for heterochiral dimers (V l/mol)
$g_1, g_2, g_3$	bi-Langmuir isotherm parameters (l/mmol)
$G$	denominator in the bi-Langmuir isotherm
$h_1, h_2, h_3$	bi-Langmuir isotherm parameters
$J$	determinant of the jacobian, defined by Eq. ((27))
$K_{\text{hetero}}$	heterochiral dimerization equilibrium constant (l/mol)
$K_{\text{homo}}$	homochiral dimerization equilibrium constant (l/mol)
$m_i$	fluid concentration of enantiomers in monomeric form ( $i = R, S$ ) (M)
$M$	UV absorbance coefficient for enantiomers in monomeric form (V l/mol)
$N_i$	loading capacity in the bi-Langmuir isotherm, $N_i = h_i/g_i$ (mol/l)
$r$	overall fluid concentration of the <i>R</i> enantiomer (M)
$\bar{r}$	overall adsorbed concentration of the <i>R</i> enantiomer (M)
$R$	gas constant, $R = 0.008314$ kJ/(mol K)
$s$	overall fluid concentration of the <i>S</i> enantiomer (M)
$\bar{s}$	overall adsorbed concentration of the <i>S</i> enantiomer (M)
$t$	time (s)

### Greek letters

$\alpha$	optical rotation (mdeg)
$\delta$	polarimetric coefficient for homochiral dimers (mdeg l/mol)
$\varepsilon$	column void fraction
$\mu$	polarimetric coefficient for enantiomers in monomeric form (mdeg l/mol)

### Subscripts

$R$	<i>R</i> enantiomer
$RR$	<i>RR</i> dimer
$RS$	<i>RS</i> dimer
$S$	<i>S</i> enantiomer
$SS$	<i>SS</i> dimer

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