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Investigation into the chiral recognition mechanism of N-arylthiazolin-2(thi)one atropisomers on Chiralcel OJ by factorial design and lipophilicity approaches

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Abstract

The chiral recognition mechanism of N-arylthiazolin-2(thi)one atropisomers on Chiralcel OJ chiral stationary phase was investigated by quantifying the effects on the retention and enantioselectivity of the alkyl substitution in the series Me, Et, iPr, tBu, in the key position blocking the rotation and inducing chirality on both phenyl and heterocycle portions of the tested compounds. The response equation in a two-level 2^4 factorial design and the linear correlations between the capacity factors on Chiralcel OJ and the lipophilicity parameter were used. This treatment of the data results in the description of the molecular area involved in the enantioselective retention, in the case of a substitution providing complex steric and lipophilic interactions, thus allowing the validation of the proposed chiral recognition model.

Keywords: Factorial design; Chiral recognition; Chiral stationary phases, LC; Enantiomer separation; Lipophilicity; N-Arylthiazolin-2(thi)ones

1. Introduction

Chromatography on chiral stationary phases (CSPs) is now a widely-used method which has been successfully used for analytical as well as preparative purposes. As a consequence, a remarkable development in the synthesis of various chiral supports has taken place (715 CSPs [1]), making the choice of an appropriate CSP for a particular enantiomeric separation a difficult task. Thus, the understanding of their recognition mechanisms, i.e., specific discriminating interactions between the solute and the chiral support and their modelling have become very important.

CSPs are generally classified as molecular or supramolecular depending on the molecular or polymeric nature of the chiral selector. Among the supramolecular CSPs, cellulose-based phases have been recognised as very versatile chiral sorbents [2]. However, the chiral recognition mechanism in these CSPs is highly complex and difficult to model since the discriminating sites are multiple and competitive [3]. Consequently, minor structural modifications of solute structure may severely affect the separation [4].

One approach for modelling interactions in supramolecular CSPs is to study those series of molecules which are structurally related and are suitably substituted onto the same framework. Quantification of the substitution effects on the enantioselective

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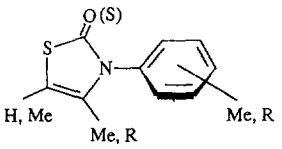


Fig. 1. General structure of N-arylthiazolin-2(thi)one atropisomers used in chromatographic studies.

retention on CSPs allows the definition of "zones" in the solute, responsible for chiral interaction, even if the precise site involved within the CSP cannot be pinpointed.

In previous studies [5], the series of N-arylthiazolin-2(thi)one atropisomers (general structure shown in Fig. 1) was dealt with. These are very good molecular models for two reasons: (1) they have two regions with different polarities (e.g., heterocycle and phenyl, amide-thioamide), thus solute interactions with CSPs could be of several types: hydrogen bonding, dipole–dipole, $\pi-\pi$ or any combination of these; (2) since substitution onto these two regions does not affect the relative bond angles of the underlying molecule, it is possible to demonstrate, in isolation, the effects arising from substitution (including lipophilicity) in very precise locations in the solute molecule.

Recently, we have reported the chromatographic study of a series of 24 N-arylthiazolin-2(thi)one atropisomers on commercially available Tris-(*p*-methylbenzoate) cellulose coated on silica (Chiralcel OJ) (Fig. 2) [6]. Treatment of the data by a factorial design and by linear correlations with the lipophilicity parameter allowed the proposition of a chiral recognition model of these compounds on Chiralcel OJ.

In this paper, we report the study of the effect on

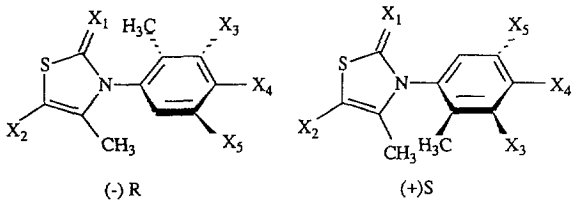


Fig. 2. Structure of N-arylthiazolin-2(thi)one atropisomers (compounds **1–24**): X_1 = oxygen or sulphur; X_2, X_3, X_4, X_5 = hydrogen or methyl [[6]].

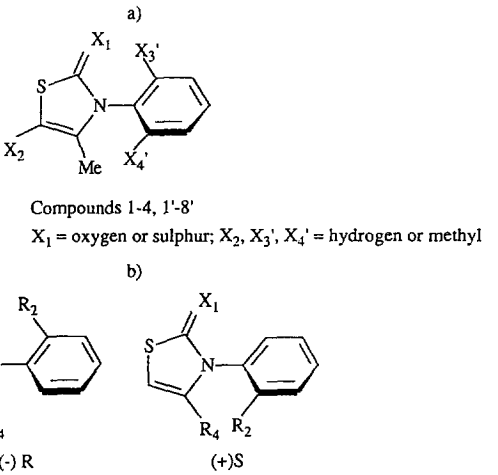


Fig. 3. Structure of N-arylthiazolin-2(thi)one used in this study.

retention and enantioselectivity on Chiralcel OJ for cases where a hydrogen has been replaced by a methyl group (Fig. 3a) and also for cases where a methyl has been replaced by an alkyl group (Fig. 3b) in the key-position blocking the rotation, on both phenyl and heterocycle portions of N-arylthiazolin-2(thi)one atropisomers. The chiral recognition model previously reported [6] is verified in the case of a more general substitution.

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** [7–9] and **25–36** [10]. Compounds **1′–8′** which are achiral were synthesised for this study from the appropriate aniline dithiocarbamate and halogenoketone derivative using the same general procedure [7] and then the thiazolinethiones were transformed into thiazolinones [8]. All the new compounds give satisfactory ^{1}H, ^{13}C NMR and mass analysis.

2.2. Eluents

Ethanol HPLC grade was used in all measurements.

2.3. Chromatographic conditions and apparatus

Determination of the lipophilicity parameter for compounds **1′–8′** was performed by reversed-phase high-performance liquid chromatography according to the procedure previously reported for compounds **1–8, 25–36** [[5]b]. The lipophilicity parameter log $k'w$ is obtained by extrapolation from the linear regression of the plot of log k', obtained on an octadecyl-modified silica column, against the percentage by volume of methanol to 100% water [11].

The chiral separations on Chiralcel OJ were performed using a commercially available column from the Daicel Company: 250×4.6 mm, 10 μm particle size. The eluent used was 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 Chiralcel OJ column was determined by injection of enriched samples previously obtained as reported [5]a.

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

2.4. Experimental design

The methodology of experimental research [12] was used to design sixteen compounds for this study (Fig. 3a). This methodology involves the construction of the experimental matrix, 2^n, as the combination of n factors with two levels (−1, +1), which allows subsequently the calculation of the coefficients of these n factors in a response polinomial equation; each coefficient quantifies the influence of each factor on the response value.

For this study, we selected four 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: two of them, X_1=O (level −1) and S (level +1), X_2=H (level −1) and Me (level +1) are common to the experimental design already reported [6]. The modification of hydrogen (level −1) to methyl (level +1) in the X'_3 position leads to (−)-enantiomer configuration of compounds **1–4** (we can call it "pro-*R*") whereas the same modification in X'_4 position leads to (+)-enantiomer of the same compounds (we can call it "pro-*S*"). When X'_3=X'_4=Me (level +1), compounds **5′–8′** are not chiral and the double substitution "pro-*R*"–"pro-*S*" might account for the simultaneous effect of "chiral" methyl.

We noted X'_3 and X'_4 to differentiate them from X_3 and X_4 in the experimental design already reported [6].

A two-level full factorial design of four factors was developed using a 2^4 matrix [12] reported in Table 1. In Table 1, X_1, X_2, X'_3, X'_4 are the factors and sign + and − indicates the level of the factor, respectively. The actual structure of the compound can be inferred by replacing ± signs by S/O or Me/H level. For instance, the compound corresponding to the first line of Table 1 for which X_1=X_2=X'_3=X'_4=−1 is N-phenyl-4-methylthiazolin-2-one, **1′**.

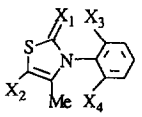
The formalism of the full 2^4 factorial design according to a mathematical model indicates that an observable response Y can be expressed by Eq. (1) [12].

$$\begin{aligned} Y = {} & b_0 + b_1X_1 + b_2X_2 + b'_3X'_3 + b'_4X'_4 + b_{12}X_1X_2 \\ & + b'_{13}X_1X'_3 + b'_{14}X_1X'_4 + b'_{23}X_2X'_3 + b'_{24}X_2X'_4 \\ & + b''_{34}X'_3X'_4 + b'_{123}X_1X_2X'_3 + b'_{124}X_1X_2X'_4 \\ & + b'_{234}X_2X'_3X'_4 + b'_{134}X_1X'_3X'_4 \\ & + b'_{1234}X_1X_2X'_3X'_4 \end{aligned} \quad (1)$$

X_1–X'_4 are the main effects whereas X_iX_j are the interaction effects between variables. The coefficients in Eq. (1) were calculated using NEMROD software [13], by solving the sixteen equations obtained by replacing the factors X_i by −1 or +1, according to the experimental design (Table 1).

A positive value of a coefficient b_i for a given main factor indicates that from the low level to the high level of that factor, the response is increased,

Table 1
Compounds, design levels and responses as lipophilicity and retention on Chiralcel OJ in ethanol in 2^4 experimental design



Compounds	Design levels				Responses	
	X_1	X_2	X_3'	X_4'	Lipophilicity log $k'w$	Chiralcel OJ ln k'
1′	−	−	−	−	2.15	0.78
2′	+	−	−	−	2.27	1.92
3′	−	+	−	−	2.75	0.34
4′	+	+	−	−	2.76	1.62
1(−)	−	−	+	−	2.62	1.07
2(−)	+	−	+	−	2.69	2.63
3(−)	−	+	+	−	3.18	0.59
4(−)	+	+	+	−	3.18	2.60
1(+)	−	−	−	+	2.62	0.16
2(+)	+	−	−	+	2.69	1.53
3(+)	−	+	−	+	3.18	−0.18
4(+)	+	+	−	+	3.18	1.30
5′	−	−	+	+	2.90	−0.78
6′	+	−	+	+	3.07	0.43
7′	−	+	+	+	3.42	−1.10
8′	+	+	+	+	3.42	0.31

whereas a negative value of a coefficient indicates a decrease in the response value.

Overfitting of the data, which is inherent in the methodology, can be a problem in studies of this type, but we do not see it as a problem in this study since our proposed model is consistent with data obtained from previous studies [6].

3. Results

For the sixteen designed compounds, the capacity factors determined on Chiralcel OJ in ethanol as well as the lipophilicity parameter are reported in Table 1.

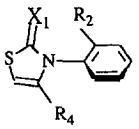
For the 2′,4-dialkyl substituted phenyl thiazolin-2-(thi)one atropisomers, the lipophilicity parameter, the capacity factors for both enantiomers, separation factor and resolution on Chiralcel OJ in ethanol are reported in Table 2. These data are reported according to the sign of the eluted enantiomer since this arrangement corresponds to the absolute configuration and not to the actual order of elution.

4. Discussion

4.1. Quantification of the methyl-blocking effect on chiral retention of N-arylthiazolin-2(thi)one atropisomers on Chiralcel OJ

In our previous paper [6], treatment of the crude chromatographic data of 24 N-arylthiazolin-2(thi)one atropisomers on Chiralcel OJ by a 3/4 2^5 experimental design and linear correlation of retention with the lipophilicity parameter of solutes allowed quantification of the effects (including the lipophilicity effect) of five selected structural parameters on retention and enantioselectivity. We considered that the interaction between structural factors in N-arylthiazolin-2(thi)one atropisomers and Chiralcel OJ is the result of two types of contribution: (1) a non-discriminating lipophilic interaction, pointed out by the linear correlation between retention on the CSP and the lipophilicity parameter (lipophilicity lines, Fig. 2 in [6]) and (2) a parameter which amalgamates all kinds of interaction responsible for the chiral dis-

Table 2
Lipophilicity parameters and chiral chromatographic characteristics for tested 2′,4-dialkyl substituted N-arylthiazolin-2-(thi)one atropisomers



Compounds	Substitution			Lipophilicity	Chiralcel OJ			
	R_2	R_4	X_1	log $k'w$	ln $k'(+)$	ln $k'(-)$	α	R_s
1	Me	Me	O	2.62	0.16	1.07	2.48	6.6
2	Me	Me	S	2.69	1.53	2.63	3.01	14.4
25	Et	Me	O	3.13	−0.38	0.42	2.25	8.3
26	iPr	Me	O	3.58	−1.15	−1.15	1.00	0.0
27	tBu	Me	O	3.89	−1.53	−1.53	1.00	0.0
28	Et	Me	S	3.21	0.43	1.82	4.03	8.0
29	iPr	Me	S	3.70	−0.40	0.04	1.56	3.3
30	tBu	Me	S	4.00	−0.81	−0.53	1.32	1.3
31	Me	Et	O	3.23	−0.44	0.73	3.23	10.6
32	Me	iPr	O	3.69	−0.92	0.07	2.70	4.0
33	Me	tBu	O	4.09	−0.71	−0.46	1.28	0.6
34	Me	Et	S	3.26	0.35	1.77	4.14	14.8
35	Me	iPr	S	3.75	−0.29	0.96	3.51	9.1
36	Me	tBu	S	4.15	−0.36	0.45	2.24	3.3

crimination by attractive or repulsive effects superimposed upon lipophilicity.

Using the same procedure to quantify the effects on the enantiomeric retention on CSP of the substitutions "pro-*R*" and "pro-*S*" (X'_3, X'_4), which induce the chirality in N-arylthiazolin-2(thi)one atropisomers, we applied a two step treatment of the data: first, we plotted ln k' for compounds **1–4**, **1′–8′** versus the log $k'w$ parameter in respect to the lipophilicity lines previously determined (Fig. 2 in [6]) separately for thiazolinones and thiazolinethiones (Fig. 4); second, we calculated ln k'_{calc} on the lipophilicity lines (using the lipophilicity equations given in Fig. 4 and log $k'w$ values reported in Table 1) and vertical

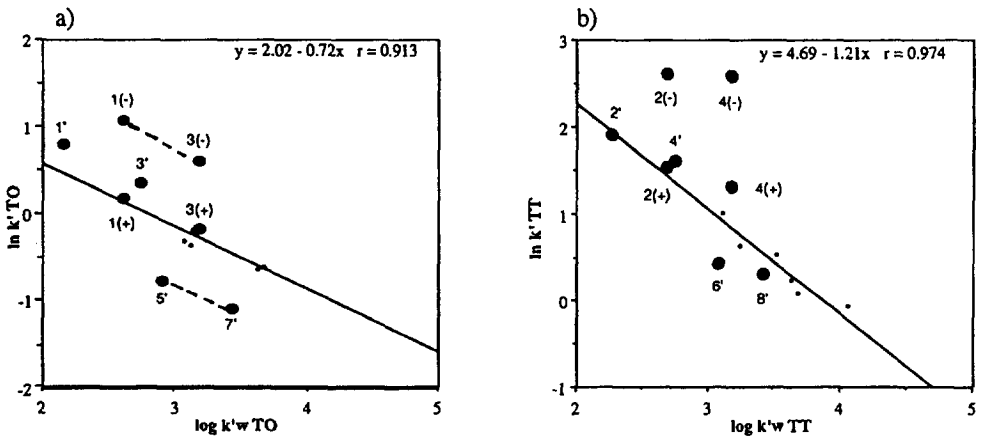


Fig. 4. Plots of the retention in ethanol on Chiralcel OJ (ln k') versus log $k'w$ with respect to the lipophilicity lines (equations from Ref. [6]) for (a) thiazolinones (TO) and (b) thiazolinethiones (TT) (structure as in Table 1).

Table 3
Capacity factors calculated on the lipophilicity lines ($\ln k'_{calc}$) and experimental deviations ($\ln k'_{d}$) from these lines on Chiralcel OJ for compounds 1–4, 1′–8′

Compounds	Design levels				Reponses on Chiralcel OJ	
	X_1	X_2	X'_3	X'_4	$\ln k'_{calc}$	$\ln k'_{d}$
1′	−	−	−	−	0.46	0.31
2′	+	−	−	−	1.94	−0.02
3′	−	+	−	−	0.02	0.31
4′	+	+	−	−	1.34	0.26
1(−)	−	−	+	−	0.12	0.94
2(−)	+	−	+	−	1.43	1.20
3(−)	−	+	+	−	−0.28	0.87
4(−)	+	+	+	−	0.84	1.75
1(+)	−	−	−	+	0.12	0.03
2(+)	+	−	−	+	1.43	0.09
3(+)	−	+	−	+	−0.28	0.10
4(+)	+	+	−	+	0.84	0.45
5′	−	−	+	+	−0.08	−0.69
6′	+	−	+	+	0.97	−0.54
7′	−	+	+	+	−0.45	−0.64
8′	+	+	+	+	0.55	−0.24

(experimental) deviations from these lines, $\ln k'_{d}$, for the sixteen compounds (Table 3), where $\ln k'_{d} = \ln k'$ (Table 1) $- \ln k'_{calc}$.

The response equation obtained by calculating coefficients in Eq. (1) is:

$$\begin{aligned}\ln k'_{d} = {} & 0.26 + 0.10X_1 + 0.09X_2 + 0.07X'_3 \\ & - 0.44X'_4 + 0.09X_1X_2 + 0.10X_1X'_3 \\ & + 0.01X_1X'_4 + 0.01X_2X'_3 + 0.10X_2X'_4 \\ & - 0.41X'_3X'_4 + 0.01X_1X_2X'_3 - 0.02X_1X_2X'_4 \\ & - 0.01X_2X'_3X'_4 - 0.08X_1X'_3X'_4 \\ & - 0.02X_1X_2X'_3X'_4 \end{aligned} \quad (2)$$

The coefficients in Eq. (2) account for attractive or repulsive substitution effects in respect to lipophilicity interaction. The most significant coefficient in Eq. (2) is $b'_3b'_4 = -0.41$, which accounts for the strong repulsive effect of the simultaneous substitution $X'_3 = X'_4 = Me$. The coefficients of each of the X'_3 and X'_4 factors are not interpretable since the interaction $X'_3X'_4$ exists. Thus, we separated Eq. (2) into two equations: one for $X'_4 = -1(H)$ and the other for $X'_3 = -1(H)$. We obtained Eqs. (3,4) in which the coefficients account for the effects in respect to lipophilicity of solely X'_3 "pro-*R*" and X'_4 "pro-*S*", respectively.

$$\begin{aligned}\ln k'_{\text{"pro-}R\text{"}} = {} & 0.70 + 0.09X_1 + 0.09X_2 + 0.48X'_3 \\ & + 0.11X_1X_2 + 0.19X_1X'_3 + 0.03X_2X'_3 \\ & + 0.04X_1X_2X'_3 \end{aligned} \quad (3)$$

$$\begin{aligned}\ln k'_{\text{"pro-}S\text{"}} = {} & 0.19 + 0.01X_1 + 0.08X_2 - 0.02X'_4 \\ & + 0.07X_1X_2 + 0.09X_1X'_4 + 0.01X_2X'_4 \\ & + 0.001X_1X_2X'_4 \end{aligned} \quad (4)$$

The "pro-*R*" methyl has a strong attractive effect in respect to the lipophilicity ($b'_3 = 0.48$) whereas "pro-*S*" methyl has only a lipophilicity effect ($b'_4 0$). These effects are confirmed by the inspection of the plots ln k' versus log $k'w$ (Fig. 4). (+)-Enantiomers of compounds **1**, **3** ($X'_4 = Me$) are situated on the lipophilicity line whereas (−)-enantiomers of the same compounds ($X'_3 = Me$) are retained more than expected on the lipophilicity ground. Compounds for which $X_2 = Me$ are situated on parallels to the lipophilicity line and which are passing by compounds for which $X_2 = H$, as a result of the lipophilic effect of X_2. For thiazolinethiones, the situation is similar but in the absence of substitution in X_2. A methyl in X_2 probably induces an electronic effect reinforcing C=S dipole, which leads to an "attractive" effect for compounds **4′**, **8′**, **4(+)**, **8(+)**, **4(−)**, **8(−)**.

We observe that compound **1′** ($X_1 = O$, $X_2 = X'_3 = X'_4 = H$), substituted only by a methyl in 4-position of the heterocycle, is more retained than expected on the lipophilicity ground, whereas compound **2′** ($X_1 = S$, $X_2 = X'_3 = X'_4 = H$) is situated on the lipophilicity line. Probably insertion of the non-substituted thiazolinone is larger than the corresponding thiazolinethione, because of the higher basicity or the smaller dimension of the oxygen atom. However, substitution in the 4-position of the heterocycle by an alkyl group (see Section 4.2 below) might account for the "sensitivity" to interaction of this rotation-blocking position.

The chiral recognition model previously proposed for the interaction of N-arylthiazolin-2(thi)one atropisomers with Chiralcel OJ [6] involves a primary

interaction between the dipoles of the heterocyclic region with the C=O groups of the CSP which directs the individual enantiomers of solutes towards different sites on the CSP (Fig. 5, dipole interaction represented by dotted lines).

We have pointed out [6] that the most discriminatory effects are due to a basic attraction of compounds **1** and **2**, the origin being unknown (in this study X_1=O, S; X_2=X_4'=H; X_3'=Me) and to a strong repulsion for X_3=Me, both in the (−)-enantiomer and considered in respect to the lipophilicity interaction (Fig. 5). The present study of the effects of "pro-*R*"–"pro-*S*" methyl on chiral discrimination of N-arylthiazolin-2(thi)one atropisomers on Chiralcel OJ confirms that the basic discriminatory attraction is due to the replacing of a hydrogen by a methyl in the "pro-*R*" position, whereas the "pro-*S*" position is only lipophilic. This might be an indication of chiral effects in supramolecular CSPs due to minor modifications but in very precise location on the solute molecules.

It is worth noting that simultaneous substitution "pro-*R*"–"pro-*S*" induces a neat repulsive effect (Fig. 4, compounds **5′–8′**) which might be due to a lack of insertion in the CSP. Since strong repulsion was pointed out in the (−)-enantiomer in the X_3 position (Fig. 5) [6], we might consider that achiral compounds **5′–8′** "mimic" the behaviour of the (−)-*R* configuration of N-arylthiazolin-2(thi)one atropisomers when substituted onto an axis of stacking within Chiralcel OJ CSP.

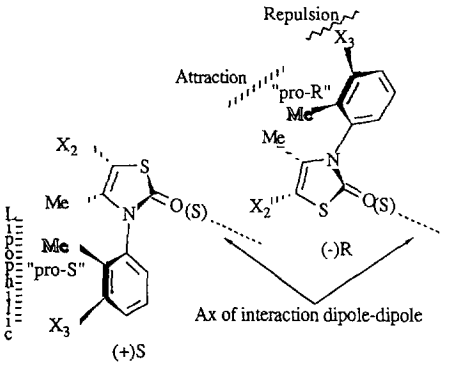


Fig. 5. Chiral recognition model of N-arylthiazolin-2(thi)one atropisomers on Chiralcel OJ (eluent ethanol).

4.2. Chromatographic behaviour of alkyl substituted derivatives

Replacement of the methyl group in the 4-position of the heterocyclic part or in the ortho-position of the aryl in reference molecules **1** and **2** by an alkyl in the series Et, iPr, tBu leads to the series of molecules depicted in Fig. 3b, compounds **25–36**. Such structural modifications are situated in the positions blocking the rotation in N-arylthiazolin-2(thi)one and in the vicinity of the previously studied X_2 or X_3 modifications and are expected to be related to the steric and lipophilic change introduced when R_2= "pro-*R*" or "pro-*S*" methyl, X_2 or X_3=methyl.

Inspection of the crude data, reported in Table 2, shows that whatever the enantiomer set (laevorotatory or dextrorotatory), whatever the nature of X_1 (oxygen or sulphur), and whatever R_2 or R_4 are concerned, substitution of a methyl by a larger alkyl group results in smaller capacity factors than those observed for the reference molecules **1** and **2**, the (−)-enantiomer is always retained more than the (+)-enantiomer and sulphur compounds are retained more than oxygen compounds. A simplistic explanation is the normal dependence higher lipophilicity-less retention on HPLC straight phase and/or steric exclusion of bigger alkyl groups. However, only a quantification of the alkyl effects by the correlation between chiral retention on Chiralcel OJ and the lipophilicity parameter allows a chiral recognition model to be proposed.

Substitution by an alkyl in the series Et, iPr, tBu of methyl "pro-*S*" (Fig. 5) is expected to be lipophilic since a methyl in this position has a lipophilic effect on retention on Chiralcel OJ, whereas substitution by an alkyl in the same series of methyl "pro-*R*" (Fig. 5) is expected to provide combined effects of attraction–repulsion, since a methyl in this position has an attractive effect on retention and it is situated in the vicinity of the repulsive X_3.

Plotting ln $k'(+)$ and ln $k'(-)$ of thiazolinones and thiazolinethiones alkyl substituted in R_2 versus log $k'w$ parameter (Fig. 6a, Fig. 6b) shows that the retention of the (+)-enantiomer in the series Me, Et, iPr, tBu is linearly correlated with the lipophilicity. Nevertheless, the sensitivity of retention to alkyl lipophilicity is greater than to methyl lipophilicity, as

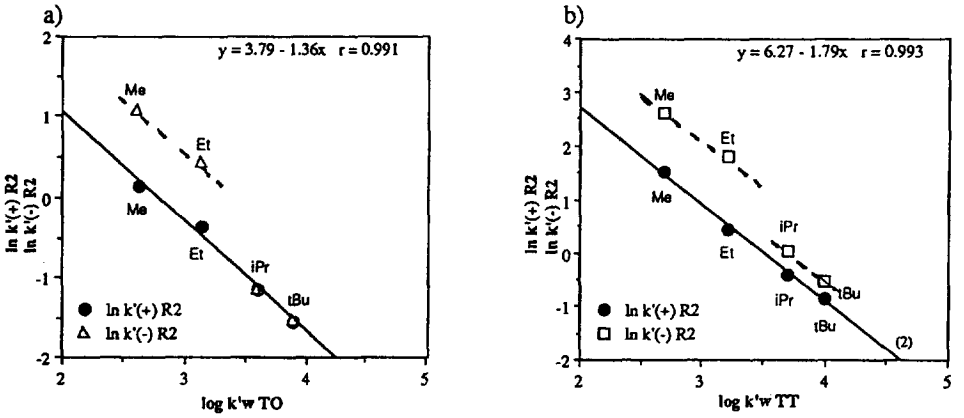


Fig. 6. Plots of (+)- and (−)-enantiomer on Chiralcel OJ [ln $k'(+)$, ln $k'(-)$] versus log $k'w$ for (a) thiazolinones (TO) and (b) thiazolinethiones (TT) alkyl substituted in R_2 (compounds **1**, **2**, **25–30**).

shown by the difference in slopes in Figs. 4 and 6, the thiazolinethiones slope is always greater than for thiazolinones.

For the (−)-enantiomer of both thiazolinones-thiazolinethiones (Fig. 6), substitution by an Et exhibits only a lipophilic effect superimposed on the basic attraction of methyl "pro-*R*", since it is situated on the parallel to lipophilicity line passing by methyl-substituted compounds, whereas iPr and tBu induce a repulsive effect in respect to this attraction. Experimentally, this results in good enantioselectivities for methyl and ethyl-substituted compounds **1**, **2**, **25**, **28**, and poorer or null for iPr or tBu-substituted compounds **26**, **27**, **29**, **30** (Table 2).

The three dimensional nature of alkyl substituents, depicted in a conformational representation in Fig. 7, might be the cause since iPr and tBu substituents have one of the methyl very close or in the same plan, respectively, of X_3 repulsive modification.

This behaviour of 2′-alkyl substituted N-aryl thiazolin-2-(thi)one atropisomers is similar when using hexane–2-propanol 90:10 eluent on Chiralcel OJ (data not reported), however slopes of the correlation ln $k'(+)$−log $k'w$ for thiazolinones and thiazolinethiones are greater and lesser, respectively, than those obtained in ethanol eluent.

Substitution by an alkyl in series Et, iPr, tBu in the R_4 position is situated in the vicinity of X_2 modification which has mainly a lipophilic effect (Fig. 5) and it is expected to also provide a lipophilicity effect on the retention for both enantiomers of N-aryl thiazolin-2-(thi)ones on Chiralcel OJ. Plotting ln $k'(+)$ and ln $k'(-)$ of thiazolinones and thiazolinethiones substituted in R_4 versus log $k'w$ (Fig. 8) points out that the retention of the (−)-enantiomer is linearly correlated with the lipophilicity in the series Me, Et, iPr, tBu, this effect being superimposed on the basic attraction for methyl "pro-*R*". The slopes of these correlations are always greater than those observed for methyl substituted

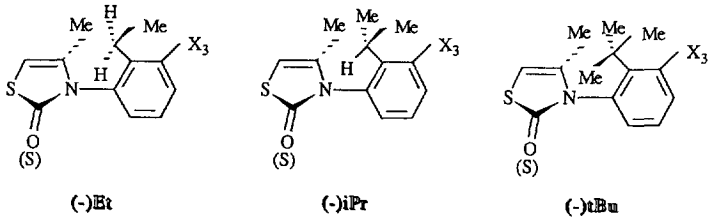


Fig. 7. Conformations of (−)-enantiomer of N-arylthiazolin-2(thi)one in the series of R_2 substituted alkyls.

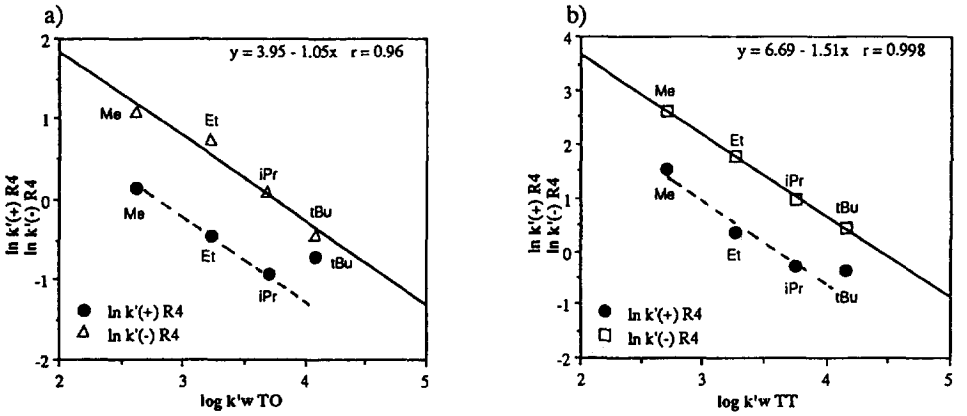


Fig. 8. Plots of (+)- and (−)-enantiomer on Chiralcel OJ [ln $k'(+)$, ln $k'(-)$] versus log $k'w$ for (a) thiazolinones (TO) and (b) thiazolinethiones (TT) alkyl substituted in R_4 (compounds **1**, **2**, **31**–**36**).

compounds (Figs. 8 and 4). Passing a parallel to this lines by the methyl compounds (+)-enantiomers (dotted lines in Fig. 8), we observe that substitution by Et and iPr induce only a lipophilic effect on the retention of (+)-enantiomers (substituted compounds Et-iPr are situated on or very near to this parallel). Only tBu gives rise to an attraction effect (more important for thiazolinones), probably either by an electronic effect on the C=O(S) dipole or by a Van der Waals supplementary component of interaction. Experimentally, this results in good enantioselectivities for Me, Et, iPr substituted compounds **1**, **2**, **31**, **32**, **34**, **35**, and poorer for tBu substituted compounds **33**, **36**.

Almost similar effects are observed for 4-alkyl substituted N-arylthiazolin-2-(thi)one atropisomers in hexane–2-propanol 90:10 eluent on Chiralcel OJ (data not reported), however the correlations are not as good as those obtained in ethanol eluent since substitution by tBu induces an attractive effect, in respect to lipophilicity, for both enantiomers.

We observe that the effects of alkyl substitution in the R_4 blocking position are mainly lipophilic, excepting the tBu substitution, thus this position might be considered to be less sensitive to chiral interactions within the CSP.

This study of the effects of alkyl substitution in series Me, Et, iPr, tBu in R_2 and R_4 positions of N-arylthiazolin-2-(thi)one atropisomers on chiral retention on Chiralcel OJ allows us to confirm the chiral recognition model proposed for methyl substituted N-arylthiazolin-2-(thi)one atropisomers (Fig. 5). Furthermore, the good correlation between the capacity factors of 2′,4-dialkyl substituted N-arylthiazolinethione atropisomers and capacity factors of 2′,4-dialkyl substituted N-arylthiazolinone atropisomers (Fig. 9), obtained on Chiralcel OJ in ethanol eluent, points out the similarity of substitution effects in the two series of compounds, combined with the primary dipole–dipole interaction within the CSP which induces more retention for sulphur compounds (slope >1, Fig. 9).

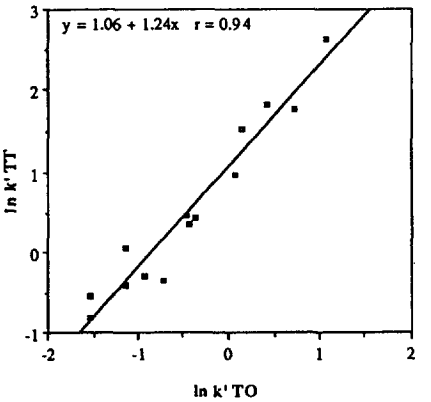


Fig. 9. Linear correlation between the capacity factors of 2′,4-dialkyl substituted N-arylthiazolin-2-one and the capacity factors of 2′,4-dialkyl substituted N-arylthiazolin-2-thione atropisomers on Chiralcel OJ in ethanol.

5. Conclusions

In this study we investigated the chiral recognition mechanism of N-arylthiazolin-2-(thi)one atropisomers on the commercially available chiral sorbent Chiralcel OJ.

The methodology of the experimental research was used to design sixteen compounds for which hydrogen is replaced by a methyl group in the key positions blocking the rotation of N-arylthiazolin-2-(thi)one compounds (Fig. 3a). This substitutions are denoted "pro-*R*" and "pro-*S*" depending on the resulting enantiomer. Experimental deviations of ln k' on Chiralcel OJ in respect to the lipophilicity lines previously reported [6] together with the responses equations in a 2^4 experimental design were used to quantify the effects on the enantioselective retention on CSP of the methyl-blocking substituents. It results in pointing out a basic discriminatory attraction, in respect to the lipophilicity interaction, due to the replacing of a hydrogen by a methyl in the "pro-*R*" position, whereas the "pro-*S*" position is only lipophilic. This might be an indication of chiral effects in supramolecular CSPs due to minor modifications but in very precise location on the solute molecules.

The replacement of a methyl group by an alkyl group in the series Et, iPr, tBu in the positions blocking the rotation N-arylthiazolin-2-(thi)one atropisomers gives rise to a series of compounds (Fig. 3b) which were also chromatographed on Chiralcel OJ. Linear correlations between ln k' on CSP and the lipophilicity parameter of this tested compounds allowed the quantification of the alkyl effects on the enantioselective retention on CSP. The chiral recognition model of N-arylthiazolin-2-(thi)one atropisomers on Chiralcel OJ, proposed in the case of methyl substitution, is confirmed in the case of the alkyl substitution which provide different steric and lipophilic interactions.

An important issue of the study of the chromatographic behaviour of N-arylthiazolin-2-(thi)one atropisomers ([6] and the present study) is the relevance of the linear correlation between the retention on CSP (expressed by ln k') and the lipophilicity parameter of the tested compounds. This allows us to define the lipophilic non-enantiodiscriminatory interaction within the CSP in respect to which attractive or repulsive enantiodiscriminatory effects of substitution in tested compounds are pointed out. This treatment of the experimental data is extremely useful when a chiral recognition model is proposed.

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