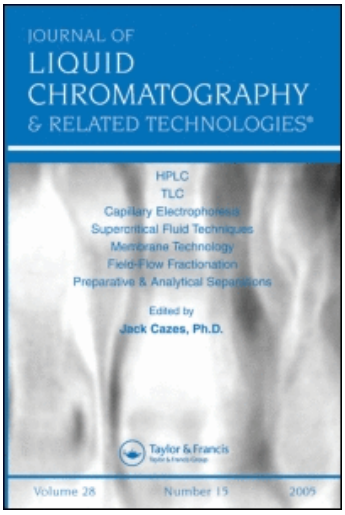

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Effect of Temperature on Retention and Enantiomeric Separation of Chiral Sulfoxides using Teicoplanin Aglycone Chiral Stationary Phase

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Effect of Temperature on Retention and Enantiomeric Separation of Chiral Sulfoxides using Teicoplanin Aglycone Chiral Stationary Phase

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Abstract: The effect of temperature on the LC resolution of racemic aromatic sulfoxides was studied between 10 and 50°C in the polar organic mode on a teicoplanin aglycone chiral stationary phase (CSP). The set of 10 chiral sulfoxides compounds consisted of 2-,3-,4-toluyl methyl sulfoxides and phenyl methyl sulfoxides with different 2-,3-,4-halogen substituents on the aromatic ring. The van't Hoff plots were constructed to determine the thermodynamic data, and in order to promote an understanding of the mechanism of enantioseparation. The van't Hoff plots (ln k versus $1/T$ and ln α versus $1/T$) were linear for all enantiomers. Plots of ln α versus $1/T$ afforded thermodynamic parameters, such as the change in enthalpies $\Delta(\Delta H_{2,1})$ and the change in entropies $\Delta(\Delta S_{2,1})$ for the sulfoxide enantiomers. If $\Delta(\Delta H_{2,1})$ and $\Delta(\Delta S_{2,1})$ are invariant with temperature, the $\Delta(\Delta G_{2,1})$ values can be determined using the Gibbs-Helmholtz equation. The influence of different substituents and their position on the aromatic ring of the sulfoxides on their enantioseparation was correlated to the thermodynamic data. The elution order of the sulfoxide enantiomers does not reverse in the temperature range of 10 to 50°C. All chiral sulfoxides separated

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on teicoplanin aglycone CSP showed the (S)-(+)-enantiomer eluting first at all temperatures.

Keywords: Chiral separation, HPLC, Teicoplanin aglycone CSP, Thermodynamic study, Chiral compounds, Sulfoxides

INTRODUCTION

The macrocyclic glycopeptides CSP's are very useful for the separation of enantiomers, including chiral sulfoxide molecules.[1] Macrocyclic antibiotics possess several characteristics that allow them to interact with a variety of analytes and allow them to serve as chiral selectors. They have numerous stereogenic centres and a variety of functional groups, allowing them to have multiple interactions with chiral molecules.[2]

Chirality remains an important consideration for many compounds such as pharmaceuticals, biological molecules, and agrochemicals, to name a few. In many cases, only one isomer in a chiral compound is responsible for the desired activity, while the other isomer may exhibit no therapeutic value and may potentially cause unsuspected effects.[3–5]One of the two enantiomers of a drug may be toxic or sometimes inactive with respect to biological systems. Because of the different biological activities of enantiomers, the preparation of highly enantio-pure compounds is of utmost importance.[6]

The sulfoxides are organic compounds that are, by convention, drawn with an S═O double bond. Given the unshared pair of electrons on the sulphur, they are not planar molecules. Consequently, when there are two different substituents on sulphur, the molecule is chiral. A more correct view of sulfoxides is that the S–O bond is more ylide-like, i.e., the molecule bears no overall charge but has a negatively charged oxygen atom bonded to a positively charged sulfur atom.[7] The chiral sulfoxides are a large group of organic compounds that are useful in organic synthesis as intermediates in synthetic reactions and asymmetric synthesis.[8,9] Recently, Armstrong and co-workers published a series of separations of chiral sulfoxides using macrocyclic glycopeptides as chiral stationary phases.[1]

In this paper, we explore the influence of temperature on chiral recognition of a series of closely related chiral sulfoxides. The effect of temperature on their retention was studied in order to estimate the interaction/separation mechanism on the teicoplanin aglycone CSP. Temperature is a critical parameter in chromatography and studying its effect on a separation is the key to understanding the mechanism governing the chromatographic process. The effect of temperature on the resolution and selectivity factors for a set of structurally related chiral compounds is often interpreted using van't Hoff plots generated from the chromatographic data. For most separations, these plots are linear, indicating that the retention and/or selective processes governing the separation are unchanged over the temperature

range studied.[10] The aim of this work was to evaluate enantiomeric separations, of related chiral sulfoxides from a thermodynamic point of view of on a teicoplanin aglycone chiral stationary phase (Chirobiotic TAG).

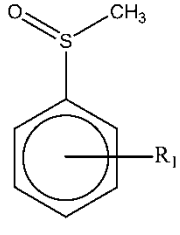
EXPERIMENTAL

Materials

The names and structures of the chiral sulfoxides used in this study are given in Figure 1. All of the sulfoxide compounds used in this study were prepared at the Department of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, according to the method previously described in literature.[11,12] HPLC grade solvent (methanol) was obtained from Merck (Germany).

Equipment

The HPLC chromatographic system Hewlett Packard (series 1100) consisted of a quaternary pump, an injection valve (Rheodyne 7724i) with a 20 μL sample loop, switching valve (Valco), and a photodiode array detector. The column temperature was controlled in a column temperature box (LCT 5100, INGOS, Czech Republic).



1⇒ 4-Toluyl methyl sulfoxide
2⇒ 3-Toluyl methyl sulfoxide
3⇒ 2-Toluyl methyl sulfoxide
4⇒ 4-Bromophenyl methyl sulfoxide
5⇒ 3-Bromophenyl methyl sulfoxide
6⇒ 2-Bromophenyl methyl sulfoxide
7⇒ 4-Chlorophenyl methyl sulfoxide
8⇒ 3-Chlorophenyl methyl sulfoxide
9⇒ 2-Chlorophenyl methyl sulfoxide
10⇒ 4-Fluorophenyl methyl sulfoxide

4-position		3-position		2-position	
Analyte	R_1	Analyte	R_1	Analyte	R_1
1	$-CH_3$	2	$-CH_3$	3	$-CH_3$
4	–Br	5	–Br	6	–Br
7	–Cl	8	–Cl	9	–Cl
10	–F				

Figure 1. Description and numbering of the sulfoxides used in this study.

Methods

A teicoplanin aglycone (Chirobiotic TAG) CSP (250×4,6 mm I.D.) (Astec, USA) was used for the separation of enantiomers of chiral substituted phenyl sulfoxides. The analytes were dissolved in methanol (concentration 1 mg/mL). UV absorption at a wavelength of 254 nm was used for detection. The teicoplanin aglycone was used in a polar organic mode, 100% methanol was used as mobile phase. Separations were carried out at a flow rate of 1.0 mL/min. Thermodynamic data were measured under isothermal conditions over a temperature range of 10–50°C at 10°C intervals. The precision of the controlled temperature was ±0.1°C. Higher temperatures were not used in order to protect the column from degradation. The (S)-(+)-enantiomer eluted first, for all the chiral sulfoxides separated on the teicoplanin aglycone CSP.[1]

RESULTS AND DISCUSSION

The effect of temperature on the separation of chiral sulfoxides was investigated in the polar organic mode on the teicoplanin aglycone chiral stationary phase CSP (Chirobiotic TAG). In general macrocyclic glycopeptides can interact with analytes via hydrophobic, dipole-dipole, π-π interactions, hydrogen bonding, as well as steric repulsion. The structure of these chiral selectors has been given in previous articles.[2] The molar mass of used teicoplanin aglycone ($C_{58}H_{45}Cl_2N_7O_{18}$) is M_r 1197. Methanol was used as the only component of mobile phase. This simple, single-component mobile phase greatly simplifies the interpretation of results on the Chirobiotic TAG column.

Four different kinds of chiral sulfoxide compounds were successfully separated. One was methyl 2-,3-,4-toluyl sulfoxide. The others included 2-, 3-,4–substituted chlorophenyl and bromophenyl methyl sulfoxides, and 4-fluorophenyl methyl sulfoxide. Table 1 lists retention data for the 10 chiral sulfoxides separated on Chirobiotic TAG column at different temperatures.

Previous studies indicated that there are at least two significant effects of temperature on the chromatographic separation of enantiomers: the influence on viscosity, (which affects the diffusion coefficient of solutes), and a thermodynamic effect.[13–17]

Despite the increase in efficiency at higher temperatures, enantiomeric resolution can still diminish due to the decreasing enantioselectivity factors (see Figure 2).

The dependencies of the retention factors of the chiral sulfoxides on the position of the Br substituent are given in Figure 3. The sulfoxides with substituents in the 2-position of the aromatic ring were the most retained. The least retained structural isomers were the ones with substituents in the 3-position. This trend was the same in all cases. The enantioselectivity

Table 1. Dependences of enantiomer retention factors (k_1), enantioselectivity factors (α) and resolutions (R_{21}) for sulfoxides with substituents in 2-position, 3-position and 4-position on temperature. (See Experimental for details)

	Temperature														
	283 K			293 K			303 K			313 K			323 K		
Analyte	k_1	α	R_{12}	k_1	α	R_{12}	k_1	α	R_{12}	k_1	α	R_{12}	k_1	α	R_{12}
1	0,74	1,36	2,3	0,66	1,35	2,1	0,58	1,33	1,9	0,53	1,29	1,5	0,47	1,27	1,2
2	0,56	1,50	2,8	0,5	1,49	2,5	0,44	1,47	2,2	0,41	1,43	1,8	0,37	1,41	1,6
3	0,82	1,32	2,2	0,73	1,30	2,1	0,65	1,27	1,6	0,58	1,24	1,4	0,53	1,22	1,1
4	0,8	1,54	3,8	0,72	1,51	3,4	0,65	1,46	2,6	0,58	1,41	2,2	0,53	1,38	1,9
5	0,64	1,62	3,9	0,57	1,61	3,4	0,51	1,55	2,9	0,47	1,49	2,5	0,43	1,46	2,0
6	0,89	1,58	4,3	0,8	1,55	3,9	0,71	1,48	3,2	0,64	1,42	2,6	0,58	1,37	2,1
7	0,74	1,62	4,0	0,65	1,59	3,8	0,58	1,54	3,1	0,53	1,47	2,5	0,48	1,44	2,1
8	0,59	1,59	3,4	0,52	1,56	3,1	0,47	1,51	2,5	0,42	1,46	2,1	0,39	1,43	1,7
9	0,78	1,54	3,9	0,69	1,51	3,3	0,62	1,44	2,7	0,56	1,38	2,1	0,51	1,34	1,7
10	0,64	1,73	4,6	0,57	1,69	4,1	0,51	1,63	3,3	0,46	1,56	2,8	0,41	1,52	2,2

For $n = 3$; $k_1 \pm 0.01$, $\alpha \pm 0.01$ $R_{12} \pm 0.1$.

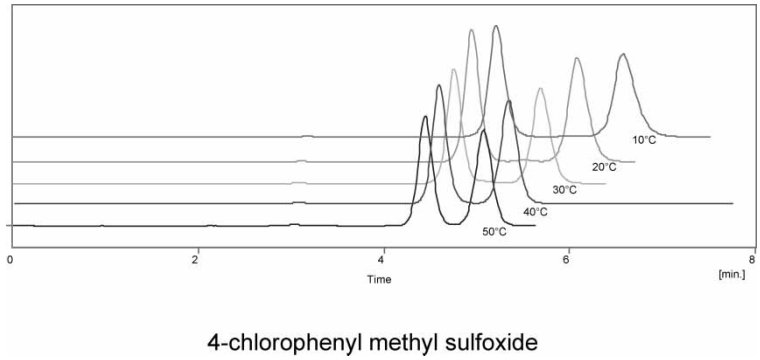


Figure 2. Effect of temperature on the retention and chiral resolution of 4-chlorophenyl methyl sulfoxide. Chromatographic conditions: Column Chirobiotic TAG (250 × 4,6 mm I.D), 1 mL/min methanol mobile phase, UV detection at 254 nm.

factor increases with increasing electronegativity of the substituent on the 4-position of the phenyl ring (see Figure 4). This fact is evident at all studied temperatures and is characteristic just for the 4-substituted compounds. In addition, for halogens, the 4-substituents resonance form (quinoidal form) can be formed (Figure 5). The formation of the resonance forms is not possible in the case of 4-toluyl methyl sulfoxides. The presence of the CH_3 group has a different effect on the aromatic ring as compared to electronegative atoms.

In the case of chiral sulfoxides with the halogen atom in 4-position, the better chiral resolution was achieved for chiral sulfoxides with the more electronegative halogen atom (see Figure 6a). On the other hand, in the case of 3-, and 2-positions on the aromatic ring, there is a very different influence on the enantioselectivity and chiral resolution (see Figure 6b, 6c).

Thermodynamic Parameters in the Polar Organic Mode

Direct enantiomeric separations are based on the formation of reversible diastereomeric associates or complexes that are created by intermolecular interactions of individual enantiomers with a chiral selector.[18] This formation process can be characterized by the Gibbs-Helmholtz thermodynamic parameters (ΔG°, ΔH°, ΔS°).

In order to calculate the thermodynamic parameters and acquire information of value for an understanding of enantiomeric retention, selectivity and/or mechanism for this CSP, van't Hoff plots were constructed using (1)

$$\ln k_i = \frac{-\Delta H_i}{RT} + \frac{\Delta S_i}{R} + \ln \varphi \qquad (1)$$

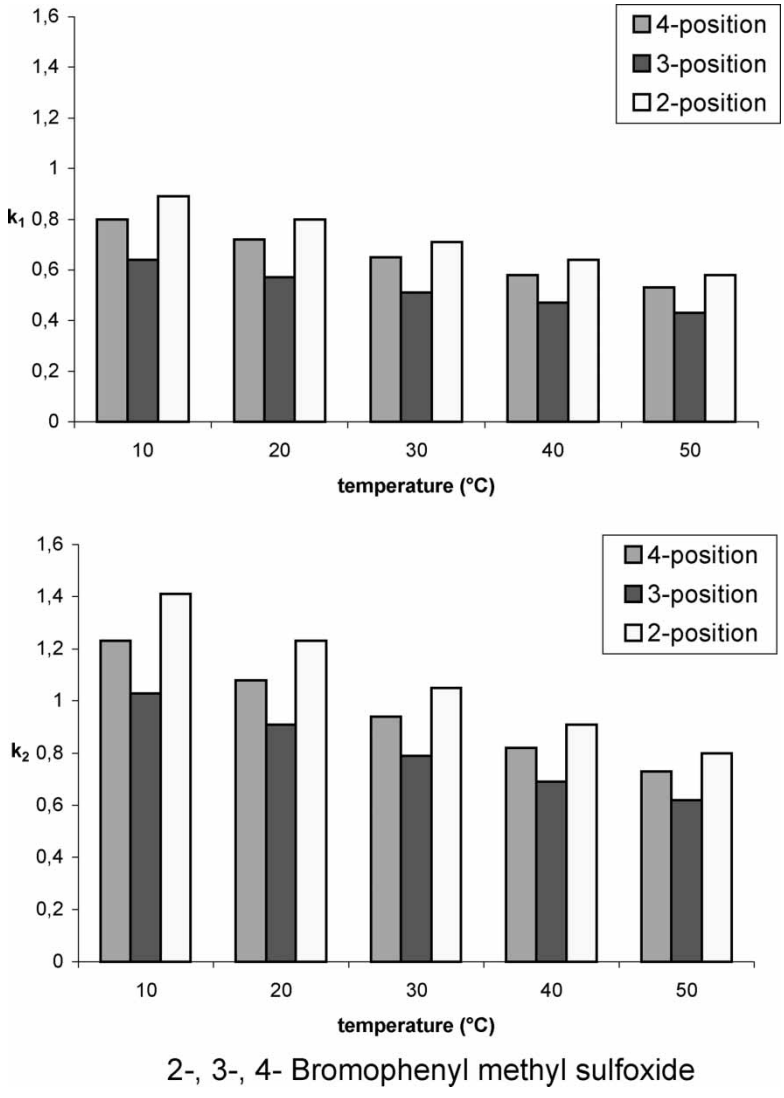


Figure 3. The influence of temperature on retention factors for first eluted (k_1) and second eluted enantiomer (k_2) of 4, 5, and 6 analyte. (See Experimental for details).

where k_i is the retention factor of a solute, ΔH_i is the enthalpy of transfer for this solute in the chromatographic system, ΔS_i is the entropy of transfer for this solute, φ is the phase ratio of the chromatographic column.

Data obtained from the van't Hoff plots also can provide some insight concerning the relative influence of energetic and steric contributions to the enantioseparation of sulfoxides. The van't Hoff plots were linear in the temperature range of this study. When a plot of ln k versus $1/T$ is linear, then the

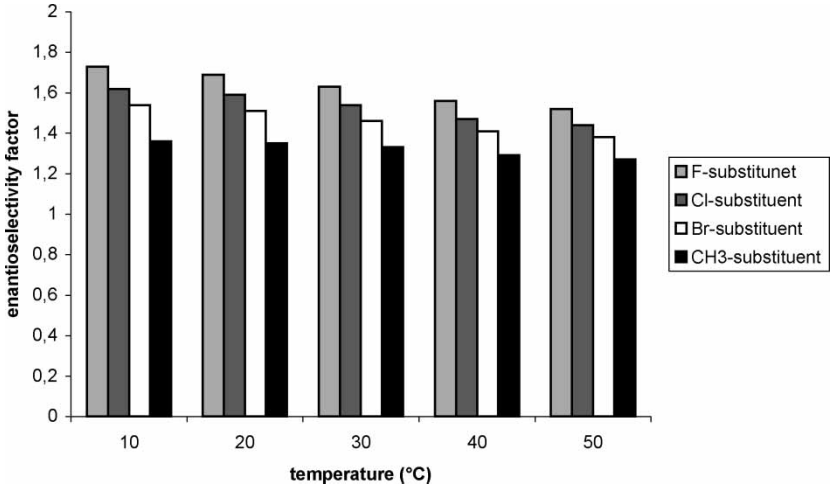


Figure 4. Dependence of enantioselectivity factor on temperature for analytes: 1, 4, 7, and 10. (See Experimental for details).

slope is $-\Delta H_i/R$ and the intercept is $\Delta S_i/R + \ln\varphi$, which are invariant with temperature. Figure 7 gives typical examples of the linear dependence of the natural logarithms of retention factors ($\ln k_i$) with the inverse of temperature ($1/\mathrm{T}$) for the first and second eluted enantiomers of chiral sulfoxides. The list of thermodynamic data obtained from the van't Hoff plots for all of the studied compounds is presented in Table 2.

The correlation coefficients of the van't Hoff plots were in the range 0.997–0.999. It can be concluded, that there is no change in the separation mechanism within the range of studied temperatures.

From the thermodynamic data listed in Table 2, it is evident that the values of the intercepts ($\Delta S_i/R + \ln\varphi$) were negative in all cases. Also, the ($\Delta S_i/R + \ln\varphi$) values for the first eluted enantiomer were always less negative than those for the second eluted enantiomer. In every case, the second eluted enantiomers always had bigger slopes of $-\Delta H_i/R$ and, at the same time.

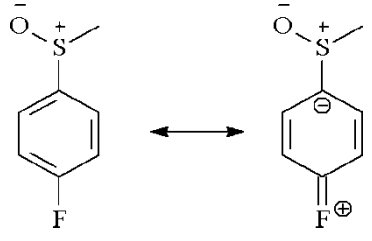
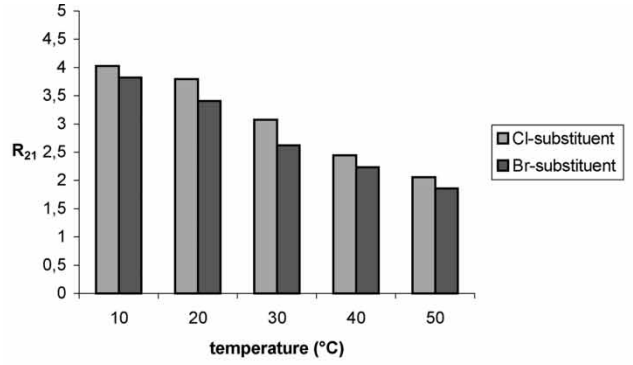
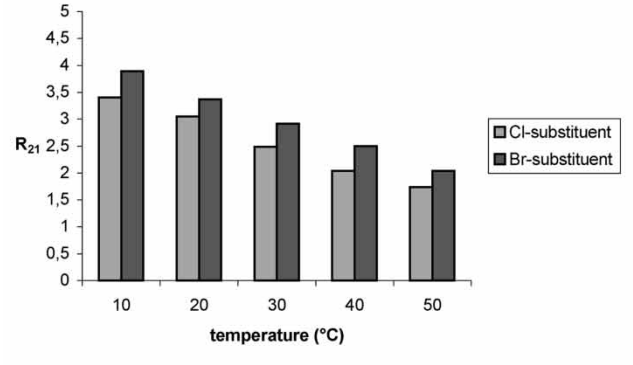


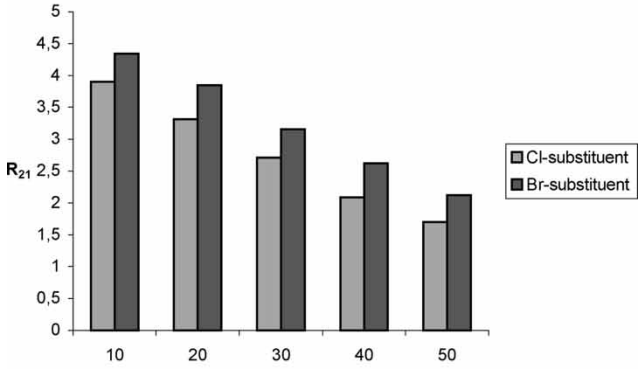
Figure 5. The structure of sulfoxides with F-substituent in 4-position. X-represents halogen atom.



6a 4-position



6b 3-position



6c 2-position

Figure 6. The influence of temperature on resolution (R_{21}) for sulfoxides with different polarity of substituents in 4-position (6a), 3-position (6b), and 2-position (6c). (See Experimental for details).

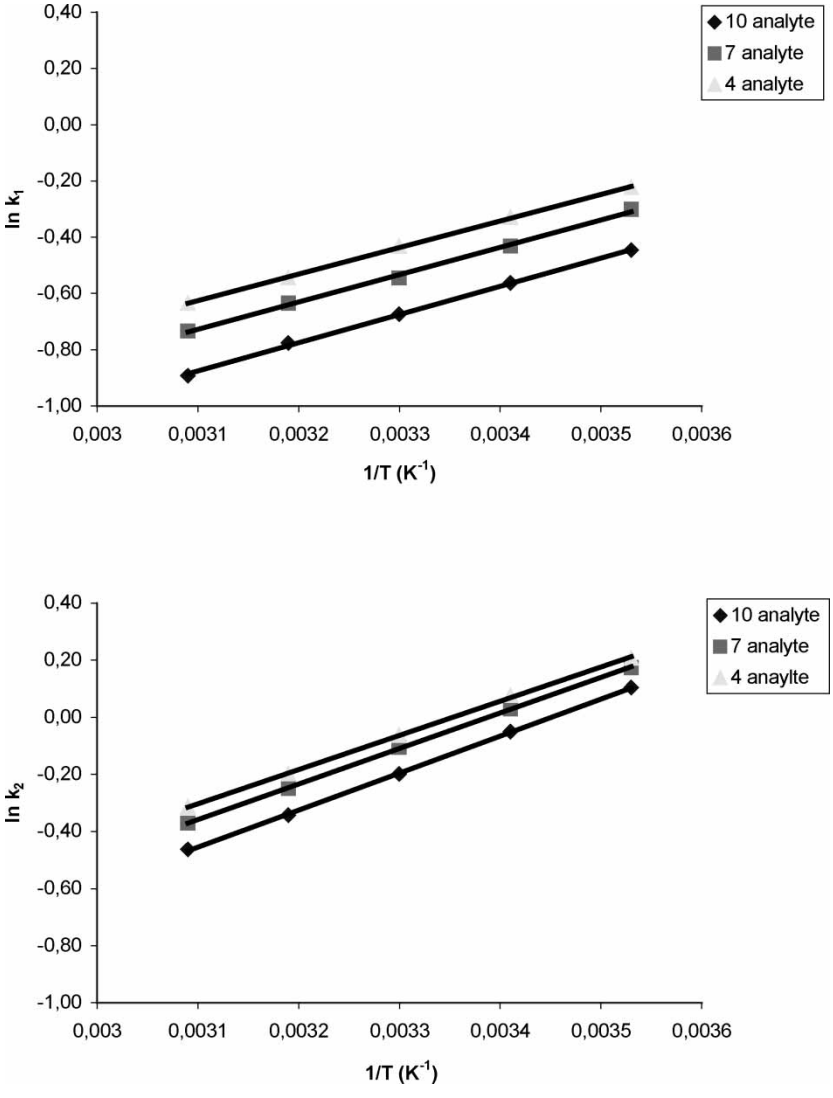


Figure 7. Dependence of natural logarithms of retention factors (ln k_i) on the inverse of temperature (1/T) for analyte-10, -4, and 7. (See Experimental for details).

In general, the calculation of ΔS_i from the intercept requires knowledge of the phase ratio φ. When the dead volume of the column and the technical data are known, phase ratio φ could be calculated.[19] The corresponding $\Delta(\Delta H_{2,1})$ and $\Delta(\Delta S_{2,1})$ values can be obtained as the differences $\Delta H_2 - \Delta H_1$ and $\Delta S_2 - \Delta S_1$, or can be estimated from the selectivity factor (α), which is related to the difference in Gibbs free energy of association

Table 2. The results of linear regression for the first eluted enantiomers, S -(+) form, and the second eluted enantiomers, R (−) form, of all studied sulfoxides. (See Experimental for details)

Analyte	$-(\Delta H_1/R)$	$\Delta S_1/R + \ln \varphi$	Correlation coefficient, r	$-(\Delta H_2/R)$	$\Delta S_2/R + \ln \varphi$	Correlation coefficient, r
4-Position						
1	1026 ± 35	−3,92 ± 0,11	0,998	1190 ± 16	−4,19 ± 0,05	0,999
4	936 ± 9	−3,52 ± 0,03	0,999	1199 ± 22	−4,02 ± 0,07	0,999
7	964 ± 26	−3,71 ± 0,09	0,999	1236 ± 11	−4,19 ± 0,04	0,999
10	999 ± 18	−3,97 ± 0,06	0,999	1282 ± 14	−4,43 ± 0,05	0,999
3-Position						
2	928 ± 42	−3,86 ± 0,14	0,997	1091 ± 14	−4,02 ± 0,05	0,999
5	891± 22	−3,60 ± 0,08	0,999	1181 ± 30	−4,13 ± 0,10	0,999
8	946 ± 32	−3,88 ± 0,11	0,998	1208 ± 11	−4,33 ± 0,04	0,999
2-Position						
3	991 ± 17	−3,70 ± 0,06	0,999	1236 ± 17	−4,27 ± 0,06	0,999
6	972 ± 22	−3,55 ± 0,08	0,999	1290 ± 30	−4,20 ± 0,10	0,999
9	955 ± 14	−3,63 ± 0,05	0,999	1327 ± 17	−4,49 ± 0,06	0,999

$\Delta(\Delta G_{2,1})$ for an enantiomeric pair as shown below:

$$\Delta(\Delta G_{2,1}) = -RT \ln \alpha = \Delta(\Delta H_{2,1}) - T\Delta(\Delta S_{2,1}) \quad (2)$$

The $\Delta(\Delta H_{2,1})$ and $\Delta(\Delta S_{2,1})$ values obtained by the two different ways should be identical within experimental error.[17] Figure 8 shows van't Hoff plot of ln α versus $1/T$ for selected sulfoxides. The value of thermodynamic data for all sulfoxides is given in Table 3. The correlation coefficients for these plots were in the range 0.981–0.999.

The values of $-\Delta(\Delta H_{2,1})$ and $\Delta(\Delta S_{2,1})$ are also presented in Table 3. The values of $-\Delta(\Delta H^{\circ})$ are in the range 1355–2935 J · mol^{-1}.

A characteristic of 4-position chiral sulfoxides with a halogen atom is the increase in values of $-\Delta(\Delta H_{2,1})$, with increasing the electronegativity of halogen atoms. The possibility of formation of resonance forms in the case of 4-position chiral sulfoxides with a halogen atom increases, as well as the possibility of energic interactions increasing (i.e., dipole interactions), which have a positive influence on enantioseparation. The changes in values of $\Delta(\Delta S_{2,1})$ are not as significant as it is in the case of changes of $\Delta(\Delta H_{2,1})$, which are significantly different for each analyte from the group of 4-position sulfoxides.

In the case of 3-,2-position sulfoxides, there is observed a different, opposite trend, as it is in the case of 4-position sulfoxides. From the list of thermodynamic data, it is clear that the biggest values in changes of $\Delta(\Delta H_{2,1})$ are correspondent with 5-analyte from the group of 3-position sulfoxides and with

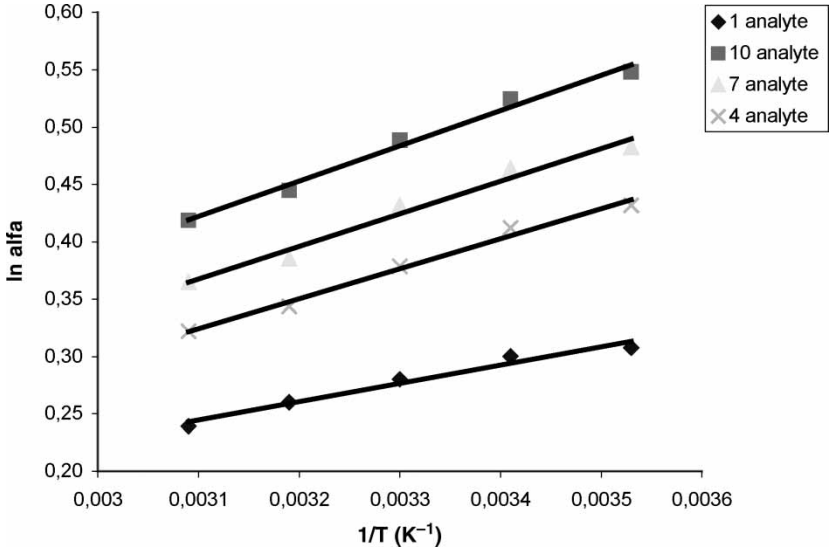


Figure 8. Dependence of natural logarithms of enantioselectivity factor (ln α) on the inverse of temperature ($1/T$) for analyte-10, -4, -7, and -1. (See Experimental for details).

Table 3. Thermodynamic data for the first eluted enantiomers, S -(+) form, and the second eluted enantiomers, R -(−) form, of all studied sulfoxides. (See Experimental for details)

Analyte	$-\Delta(\Delta H_{2,1})/R$	$\Delta(\Delta S_{2,1})/R$	Correlation coefficient, r	$\Delta(\Delta H_{2,1})$ (J/mol)	$\Delta(\Delta S_{2,1})$ (J/mol/K)	α (293 K)	$\Delta(\Delta G_{2,1})_{293\,K}$ (J/mol)	T_{iso} (K)
4-Position								
1	163 ± 13	−0,26 ± 0,04	0,990	−1355	−2,16	1,35	−722	627
4	263 ± 18	−0,49 ± 0,06	0,992	−2187	−4,07	1,51	−993	537
7	281 ± 21	−0,50 ± 0,08	0,992	−2336	−4,16	1,59	−1118	562
10	309 ± 20	−0,54 ± 0,07	0,993	−2569	−4,49	1,69	−1254	572
3-Position								
2	163 ± 13	−0,16 ± 0,04	0,990	−1355	−1,33	1,49	−965	1019
5	245 ± 28	−0,37 ± 0,09	0,981	−2037	−3,08	1,61	−1136	662
8	236 ± 11	−0,37 ± 0,04	0,997	−1962	−3,08	1,56	−1061	638
2-Position								
3	181 ± 3	−0,36 ± 0,01	0,999	−1505	−2,99	1,30	−623	503
6	353 ± 27	−0,78 ± 0,09	0,991	−2935	−6,48	1,55	−1035	453
9	336 ± 25	−0,75 ± 0,08	0,992	−2794	−6,24	1,51	−967	448

6-analyte from the group of 2-position sulfoxides. In the case of 3-,2-position sulfoxides there is no possibility of formation resonance forms, as it is in the case of 4-position chiral sulfoxides with a halogen atom on an aromatic ring. The changes in $\Delta(\Delta S_{2,1})$ are not as significant as it is in case of changes $\Delta(\Delta H_{2,1})$ values.

In the case of halogen substituted sulfoxides that are very similar in the values of $\Delta(\Delta S_{2,1})$, but significantly different in changes of $\Delta(\Delta H_{2,1})$ values, it can be assumed that energic interactions have a dominant influence on enantioseparation. For example, in the case of analytes 5 and 8 that are differently separated, they have the same values of $\Delta(\Delta S_{2,1})$ but they are different in changes of $\Delta(\Delta H_{2,1})$ values.

On the other hand, for the group of toluyl methyl sulfoxides, dominant influence of steric interactions is a characteristic. The smallest differences in $\Delta(\Delta H_{2,1})$ values belong to 3– and 4– toluyl methyl sulfoxides. The value of $-1355\,(\mathrm{J/mol})$ represents the smallest enthalpic difference between these two enantiomers. In spite of having the same values of $\Delta(\Delta H_{2,1})$, they have a different value of $\Delta(\Delta S_{2,1})$ and they are differently separated. The better enantiomeric separation was obtained in the case of 3– toluyl methyl sulfoxide. Probably the dominant influence on enantioseparation has steric interactions and plays a very important role in the position of CH_3 group on aromatic ring of sulfoxides.

Sulfoxides with substituents in the 3-position had the lowest $\Delta(\Delta S_{2,1})$ values. In the case of studied sulfoxides with substituents in 2-position, the biggest values of $\Delta(\Delta S_{2,1})$ were observed. The values of $-\Delta(\Delta S_{2,1})$ for all sulfoxides were in the range 1,33–6,48 $(\mathrm{J.mol^{-1}.K^{-1}})$.

The $(\Delta(\Delta G_{2,1})$ values are proportional to values of enantioselectivity factor (α). The values of $-(\Delta(\Delta G_{2,1})$ were in range 623–1254 $(\mathrm{J.mol^{-1}})$. The biggest value of $-(\Delta(\Delta G_{2,1})$ belongs to the best separated couple of enantiomers, 4-fluorophenyl methyl sulfoxide. On the other hand, the smallest value of $-(\Delta\,(\Delta G_{2,1})$ belongs to 2-toluyl methyl sulfoxide.

At a certain temperature, when $(\Delta(G_{2,1}) = 0$, the enantiomers are not separated. This temperature is known as enantioselective temperature (T_{iso}) and can be defined as the ratio:

$$T_{iso} = \frac{\Delta(\Delta H_{2,1})}{\Delta(\Delta S_{2,1})} \tag{3}$$

In addition, knowing the (T_{iso}) of certain analytes under given experimental conditions might be helpful in the determination of optical purities, as the elution order will be reversed.[20] In the case of sulfoxide separation, the enantioselective temperature was determined and for all sulfoxides was higher than the highest temperature used for enantioseparation of sulfoxides. The individual (T_{iso}) was in the range (448–1019 K) and we can suppose, there was no change in elution order of studied compounds in the range 10–50°C.

CONCLUSION

The mechanism of enantioseparation is independent of temperature within the range of this study. The values of $\Delta(\Delta H_{2,1})$, $\Delta(\Delta S_{2,1})$ and $\Delta(\Delta G_{2,1})$ were determined.

It can be concluded, that energic and steric interactions play very important roles during the enantioseparation of sulfoxides, but in the case of toluyl methyl sulfoxides (analytes 1, 2, and 3) the steric interactions probably have the dominant influence on the enantioseparation. The position of CH_3 functional group on the aromatic ring of chiral sulfoxides is a very important role.

In the case of halogen sulfoxides the steric interactions also play a very important role, but, probably, the energic interactions have the dominant influence on the enantioseparation. It relates also with the electronegativity of halogen atoms and formation of resonance forms in the case 4-position halogen sulfoxides. It can be assumed that the probability of the resonance form formation and the occurrence of the dipole-dipole interactions have a positive influence on the enantioseparation.

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