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Factorial design approach to studying the high-performance liquid chromatographic chiral separation of N-arylthiazolin-2-(thi)one atropisomers on CHIRALCEL OJ

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Abstract

A two-level partial factorial design was applied to quantify the effect (including the lipophilicity effect) of five selected structural parameters on the retention and chiral separation of atropisomers of N-arylthiazolin-2-(thi)one atropisomers CHIRALCEL OJ in hexane–2-propanol (9:1) and ethanol eluents. The linear correlation between the capacity factors on CHIRALCEL OJ and the lipophilicity parameter indicates the non-discriminating lipophilicity contribution of structural factors on the retention of each enantiomer. Treatment of the lipophilicity freed data indicates attractive or repulsive structural effects responsible for the discriminating interactions. This results in a clear description of the molecular area involved in the enantioselective retention of the tested compounds on CHIRALCEL OJ, thus facilitating the proposition of a chiral recognition mechanism.

1. Introduction

Chiral recognition mechanisms in supramolecular chiral stationary phases (CSPs), such as cellulose ester derivatives, appear to be highly complex and difficult to model since the discriminating sites are not clearly identified, in contrast to molecular CSPs in which the chiral selector is well defined [1–3]. Enantiomer inclusion in chiral cavities which might be multiple and competitive in cellulose-based CSPs seems to be responsible for the chiral discrimination [4]. However, few attempts to obtain quantitative relationships between solute structure and enantioselectivity on this type of CSP have been reported [5,6].

In supramolecular CSPs, one approach might be to develop a series of molecules which are structurally related and which differ by appropriate substitutions around the same framework. We have already applied the methodology of experimental research for the design of a limited series of N-arylthiazolin-2-(thi)one atropisomers in order to quantify the substitution effects on the retention of each enantiomer on cellulose-based CSPs [7,8]. Stereoselectivity results from the difference in these substitution effects between the two members of the enantiomeric couple. We have also pointed out that the lipophilic non-chiral interaction of the tested compounds with cellulose ester phases was an important parameter to be taken into account in order to link the behaviour of the different structurally related atropisomer series [9].

This paper deals with the quantitative effect (including lipophilicity effect) of the replacement

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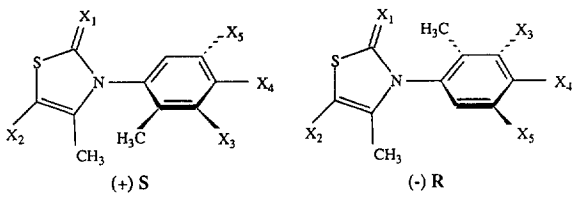

Fig. 1. Structure of N-arylthiazolin-2-(thi)one atropisomers (compounds **1–24**): X_1 = oxygen or sulphur; X_2, X_3, X_4, X_5 = hydrogen or methyl.

of a hydrogen (level −1) by a methyl group (level +1) on the chiral separation and retention of N-arylthiazolin-2-(thi)one atropisomers on commercially available tris-(*p*-methylbenzoyl)-cellulose coated on silica (CHIRALCEL OJ). The modifications of hydrogen to methyl are effected on various positions, X_2, X_3, X_4, X_5, involving the aryl ring or the heterocyclic part, where X_1 is an oxygen (level −1) or a sulphur (level +1) (Fig. 1). These modifications involve the design of 24 compounds reported in Fig. 1 with the absolute configuration. A tentative model of chiral recognition emerges from the quantitative treatment of the substitution effects.

2. Experimental

2.1. Compounds

The synthesis, stereodynamics and relationship between the sign of the rotatory power and the absolute configuration have already been described for compounds **1–8** and **17–20** [10–12]. Compounds **9–16** and **21–24** were synthesized for this study [13] from appropriate aniline dithiocarbamate and halo ketone derivatives using the same general procedure [10]. All the new compounds gave satisfactory ^1H and ^{13}C NMR and mass analyses. Each new compound was totally or partially separated into its enantiomers on a microcrystalline cellulose triacetate preparative column already described [9]. The optically pure or enriched thiazolinethione derivatives (TT) were used to prepare the corresponding thiazolinone derivatives (TO) in order to check the preservation of the sign of the rotatory power for the same absolute configuration, since the TT–TO transformation occurs without rotation around the pivot bond and thus retains the configuration [11]. The consistency of the rotatory powers and the uniformity of the elution order on a Whelk-01 column [14] give the relationship between the sign of the rotatory power and the absolute configuration as given in Fig. 1.

2.2. Eluents

All the eluents were of HPLC grade.

2.3. Chromatographic conditions and apparatus

Determination of lipophilicity parameter for compounds **9–24** was performed by reversed-phase HPLC according to the procedure previously reported for compounds **1–8** [9].

The chiral separations on CHIRALCEL OJ were performed using a commercially available column from Daicel (250 × 4.6 mm I.D., 10 μm particle size). The eluents used were hexane–2-propanol (9:1) at a flow-rate of 1 ml/min and ethanol at a flow-rate of 0.65 ml/min. The hold-up time was determined by injection of 1,3,5-tri-*tert.*-butylbenzene.

The elution order on the CHIRALCEL OJ column was determined by injection of enriched samples previously obtained as reported [9].

HPLC experiments were performed at a controlled temperature of 25°C with a Merck–Hitachi LiChrograph L-6000 HPLC pump, a Merck–Hitachi LiChrograph L-4000 UV detector (detection at 254 nm) and a Merck D-2500 recorder.

2.4. Experimental design

The methodology of experimental research [15] was used to design 24 compounds for this study. We are interested in five structural modifications which may affect the spatial steric requirement, lipophilicity, dipole moment and basicity of the heterocyclic and aryl parts of the N-arylthiazolin-2-(thi)one atropisomers, denoted X_1–X_5 (compounds **1–24**, Fig. 1). A two-level

partial factorial design of five factors was developed using a 3/4 2^5 matrix, reported in Table 1. Each structural factor has two levels: X_1 is oxygen (level −1) or sulphur (level +1), X_2–X_5 are hydrogen (level −1) or methyl (level +1). The 3/4 2^5 matrix, leading to the design of 24 compounds, was built from a linear combination of these five factors with two levels from three fractional factorial matrices 2^5 with constant independent generators: $I = 35 = -3 = -5$; $I = -35 = 3 = -5$; $I = -35 = -3 = 5$. Compounds **1**–**24** are identified by replacing the sequence of +/− signs, which affect the factors X_1–X_5, by the actual level according to the definition given above. For instance, the compound corresponding to the first line of the Table 1 for which $X_1 = X_2 = X_3 = X_4 = X_5 = -1$ corresponds to 3-(2′-methylphenyl)-4-thiazolin-2-one (**1**).

The formalism of the partial factorial design 3/4 2^5 according to a mathematical model indicates that an observable response Y can be expressed by the equation

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_5X_5 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{14}X_1X_4 + b_{24}X_2X_4 + b_{34}X_3X_4 + b_{15}X_1X_5 + b_{25}X_2X_5 + b_{45}X_4X_5 \quad (1)$$

X_1–X_5 are the main effects whereas X_iX_j are the interaction effects between variables. The coefficients in Eq. 1 were calculated using NEMROD software [16].

A positive value of a coefficient b_i for a given main factor indicates that on going from the low level to the high level of that factor, the response is increased, whereas a negative value of a coefficient indicates a decrease in the response value.

3. Results

For the 24 designed compounds, the capacity factors of both enantiomers were determined on CHIRALCEL OJ in two mobile phases: hexane–2-propanol (9:1) and ethanol. These data are reported in Table 1 according to the sign of the eluted enantiomer, since this arrangement corresponds to the absolute configuration and not according to the actual order of elution [Table 1: $k'(+)$, $k'(-)$, ln $k'(+)$, ln $k'(-)$ and ln $k'(+)/k'(-)$]. The lipophilicity parameters for all the tested compounds, expressed as log k'_w, are reported in Table 1.

The calculation of the coefficients b_i and b_{ij} according to Eq. 1 was performed for ln $k'(+)$, ln $k'(-)$ and ln $k'(+)/k'(-)$ as chiral separation responses in the two eluent systems and for the lipophilic parameter log k'_w [16]. The results are reported in Table 2.

4. Discussion

We attempted to model chiral recognition by quantifying substituent effects on the enantioselective retention of N-arylthiazolin-2-(thi)one atropisomers. Therefore, we considered that the interaction between structural factors X_1–X_5 and CHIRALCEL OJ is the result of two types of contributions: a non-discriminating lipophilic interaction and the other which amalgamates all kind of interactions responsible for the chiral discrimination by attractive or repulsive effects superimposed on the lipophilicity. The coefficients for ln $k'(+)$ and ln $k'(-)$ responses, reported in Table 2, account quantitatively for these mixed contributions.

In order to separate the non-discriminating contribution due to lipophilicity and discriminating interactions of the substituents, a stepwise procedure was applied. The first step was to consider the lipophilicity results. Inspection of the data (Table 2) indicates that the main effects on lipophilicity, expressed as log k'_w, arise from the structural modifications X_2–X_5 which have large positive coefficients, whereas the change from oxygen to sulphur (X_1 factor) does not affect the lipophilicity. The very low sensitivity of log k'_w to X_1, expressed by its very small coefficient in the log k'_w response (Table 2, $b_1 = -0.01$), indicates the independence of lipophilicity measurements from hydrogen bonding properties of the compounds, as we have already reported in a study of eight compounds belong-

Table 1
Compounds, design levels and responses as lipophilicity and chromatographic chiral separation on CHIRALCEL OJ using hexane–2-propanol (9:1) and ethanol as eluents in the 3/4 2^5 factorial design

Compound	Design level					Log k'_w	Response												
	X_1	X_2	X_3	X_4	X_5		Hexane–2-propanol (9:1)[a]							Ethanol[a]					
							$k'(+)$	$k'(-)$	α	R_s	Ln $k'(+)$	Ln $k'(-)$	Ln $k'(+)/k'(-)$	$k'(+)$	$k'(-)$	α	R_s	Ln $k'(+)$	Ln $k'(-)$	Ln $k'(+)/k'(-)$
1	−	−	−	−	−	2.62	10.02	14.40	1.44	4.7	2.30	2.66	−0.36	1.18	2.93	2.48	6.6	0.16	1.07	−0.91
2	+	−	−	−	−	2.69	28.06	67.00	2.38	12.4	3.33	4.20	−0.87	4.64	13.98	3.01	14.4	1.53	2.63	−1.10
3	−	+	−	−	−	3.18	6.42	6.42	1.00	0.0	1.86	1.86	0.00	0.83	1.81	2.18	6.8	−0.18	0.59	−0.77
4	+	+	−	−	−	3.18	18.51	39.58	2.14	8.6	2.92	3.68	−0.76	3.68	13.49	3.66	12.2	1.30	2.60	−1.30
5	−	−	+	−	−	3.12	6.47	3.89	1.66	5.1	1.86	1.36	0.50	0.69	0.37	1.86	2.5	−0.37	−0.99	0.62
6	+	−	+	−	−	3.12	19.42	10.43	1.86	7.1	2.96	2.34	0.62	2.73	1.06	2.56	5.4	1.00	0.06	0.94
7	−	+	+	−	−	3.65	4.81	2.34	2.05	6.0	1.57	0.85	0.72	0.54	0.28	1.89	3.0	−0.62	−1.26	0.64
8	+	+	+	−	−	3.59	17.78	6.42	2.77	8.2	2.87	1.86	1.02	2.52	0.88	2.86	7.6	0.92	−0.12	1.05
9	−	−	−	+	−	3.14	7.65	14.08	1.83	7.0	2.03	2.65	−0.62	0.83	1.96	2.36	5.2	−0.18	0.67	−0.86
10	+	−	−	+	−	3.25	16.20	44.45	2.74	8.5	2.78	3.80	−1.02	1.90	6.13	3.22	9.0	0.64	1.81	−1.17
11	−	+	−	+	−	3.67	4.31	5.06	1.17	1.5	1.46	1.62	−0.16	0.55	1.02	1.87	2.7	−0.60	0.02	−0.62
12	+	+	−	+	−	3.52	10.35	18.07	1.74	5.1	2.34	2.90	−0.56	1.68	5.05	3.00	17.7	0.52	1.62	−1.09
13	−	−	+	+	−	3.51	6.50	3.04	2.13	8.0	1.87	1.11	0.76	0.73	0.33	2.19	3.6	−0.31	−1.10	0.78
14	+	−	+	+	−	3.53	17.76	7.34	2.42	9.3	2.87	2.00	0.88	1.96	0.77	2.54	5.6	0.67	−0.26	0.93
15	−	+	+	+	−	4.08	4.43	1.84	2.40	5.1	1.48	0.61	0.87	0.51	0.24	2.15	3.0	−0.66	−1.43	0.76
16	+	+	+	+	−	3.97	14.45	4.28	3.37	8.2	2.67	1.45	−1.22	1.92	0.60	3.20	6.0	0.65	−0.51	1.16
17	−	−	−	−	+	3.07	6.64	8.51	1.28	2.5	1.89	2.14	−0.25	0.74	1.47	1.99	4.0	−0.30	0.38	−0.69
18	+	−	−	−	+	3.16	11.37	26.19	2.30	8.9	2.43	3.26	−0.83	1.55	4.80	3.08	8.8	0.44	1.56	−1.12
19	−	+	−	−	+	3.62	4.38	4.38	1.00	0.0	1.48	1.48	0.00	0.52	1.18	2.24	3.6	−0.64	0.16	−0.80
20	+	+	−	−	+	3.63	7.45	17.46	2.34	8.0	2.00	2.86	−0.85	1.25	5.95	4.76	10.0	0.22	1.78	−1.56
21	−	−	−	+	+	3.61	6.97	13.33	1.91	6.0	1.94	2.59	−0.64	0.87	1.16	1.32	1.5	−0.13	0.15	−0.28
22	+	−	−	+	+	3.68	8.22	26.61	3.23	12.6	2.10	3.28	−1.17	1.08	2.66	2.46	7.6	0.07	0.98	−0.90
23	−	+	−	+	+	4.16	4.10	4.73	1.15	1.0	1.41	1.55	−0.14	0.56	0.68	1.22	0.6	−0.58	−0.38	−0.20
24	+	+	−	+	+	4.06	5.34	11.86	2.22	5.5	1.67	2.47	−0.80	0.92	2.42	2.62	6.0	−0.08	0.88	−0.96

[a] Experimental conditions: temperature, 25°C; column, 250 × 4.6 mm I.D.; flow-rate, 1 ml/min [hexane–2-propanol (9:1)] and 0.65 ml/min (ethanol).

Table 2
Coefficients in response equations of lipophilicity (log k'_w) and enantiomer retention [ln $k'(+)$; ln $k'(-)$] for thiazolin(thi)ones on CHIRALCEL OJ in 3/4 2^5 factorial design

Coefficient	Log k'_w	Hexane–2-propanol (9:1)		Ethanol	
		Ln $k'(+)$	Ln $k'(-)$	Ln $k'(+)$	Ln $k'(-)$
b_0	3.59	2.06	1.95	0.02	−0.01
b_1	−0.01	0.38	0.49	0.47	0.55
b_2	0.25	−0.17	−0.31	−0.11	−0.10
b_3	0.21	−0.05	−0.74	−0.12	−1.04
b_4	0.23	−0.06	−0.07	−0.06	−0.20
b_5	0.23	−0.25	−0.23	−0.26	−0.34
b_{12}	−0.03	0.02	0.04	0.05	0.08
b_{13}	−0.01	0.05	−0.13	0.02	−0.15
b_{23}	0.01	0.05	0.08	0.02	0.02
b_{14}	−0.01	−0.05	−0.09	−0.10	−0.08
b_{24}	−0.01	−0.02	−0.06	0.00	−0.05
b_{34}	−0.02	0.09	0.01	0.11	0.11
b_{15}	0.00	−0.14	−0.10	−0:15	−0.09
b_{25}	0.00	0.00	0.02	0.00	0.05
b_{45}	0.01	0.07	0.10	0.12	0.03

ing to a 2^3 experimental design [9]. Further, the contribution to lipophilicity when hydrogen is substituted by a methyl group on the heterocycle or on whatever position of the aryl ring is the same since coefficients associated with X_2–X_5 are almost equal ($0.25 \approx 0.21 \approx 0.23 = 0.23$, log k'_w, Table 2).

In a second step, inspection of ln $k'(+)$ and ln $k'(-)$ data (Table 2) indicates that X_1 is affected by a large positive coefficient in both responses under the two elutions, which accounts for the large retention of sulphur compounds compared with oxygen analogues (Table 1). The next step in our calculations is the separation of the data into thiazolinone and thiazolinethione series, since this modification has no effect on lipophilicity, whereas it greatly affects the retention of enantiomers. This separation gives rise to a 3/4 2^4 matrix for each series. The data are treated according to the equation [16]

$$Y = b_0 + b_2X_2 + b_3X_3 + b_4X_4 + b_5X_5 + b_{23}X_2X_3 + b_{24}X_2X_4 + b_{34}X_3X_4 + b_{25}X_2X_5 + b_{45}X_4X_5 \quad (2)$$

The coefficients of the terms of Eq. 2 for ln $k'(+)$, ln $k'(-)$, ln $k'(+)/k'(-)$ and log k'_w responses are reported in Table 3 for thiazolinones and in Table 4 for thiazolinethiones.

The next step in the treatment of the data is the determination of the reference lipophilicity lines. One observes that the coefficients of the X_2–X_5 factors are positive in log k'_w response; for these factors, the lipophilicity contribution should result in negative coefficients in the ln $k'(+)$ or ln $k'(-)$ responses, since higher lipophilicity results in shorter retention in HPLC on a normal stationary phase. Thus, summing the respective coefficients for the retention and the lipophilicity responses (algebraical sum) gives the coefficients of the ln $k'(+)_d$ response, which is corrected by the lipophilicity contribution. Similar treatment using ln $k'(-)$ and log k'_w affords ln $k'(-)_d$ (Tables 3 and 4).

Similar coefficients in the ln $k'(+)_d$ and ln $k'(-)_d$ equations indicate the lipophilic effect of the corresponding structural factors. The selection of all the factors affected with similar coefficients results in a series of compounds for which ln $k'(+)$ or ln $k'(-)$ will be linearly correlated with log k'_w. [In the case of the compounds substituted only with methyl groups (as in the present report where X_2–X_5 vary from H to Me), the lipophilic coefficients of the

Table 3
Coefficients in response equations of lipophilicity (log k'_w), enantiomer retention [ln $k'(+)$; ln $k'(-)$], deviations from lipophilicity [ln $k'(+)_d$; ln $k'(-)_d$] and enantioselectivity [ln $k'(+)/k'(-)$] for thiazolinones on CHIRALCEL OJ in 3/4 2^4 factorial design

Coefficient	Log k'_w	Response equations in hexane–2-propanol (9:1)					Response equations in ethanol				
		Ln $k'(+)$	Ln $k'(-)$	Ln $k'(+)_d$	Ln $k'(-)_d$	Ln $k'(+)/k'(-)$	Ln $k'(+)$	Ln $k'(-)$	Ln $k'(+)_d$	Ln $k'(-)_d$	Ln $k'(+)/k'(-)$
b_0	3.60	1.68	1.46	5.29	5.06	0.22	−0.45	−0.56	3.15	3.04	0.11
b_2	0.27	−0.20	−0.34	0.07	−0.06	0.13	−0.17	−0.17	0.10	0.10	0.00
b_3	0.22	−0.11	−0.61	0.11	−0.39	0.50	−0.14	−0.90	0.07	−0.67	0.74
b_4	0.24	−0.01	0.00	0.22	0.24	−0.01	0.03	−0.13	0.27	0.10	0.16
b_5	0.23	−0.11	−0.13	0.11	0.10	0.01	−0.10	−0.25	0.12	−0.02	0.15
b_{23}	0.00	0.04	0.10	0.04	0.10	−0.06	0.02	0.06	0.02	0.06	−0.04
b_{24}	0.00	−0.03	−0.05	−0.03	−0.05	0.02	−0.02	−0.04	−0.02	−0.04	0.02
b_{34}	−0.02	0.07	−0.03	0.05	−0.05	0.10	0.09	0.08	0.07	0.06	0.01
b_{25}	0.00	0.01	0.01	0.01	0.02	−0.01	0.00	0.04	0.00	0.05	−0.05
b_{45}	0.01	0.08	0.09	0.09	0.10	−0.01	0.12	0.02	0.13	0.03	0.09

structural factors are almost identical even in the initial ln $k'(+)$ equations (Tables 3 and 4), since they are similar in the log k'_w equation. However, in a general case involving different types of substituents, only the corrected equations ln $k'(+$ or $-)$ have similar coefficients for pure lipophilic contributing factors.]

Inspection of the ln $k'(+)_d$ and ln $k'(-)_d$ responses in Tables 3 and 4 indicates that, on the whole, the greatest number of similar coefficients are those of ln $k'(+)_d$, meaning that the (+)-enantiomer is better correlated with the lipophilicity parameter than ln $k'(-)_d$. Thus, the lipophilicity lines are obtained by the correlation of capacity factors expressed as ln $k'(+)$ (data reported in Table 1) of the compounds presented in Fig. 2 (see below for an example of the selection of compounds), provided that the data are treated separately for the thiazolinone and thiazolinethione derivatives. For instance, inspection of the coefficients of the equation for ln $k'(+)_d$ for the thiazolinones in ethanol (Table 3) indicates that three coefficients are very similar: b_2, b_3 and b_5. The combination of the corresponding factors X_2, X_3 and X_5 with two levels (H, Me) results in compounds **1**, **3**, **5**, **7**, **17** and **19**. We first plot ln $k'(+)$ versus log k'_w for this basic set of compounds (data in Table 1) and a

Table 4
Coefficients in response equations of lipophilicity (log k'_w), enantiomer retention [ln $k'(+)$; ln $k'(-)$], deviations from lipophilicity [ln $k'(+)_d$; ln $k'(-)_d$] and enantioselectivity [ln $k'(+)/k'(-)$] for thiazolinones on CHIRALCEL OJ in 3/4 2^4 factorial design

Coefficient	Log k'_w	Response equations in hexane–2-propanol (9:1)					Response equations in ethanol				
		Ln $k'(+)$	Ln $k'(-)$	Ln $k'(+)_d$	Ln $k'(-)_d$	Ln $k'(+)/k'(-)$	Ln $k'(+)$	Ln $k'(-)$	Ln $k'(+)_d$	Ln $k'(-)_d$	Ln $k'(+)/k'(-)$
b_0	3.59	2.44	2.44	6.04	6.03	0.00	0.48	0.54	4.08	4.14	−0.06
b_2	0.22	−0.14	−0.28	0.07	−0.06	0.13	−0.05	−0.03	0.16	0.18	−0.02
b_3	0.19	0.00	−0.86	0.19	−0.67	0.86	−0.09	−1.18	0.10	−0.99	1.09
b_4	0.21	−0.12	−0.14	0.10	0.07	0.02	−0.16	−0.27	0.06	−0.05	0.11
b_5	0.23	−0.39	−0.34	−0.16	−0.10	−0.05	−0.42	−0.43	−0.18	−0.19	0.01
b_{23}	0.02	0.07	0.05	0.09	0.07	0.02	0.03	−0.02	0.05	−0.01	0.06
b_{24}	−0.03	−0.01	−0.07	−0.04	−0.10	0.06	0.02	−0.04	−0.01	−0.07	0.06
b_{34}	−0.01	0.10	0.05	0.09	0.04	0.05	0.13	0.13	0.12	0.12	0.00
b_{25}	0.01	0.00	0.02	0.01	0.04	−0.02	0.00	0.04	0.01	0.05	−0.04
b_{45}	0.00	0.06	0.10	0.06	0.10	−0.04	0.12	0.04	0.13	0.04	0.08

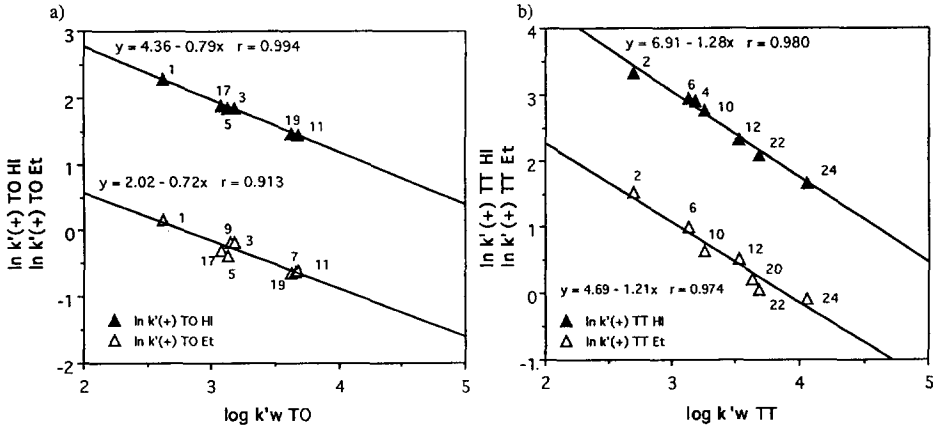

Fig. 2. Lipophilicity lines for (a) thiazolinones (TO) and (b) thiazolinethiones (TT) on CHIRALCEL OJ in hexane–2-propanol (9:1) (HI) and ethanol (Et) eluents.

more complete regression is further derived (Fig. 2a, ethanol) including all the compounds situated on or very close to the first regression. The same procedure is repeated for all the sets of data (thiazolinones, thiazolinethiones, eluent).

It appears that the slopes of the lipophilicity lines are different in the thiazolinone (TO) and thiazolinethione (TT) series, whereas they are similar regardless of the polarity of HPLC eluent. The similarity of the sensitivity in lipophilicity (given by the slope) might be taken as an intrinsic property of the CSP.

Figs. 3 and 4 report all the experimental data for (+)-enantiomers with respect to the lipophilicity lines. Figs. 5 and 6 report the experimental data for (−)-enantiomers and also lipophilicity lines and parallel (dotted lines) to those going through the reference compound **1** or **2** in which X_2–X_5 are hydrogen.

Figs. 3–6 clearly reveal the enantiomers more retained or less retained than expected on lipophilicity grounds, by considering their relative position above or below the lipophilicity lines and parallels, respectively. For instance, Fig. 4b indicates that (+)-enantiomers **4**, **8**, **14** and **16** are more retained than expected whereas (+)-enantiomer **18** is less retained than expected on lipophilicity grounds.

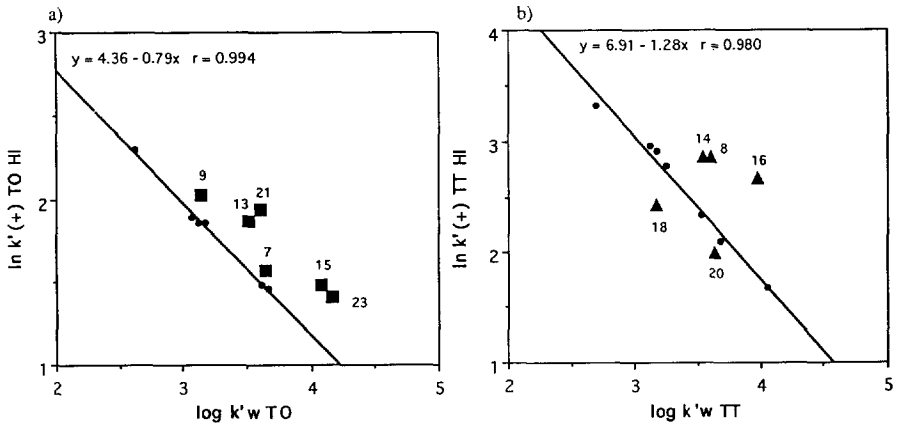

Fig. 3. Plots of (+)-enantiomer retention [ln $k'(+)$] on CHIRALCEL OJ in hexane–2-propanol (9:1) (HI) versus log k'_w with respect to the lipophilicity line for (a) thiazolinones (TO) and (b) thiazolinethiones (TT).

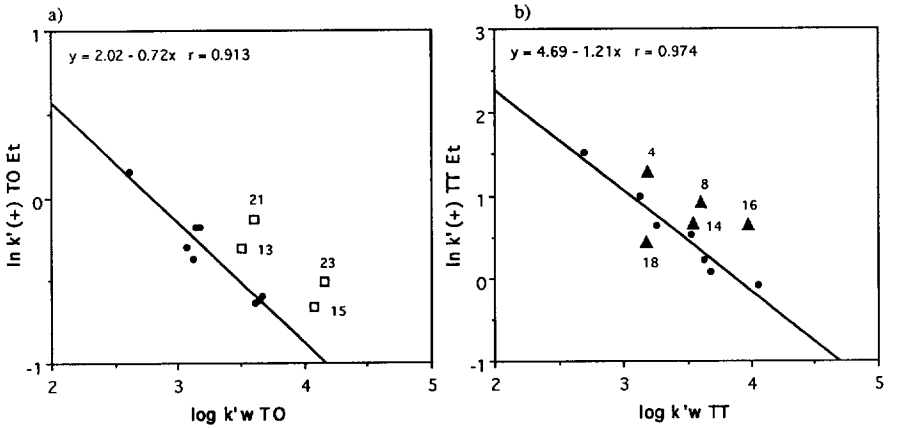

Fig. 4. Plots of (+)-enantiomer retention [ln $k'(+)$] on CHIRALCEL OJ in ethanol (Et) versus log k'_w with respect to the lipophilicity line for (a) thiazolinones (TO) and (b) thiazolinethiones (TT).

The (−)-enantiomers of the reference compounds **1** and **2** exhibit an attractive effect with respect to the initial lipophilicity lines (Figs. 5 and 6), the effects of all further substitutions being considered with respect to this basic attraction expressed by the parallel to the lipophilicity line going through compound **1** or **2**. For instance, Fig. 5a indicated that (−)-enantiomers **9** and **21** are situated above whereas (−)-enantiomers **17**, **11**, **5**, **13**, **7** and **15** are situated below the lipophilicity parallel.

For all enantiomers situated above the corresponding lipophilicity line (or parallel), a neat attractive effect results owing to the particular substitution pattern whereas all the enantiomers situated below the corresponding lipophilicity line (or parallel) exhibit a neat repulsive effect owing to the substitution involved. These indications could not have been inferred without separating the lipophilic contribution from other contributions.

In order to quantify the substitution effects due to attractive or repulsive interactions, first we calculate from the equations of the lipophilicity lines (reported in Figs. 3–6) and parallel to these, the ln $k'(+)_{calc}$ and ln $k'(-)_{calc}$, which would be the logarithms of the capacity factors in the case of strict correlation with lipophilicity in

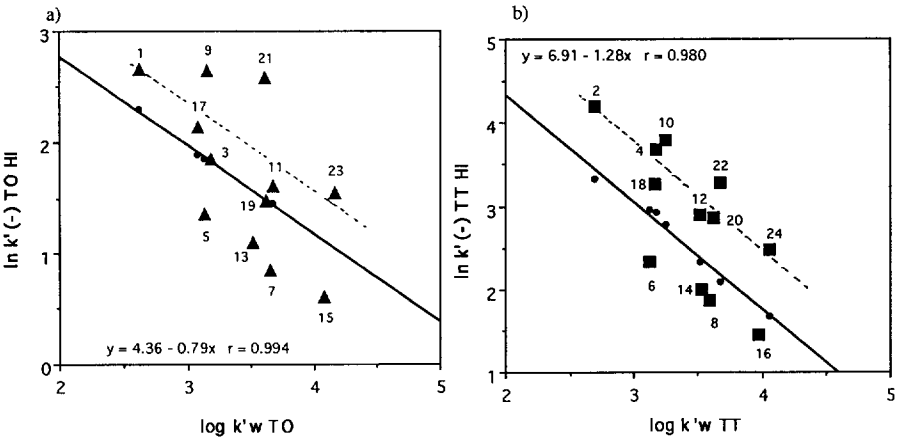

Fig. 5. Plots of (−)-enantiomer retention [ln $k'(-)$] on CHIRALCEL OJ in hexane–2-propanol (9:1) (HI) versus log k'_w with respect to the lipophilicity line for (a) thiazolinones (TO) and (b) thiazolinethiones (TT).

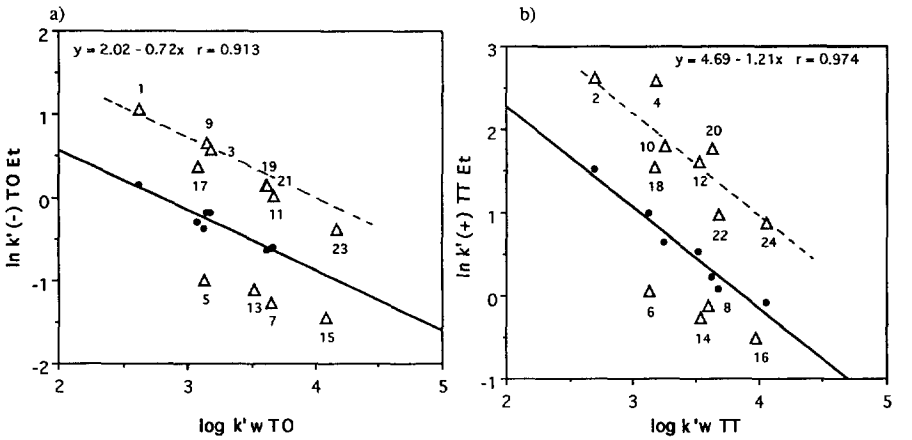

Fig. 6. Plots of (−)-enantiomer retention [ln $k'(-)$] on CHIRALCEL OJ in ethanol (Et) versus log k'_w with respect to the lipophilicity line for (a) thiazolinones (TO) and (b) thiazolinethiones (TT).

the absence of any other effect on retention. Comparison of these calculated values with experimental data (reported in Table 1) affords ln $k'(+)_D$ and ln $k'(-)_D$, which express the experimental deviations from these theoretical data sets. All these data are reported in Tables 5 and 6.

Treatment of the data in Tables 5 and 6 according to Eq. 2 results in the coefficients reported in Tables 7 and 8.

Inspection of the ln $k'(+)_D/k'(-)_D$ response coefficients shows which factors are responsible for the chiral discrimination, whereas inspection of the ln $k'(+)_D$ and ln $k'(-)_D$ response coefficients shows which structural zones are responsible for the retention of the individual enantiomers. Inspection of all ln $k'(+)_D/k'(-)_D$ response coefficients (Tables 7 and 8) indicates that, regardless of the elution system or series of compounds, the most significant discriminating factor is X_3 (coefficients 0.50, 0.74, 0.86, 1.08). However, other substitution factors induce weak discriminating effects expressed by the coefficients given in bold type [ln $k'(+)D/k'(-)_D$, Tables 7 and 8]. The origin of all these effects can be evidenced by considering each response

Table 5
Calculated values on the lipophilicity line [ln $k'(+)_{calc}$] and on the parallel [ln $k'(-)_{calc}$] and experimental deviations of enantiomers [ln $k'(+)_D$; ln $k'(-)_D$] from these lines on CHIRALCEL OJ for thiazolinones

Compound	Eluent hexane–2-propanol (9:1)				Eluent ethanol			
	Ln $k'(+)_{calc}$	Ln $k'(-)_{calc}$	Ln $k'(+)_D$	Ln $k'(-)_D$	Ln $k'(+)_{calc}$	Ln $k'(-)_{calc}$	Ln $k'(+)_D$	Ln $k'(-)_D$
1	2.29	2.65	0.01	0.00	0.13	1.02	0.03	0.05
3	1.84	2.20	0.02	−0.34	−0.28	0.60	0.10	−0.01
5	1.88	2.25	−0.02	−0.89	−0.25	0.65	−0.12	−1.64
7	1.47	1.83	0.10	−0.98	−0.62	0.26	0.00	−1.52
9	1.87	2.24	0.16	0.41	−0.25	0.64	0.07	0.03
11	1.44	1.82	0.02	−0.20	−0.63	0.25	0.03	−0.23
13	1.58	1.94	0.29	−0.83	−0.52	0.36	0.21	−1.46
15	1.12	1.49	0.36	−0.88	−0.93	−0.05	0.27	−1.38
17	1.92	2.30	−0.03	−0.15	−0.21	0.68	−0.09	−0.30
19	1.48	1.86	0.00	−0.38	−0.61	0.28	−0.03	−0.12
21	1.50	1.86	0.44	0.72	−0.59	0.29	0.46	−0.14
23	1.06	1.43	0.35	0.11	−1.00	−0.11	0.42	−0.27

Table 6
Calculated values on the lipophilicity line [ln $k'(+)_{calc}$] and on the parallel [ln $k'(-)_{calc}$] and experimental deviations of enantiomers [ln $k'(+)_D$; ln $k'(-)_D$] from these lines on CHIRALCEL OJ for thiazolinones

Compound	Eluent hexane–2-propanol (9:1)				Eluent ethanol			
	Ln $k'(+)_{calc}$	Ln $k'(-)_{calc}$	Ln $k'(+)_D$	Ln $k'(-)_D$	Ln $k'(+)_{calc}$	Ln $k'(-)_{calc}$	Ln $k'(+)_D$	Ln $k'(-)_D$
2	3.43	4.33	−0.10	−0.13	1.44	2.53	0.09	0.09
4	2.82	3.70	0.10	−0.02	0.85	1.94	0.45	0.65
6	2.90	3.78	0.06	−1.44	0.92	2.01	0.08	−1.95
8	2.29	3.18	0.58	−1.32	0.35	1.44	0.57	−1.56
10	2.73	3.62	0.05	0.18	0.75	1.85	−0.11	−0.04
12	2.37	3.27	−0.03	−0.37	0.44	1.53	0.08	0.08
14	2.37	3.26	0.50	−1.26	0.42	1.51	0.25	−1.77
16	1.80	2.69	0.87	−1.24	−0.11	0.98	0.76	−1.49
18	2.83	3.73	−0.40	−0.47	0.86	1.96	−0.42	−0.40
20	2.23	3.13	−0.23	−0.27	0.29	1.39	−0.07	0.38
22	2.16	3.06	−0.06	0.21	0.23	1.33	−0.16	−0.35
24	1.68	2.58	−0.01	−0.11	−0.22	0.87	0.14	0.00

of enantiomer retention. Further, inspection of the ln $k'(+)_D$ and ln $k'(-)_D$ responses allows the proposition of a recognition model of the tested compounds on CHIRALCEL OJ as reported in Fig. 7, where we have represented the "supermolecule" carrying all the substituents which induce interaction effects with the CSP.

The reported effects can be inferred from the ln $k'(+)_D$ and ln $k'(-)_D$ response coefficients (Tables 7 and 8) as follows. For thiazolinones in hexane–2-propanol (9:1) (Table 7, Fig. 7a), the X_4 factor gives rise to single (coefficient b_4) or combined (coefficients $b_3 + b_4$, $b_4 + b_5$) attractive effects in both enantiomers, whereas the X_2 and X_3 factors induce weak and strong repulsive effects, respectively, in the (−)-enantiomer solely. In ethanol (Table 7, Fig. 7b), similar effects are observed for the (+)-enantiomer of thiazolinones, whereas the (−)-enantiomer is influenced only by a strong repulsion of the X_3 factor and a very weak repulsion of the X_5 factor. The situation is similar for thiazolinethione derivatives (Table 8, Fig. 7), the differences resulting only from the X_2 and X_5 factors

Table 7
Coefficients in response equations of theoretical lipophilic retention [ln $k'(+)_{calc}$; ln $k'(-)_{calc}$] and of observed deviation of retentions [ln $k'(+)_D$; ln $k'(-)_D$] for thiazolinones on CHIRALCEL OJ

Coefficient	Response equations in hexane–2-propanol (9:1)					Response equations in ethanol				
	Ln $k'(+)_{calc}$	Ln $k'(-)_{calc}$	Ln $k'(+)_D$	Ln $k'(-)_D$	Ln $k'(+)_D$/ $k'(-)_D$	Ln $k'(+)_{calc}$	Ln $k'(-)_{calc}$	Ln $k'(+)_D$	Ln $k'(-)_D$	Ln $k'(+)_D$/ $k'(-)_D$
b_0	1.49	1.87	0.18	−0.41	0.59	−0.58	0.30	0.14	−0.85	0.99
b_2	−0.22	−0.22	0.01	**−0.12**	**0.11**	−0.20	−0.20	0.02	0.03	−0.01
b_3	−0.17	−0.17	0.07	**−0.43**	**0.50**	−0.16	−0.16	0.01	**−0.73**	**0.74**
b_4	−0.19	−0.19	**0.17**	**0.19**	−0.02	−0.17	−0.17	**0.20**	0.04	**0.16**
b_5	−0.18	−0.18	0.07	0.05	0.02	−0.17	−0.17	0.06	**−0.10**	**0.14**
b_{23}	0.00	0.00	0.04	0.10	−0.06	0.00	0.00	0.02	0.06	−0.04
b_{24}	0.00	0.00	−0.03	−0.05	0.02	0.00	0.00	−0.02	−0.05	0.03
b_{34}	0.02	0.02	0.05	−0.05	**0.10**	0.01	0.02	0.08	0.07	0.01
b_{25}	0.00	0.00	0.00	0.01	−0.01	0.00	0.00	0.00	0.04	−0.04
b_{45}	0.00	−0.01	0.08	**0.10**	−0.02	0.00	0.00	**0.13**	0.03	**0.10**

Table 8
Coefficients in response equations of theoretical lipophilic retention [ln $k'(+)_{calc}$; ln $k'(-)_{calc}$] and of observed deviation of retentions [ln $k'(+)_D$; ln $k'(-)_D$] for thiazolinones on CHIRALCEL OJ

Coefficient	Response equations in hexane–2-propanol (9:1)					Response equations in ethanol				
	Ln $k'(+)_{calc}$	Ln $k'(-)_{calc}$	Ln $k'(+)_D$	Ln $k'(-)_D$	Ln $k'(+)_D$/ $k'(-)_D$	Ln $k'(+)_{calc}$	Ln $k'(-)_{calc}$	Ln $k'(+)_D$	Ln $k'(-)_D$	Ln $k'(+)_D$/ $k'(-)_D$
b_0	2.27	3.17	0.16	−0.73	0.90	0.34	1.43	0.14	−0.89	1.03
b_2	−0.28	−0.28	**0.14**	0.00	**0.14**	−0.26	−0.26	**0.20**	**0.22**	−0.02
b_3	−0.25	−0.25	**0.25**	**−0.61**	**0.86**	−0.24	−0.24	**0.14**	**−0.94**	**1.08**
b_4	−0.28	−0.28	**0.16**	**0.14**	0.02	−0.26	−0.26	**0.10**	0.01	**0.11**
b_5	−0.30	−0.30	**−0.10**	−0.04	−0.04	−0.29	−0.29	**−0.13**	**−0.14**	0.01
b_{23}	−0.02	−0.02	0.09	0.07	0.02	−0.02	−0.02	0.05	0.00	0.05
b_{24}	0.03	0.03	−0.04	**−0.11**	0.07	0.04	0.03	−0.01	−0.08	0.07
b_{34}	0.02	0.01	0.09	0.04	**0.05**	0.02	0.01	**0.11**	**0.12**	0.01
b_{25}	−0.01	−0.01	0.01	0.04	−0.03	−0.01	−0.01	0.01	0.05	−0.04
b_{45}	0.00	−0.01	0.06	**0.11**	−0.05	0.00	0.00	**0.13**	0.04	**0.09**

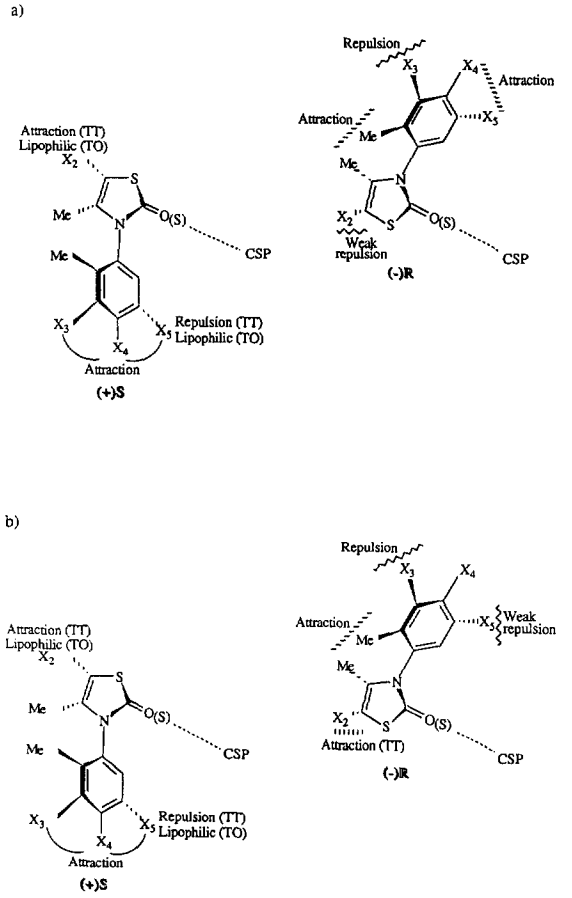

Fig. 7. Chiral recognition model of N-arylthiazolin-2-(thi)one atropisomers on CHIRALCEL OJ in (a) hexane–2-propanol (9:1) and (b) ethanol.

which give rise to an attractive and repulsive weak effect, respectively, for the (+)-enantiomer in hexane–2-propanol (9:1) and for both enantiomers in ethanol.

The recognition model of N-arylthiazolin-2-(thi)one atropisomers on CHIRALCEL OJ (Fig. 7) considers a primary interaction between the dipoles of the heterocycle part with the C=O groups of the CSP, represented by dotted lines in Fig. 7. This dipole–dipole interaction may account for the stronger retention of thiazolinethione derivatives on CHIRALCEL OJ, since the dipole moment is larger for the C=S group than for the C=O group [17,18]. Furthermore, this type of interaction may be responsible for the orientation of enantiomers towards different sites within the CSP. The results are that the behaviour of the two enantiomers is affected by different structural effects, attractive or repulsive with respect to the lipophilicity, as represented in Fig. 7. It is worth noting that the X_3 and X_5 factors, which are enantiotopic, induce generally different interactions in the two enantiomers, indicating that the insertion mechanism of the enantiomers cannot involve the same sites or orientation in these sites.

The proposed recognition model of N-arylthiazolin-2-(thi)one atropisomers on CHIRALCEL OJ holds for both hexane–2-propanol (9:1) and pure ethanol eluents. Even so, the

separations are generally better with the latter eluent.

5. Conclusion

The methodology of experimental research was used to design 24 N-arylthiazolin-2-(thi)one atropisomers which were chromatographed on CHIRALCEL OJ with two eluent systems: hexane–2-propanol (9:1) and ethanol. The mechanism of chiral recognition of the tested compounds was studied by quantification of effects (including the lipophilicity effect) of five selected structural factors on retention and enantioselectivity. The lipophilic contribution of structural factors to the retention of the studied compounds leads to a linear correlation between the capacity factors on CHIRALCEL OJ and the lipophilicity parameter. Treatment of the lipophilicity freed data according to a 3/4 2^4 experimental design shows that the replacement of a hydrogen by a methyl can result in attractive interaction with CHIRALCEL OJ as well as a strong repulsive interaction depending on the precise localization of the change. These changes affect each enantiomer in different or similar ways. The term repulsive interaction covers any kind of structural effect which actually diminishes the basic lipophilic interaction with the stationary phase; steric exclusion might be one of them. An important issue in this treatment is the description of the molecular area affecting the retention and enantioselectivity of the tested compounds on CHIRALCEL OJ, which allows the proposition of a chiral recognition model. It is worth noting that this treatment is applicable to all chiral compounds which can be connected by an experimental design.

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References

[1] W.H. Pirkle, P.G. Murray and J.A. Burke, J. Chromatogr., 641 (1993) 21–29.
[2] K.B. Lipkowitz, J. Chromatogr. A, 666 (1994) 493–503.
[3] K.B. Lipkowitz, K.M. Green, J. Yang, G. Pearl and M.A. Peterson, Chirality, 5 (1993) 51–57.
[4] E. Francotte and R.M. Wolf, Chirality, 2 (1990) 16–31.
[5] R.M. Wolf, E. Francotte and D. Lohman, J. Chem. Soc., Perkin Trans. 2, (1988) 893–901.
[6] P. Camilleri, D.J. Livingstone, J.A. Murphy and D.T., Manallack, J. Comput.-Aided Mol. Des., 7 (1993) 61–69.
[7] C. Roussel, J.L. Stein, M. Sergent and R. Phan Than Luu, in D. Stevenson and I.D. Wilson (Editors), Recent Advances in Chiral Separations, Plenum Press, New York, 1991, pp. 105–108.
[8] C. Roussel, S. Lehuédé, C. Popescu and J.L. Stein, Chirality, 5 (1993) 207–212.
[9] C. Roussel and C. Popescu, Chirality, 6 (1994) 251–260.
[10] C. Roussel, M. Adjimi, A. Chemlal and A. Djafri, J. Org. Chem., 53 (1988) 5076–5080.
[11] C. Roussel, J.L. Stein and F. Beauvais, New J. Chem., 14 (1990) 169–173.
[12] C. Roussel and A. Chemlal, New J. Chem., 12 (1988) 947–952.
[13] C. Popescu, Ph.D. Thesis, Marseilles, 1994.
[14] W.H. Pirkle, personal communication.
[15] G.E.P. Box and N.R. Draper, Empirical Model-Building and Response Surfaces, Wiley, New York, 1987.
[16] D. Mathieu and R. Phan Tan Luu, Nemrod Software, LPRAI, University of Aix-Marseilles III.
[17] C. Roussel, M. Chanon and R. Barone, in J. Metzger (Editor), Thiazole and its Derivatives, Vol. 2, Wiley, New York, 1979, Ch. 7, pp. 369–559.
[18] H. Lumbroso, Ch. Liégeois, F.A. Devillanova and G. Verani, J. Mol. Struct., 77 (1981) 239–251.