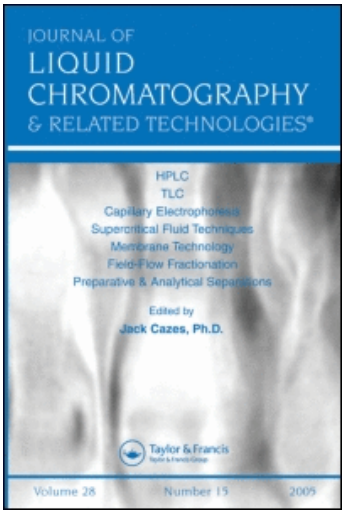

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Thermodynamic Approach to Enantioseparation of Aryl-Methyl Sulfoxides on Teicoplanin Aglycone Stationary Phase

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Abstract: Several structurally related aryl-methyl sulfoxides were chosen for a thermodynamic investigation of retention and enantioseparation on the teicoplanin aglycone chiral stationary phase in the normal phase mode. The temperature of the chromatographic column was controlled within the range of 10°C to 50°C. Van't Hoff plots showed linear dependencies between the logarithms of retention factors and reciprocal temperature. According to thermodynamic parameters (enthalpies and entropies of transfer) the enthalpy contribution seems to have a major influence on retention regardless of the structure of the studied sulfoxides. Enantioseparations of aryl-methyl sulfoxides using hexane/methanol (90/10 v/v) as the mobile phase were enthalpy driven. No coelutions of peaks or changes in the elution order were observed within the temperature range of this study. The measured value of the phase ratio can affect some parameters.

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

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INTRODUCTION

Chiral sulfoxides are a group of organic compounds that has been found to be of general interest due to their ability to participate in a variety of stereoselective interactions. This behaviour is attributed to the asymmetric environment of sulphur since it contains three types of substituents (oxygen, lone electron pair, and organic substituents). These types of molecules can be useful in organic asymmetric synthesis both as chiral auxiliaries and ligands.[1,2] Although chiral sulfoxides may undergo racemization through pyramidal inversion, this phenomenon occurs with significant rates only at high temperatures,[3] Thus, during the past few decades, many synthetic groups have engaged in the design and development of new synthetic methods for the generation of enantiomenically pure sulfoxides.[4,5]

The two most prevalent methods for the preparation of chiral sulfoxides are: asymmetric oxidation of nonsymmetric sulfides and nucleophilic addition of alkyl or aryl ligands to diastereochemically pure chiral sulfinates.[6] Owing to the importance of sulfoxides as intermediates and their synthetic versatility, selective oxidation of organic sulfides to sulfoxides has been a challenge and subject to extensive research.[7–9] Scientific and pharmaceutical interest in enantiomerically pure sulfoxides has led to the development of a number of methods, mainly catalytic, for the production of these chiral compounds.[10] In order to prepare chiral sulfoxides from organic sulfides, several different methods have been applied, including chemical[11] and biological, whole cell[12] and enzymatic[13,14] approaches. Other reported approaches have utilized inorganic vanadium(V) peroxo-complexes,[15] to mediate oxygen transfer reactions to a variety of organic compounds, including sulfides[16] and chiral Schiff-base ligated vanadium(V) peroxo-complexes that catalyzed the formation of optically active sulfoxides.[17,18]

Chiral sulfoxides have been utilized as chiral mediators for asymmetric C–C bond formation processes, as ligands in catalytic asymmetric synthesis, and in molecular recognition studies.[4] Intensive research has demonstrated the efficiency of chiral sulfoxides for controlling the stereoselectivity of a large number of reaction types including: alkylation of carbanions, Michael additions, aldolisation reactions, cycloadditions, Pummerer rearrangements, and so forth.[5]

In addition, chiral sulfoxide functionalities plays a highly important role in a variety of medicinal targets.[7,19] A number of sulfoxides are also finding applications as pharmacological or biological active compounds. For example, chiral sulfoxides in the pharmaceutical industry are important as shown in the next few examples. The chiral sulfoxide quinolone is known to inhibit

platelet adhesion by interfering with the release of 12(*S*)-hydroxyeicosatetraenoic acid from platelets.[20] The drug, Pyrazolotriazine, was developed to treat hyperuricemia and isochemic reperfusion injury. It inhibits the biosynthesis of uric acid by blocking xanthine oxidase.[21] Omeprazole, a racemic mixture, is used for digestive acid related diseases and is the prototypical compound of a class of highly potent gastric acid secretion inhibitors. Unge and coworkers[7] have also reported the asymmetric synthesis of esomeprazole, the generic name of the (*S*)-enantiomer of omeprazole.[7] A number of guanidine derivatives containing sulfoxide groups were synthesized to determine whether the target sulfoxides afford neuroprotection with a potentially improved safety profile over conventional NMDA (*N*-methyl-D-aspartate) channel blockers.[8]

In general, the chiral nature of enormous number of compounds contributes to their bioactivity and/or their various pharmaceutical/industrial uses.[22]

Owing to the existence of pharmacological and toxicological differences between stereoisomers, chiral recognition has now become an integral part of drug research and development. Regulatory authorities demand experimental proof of enantiomeric purity and bioequivalence for registration of new chiral drugs.[23] In addition, the Food and Drug Administration (FDA) has implemented policies for analyzing the enantiomers of chiral compounds.[22] Numerous analytical techniques have been developed to respond to this requirement. Of the many known methods of enantiomeric separation, high performance liquid chromatography (HPLC) with chiral stationary phases is to-date the dominant approach for analytical or preparative scale enantiomeric separations.[24–26]

A number of authors have presented the successful resolution of chiral sulfoxides on different types of chiral stationary phases.[7,27–32] Chiral macrocyclic glycopeptides stationary phases can be operated in the reversed phase, normal phase, and polar organic modes[33] and seems to be particularly adept for the enantioseparation of chiral sulfoxides.[34] Their excellent chiral recognition capabilities were well documented[33,35] and is attributed to their ability to form simultaneous polar and ionic interactions via the substituents from their multiple chiral centers and binding sites that are located in and about the cavities of the glycopeptide's basket like structure.[36,37]

In this paper, we focus on the possibility of using the teicoplanin aglycone (TAG) chiral stationary phase for the enantioseparation of aryl–methyl sulfoxides in the normal phase mode. An examination of the themodynamics of the enantioseparation is done in order to gain some insight into the separation mechanism.

EXPERIMENTAL

Materials

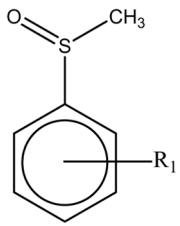
The names and structures of the chiral sulfoxides used in this study are given in Figure 1. All of the racemates used in this study were prepared at the Department of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, according to a method previously described in the literature.[38,39] HPLC grade solvents, n-hexane (hex), ethanol (EtOH), were 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, a switching valve (Valco), and a photodiode array detector. The column temperature was controlled with a column temperature box (LCT 5100, INGOS, Czech Republic).

Methods

A teicoplanin aglycon column (Chirobiotic TAG; 250 × 4, 6 mm I.D.; Astec, USA) was used for this study. The analytes were dissolved in



1 ⇒ 4-Bromophenyl methyl sulfoxide
2 ⇒ 3-Bromophenyl methyl sulfoxide
3 ⇒ 2-Bromophenyl methyl sulfoxide
4 ⇒ 4-Chlorophenyl methyl sulfoxide
5 ⇒ 3-Chlorophenyl methyl sulfoxide
6 ⇒ 2-Chlorophenyl methyl sulfoxide
7 ⇒ 4-Fluorophenyl methyl sulfoxide

4-position		3-position		2-position	
Analyte	R_1	Analyte	R_1	Analyte	R_1
1	Br	2	Br	3	Br
4	Cl	5	Cl	6	Cl
7	F				

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

methanol (concentration 1 mg/mL). UV absorption at a wavelength of 254 nm was used for detection. The teicoplanin aglycon chiral stationary phase was used in the normal phase mode. Hexane/ethanol (Hex/EtOH 90/10 v/v) was used as mobile phase. Separations were carried out at a flow rate of 1.0 mL/min. Thermodynamic data were obtained 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. The elution order was confirmed with pure standards. These facts were also in good agreement with already published details of elution order of these chiral sulfoxides in literature.[34]

RESULTS AND DISCUSSION

According to a previous study, the normal phase mode was most effective for enantioseparation of aryl-methyl sulfoxides on the chirobrotic TAG column.[34] In addition, the use of pure methanol as a mobile phase seems to be an effective approach for the enantioseparation of aryl-methyl sulfoxides on the teicoplanin aglycone CSP.[40] The thermodynamic study, used in this article, was done in order to explore the retention of aryl-methyl sulfoxides in the normal phase mode (see Experimental for details) using a teicoplanin aglycone CSP. The influence of temperature (from 10 to 50°C) on retention and the enantiomeric separation is depicted in Figure 2 and the data are summarized in Table 1. The logarithms of the retention factors ($ln\ k_i$) were plotted versus reciprocal temperature ($1/T$). Since a linear relationship ($ln\ k_i$ vs. $1/T$) was observed for all studied aryl-methyl sulfoxides with correlation coefficients greater

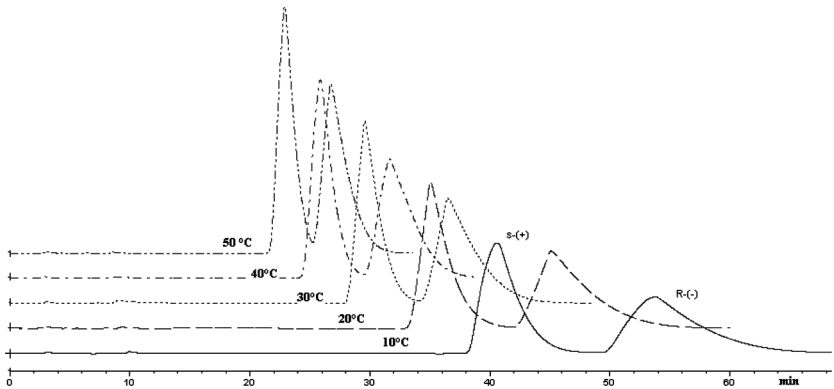


Figure 2. The influence of temperature on retention and enantioseparation of 2-chlorophenyl methyl sulfoxide. (See Experimental for details).

Table 1. Dependences of enantiomer retention factors (k_1), enantioselectivity factors (α) and resolutions (R_{21}) for aryl-methyl sulfoxides on temperature using teicoplanin aglycon CSP (250 × 4,6 mm I.D), 1 ml/min hexane/ethanol mobile phase (Hex/EtOH (90/10 v/v)), UV detection at 254 nm (See Experimental for details)

	Temperature														
	283 K			293 K			303 K			313 K			323 K		
Analyte	k_1	α	$R_{1,2}$	k_1	α	$R_{1,2}$	k_1	α	$R_{1,2}$	k_1	α	$R_{1,2}$	k_1	α	$R_{1,2}$
1	22,00	1,49	4,07	20,35	1,49	5,7	16,43	1,42	4,8	14,44	1,39	4,3	12,54	1,35	3,6
2	17,39	1,64	7,6	15,24	1,54	5,07	12,33	1,51	5,1	10,91	1,49	4,2	9,50	1,46	4,3
3	12,75	1,42	3,54	10,73	1,35	2,7	9,87	1,23	3,0	8,68	1,27	1,9	6,91	1,26	1,5
4	21,08	1,51	5,4	17,89	1,47	4,80	15,27	1,41	4,34	13,00	1,42	3,6	11,95	1,37	3,0
5	15,64	1,57	4,5	13,07	1,57	4,0	10,47	1,64	3,7	9,32	1,60	14,3	8,75	1,43	6,2
6	12,74	1,35	2,5	10,85	1,31	2,92	9,00	1,26	2,42	7,74	1,25	1,9	6,73	1,19	1,6
7	26,75	1,56	4,4	22,24	1,51	5,7	18,88	1,46	5,4	15,96	1,42	4,5	14,40	1,38	4,3

For $n = 3$ (triplicate analyzes), the ± values (95% confidence level) of k_1, α, $R_{1,2}$ for all analytes are below: $k_1 \pm 0.23$, $\alpha \pm 0.03$, $R_{1,2} \pm 0.1$.

than 0.984 (Tables 2 and 3), the van't Hoff of equation (1) could be used to calculate corresponding thermodynamic parameters:

$$\ln k_i = \frac{-\Delta H_i}{RT} + \frac{\Delta S_i}{R} + \ln \phi \tag{1}$$

where the k, R, and T are the retention factor for the solute, the gas constant and the absolute temperature, can be used to calculate the partial molar enthalpy (ΔH_i) of solute transfer (from the slope) and the partial molar entropy (ΔS_i) of solute transfer (intercept). The calculation of ΔS_i from the intercept requires a knowledge of the phase ratio, ϕ (the volume of the stationary phase, (V_s), divided by the volume of the mobile phase, (V_m)).

Equation 2 provides a general way to determine the phase ratio:

$$\phi_i = \frac{V_S}{V_m} = \frac{V_{col} - V_m}{V_m} = \frac{(V_{col}/f) - (t_o - t_{ext})}{(t_o - t_{ext})}, \tag{2}$$

where V_S and V_m are the volumes of the stationary phase and the mobile phase, respectively, f is the mobile phase flow rate. V_{col} can be calculated as: $V_{col} = 0{,}25\ \pi\ d_c^2\ l_c$ where d_c is the diameter of the column tube and l_c is the length of the column. Equation (2) indicates that the mobile phase holdup time (t_0) and the extra column holdup time (t_{ext}) should be measured.

The injection of blank mobile phase volumes produced visible detector fluctuations that were used for determination hold-up time (t_0). The extra column hold-up time (t_{ext}), was measured in the same way except with a zero volume connector instead of column. The phase ratio calculated in this way was approximately 0.540 ($\phi = 0.540 \pm 0.007$), which is greater than the value of the phase ratio published in previous papers. The ϕ parameter is always difficult to know with a high degree of accuracy because the exact volume, V_s, of the active stationary phase is not known exactly.[41] Thus, for this work, a phase ratio equal to 0.091 was used. As shown later, the phase ratio cancels when working with the enantioselective $\Delta(\Delta S_{2,1})$ entropy changes.

According to the equation 3, the distribution coefficient can be expressed in terms of the *standard energy* of solute exchange between the phases employing the traditional and well established Arrhenious equation.

$$RT \ln K_i = -\Delta G_i \tag{3}$$

Table 2. The results of linear regression ($ln\ k_1$ vs. $1/T$) and thermodynamic data for the first eluted enantiomers, S (+) form, of all studied sulfoxides CHIROBTIOTIC TAG-CSP. (See Experimental for details)

Analyte	$-(\Delta H_1/R)$	$(\Delta S_1/R + ln\ \phi)$	Correlation coefficient, r	$-\Delta H_1$ kJ/mol	$\Delta S_1{}^a$ J/(mol. K)	$\Delta S_1{}^b$ J/(mol. K)	$-\Delta G_1{}^a$ KJ/(mol. K)	$-\Delta G_1{}^b$ KJ/(mol. K)
4-position								
1	1324 ± 99	$-1{,}56 \pm 0{,}33$	0,992	11,008	7,0	−7,8	13,059	8,723
4	1330 ± 65	$-1.65 \pm 0{,}21$	0,996	11,058	6,2	−8,6	12,875	8,538
7	1438 ± 57	$-1.77 \pm 0{,}19$	0,998	11,956	5,2	−9,6	13,480	9,143
3-position								
2	1409 ± 66	$-2.11 \pm 0{,}22$	0,997	11,714	2,4	−12,4	12,417	8,081
5	1370 ± 143	$-2.11 \pm 0{,}47$	0,984	11,390	2,4	−12,4	12,093	7,757
2-position								
3	1313 ± 138	$-2.08 \pm 0{,}46$	0,984	10,916	2,6	−12,2	11,678	7,341
6	1446 ± 26	$-2.56 \pm 0{,}09$	0,999	12,022	−1,4	−16,2	11,612	7,275

$\Delta S_1{}^a$ calculated with a phase ratio, $\phi = 0{,}091$, taken from reference [41].
$\Delta S_1{}^b$ calculated with a phase ratio, $\phi = 0{,}540$, obtained from equation 2.
$\Delta G_1{}^a$ calculated with $\Delta S_1{}^a$, $T = 293$ K.
$\Delta G_1{}^b$ calculated with $\Delta S_1{}^b$, $T = 293$ K.

Table 3. The results of linear regression ($ln\ k_2$ vs. $1/T$) and thermodynamic data for the second eluted enantiomers, R (−) form, of all studied sulfoxides on CHIROBTIOTIC TAG-CSP. (See Experimental for details)

Analyte	$-(\Delta H_2/R)$	$(\Delta S_2/R + ln\ \phi)$	Correlation coefficient,r	$-\Delta H_2$ kJ/mol	$\Delta S_2{}^a$ J/(mol. K)	$\Delta S_2{}^b$ J/(mol. K)	$-\Delta G_2{}^a$ KJ/(mol. K)	$-\Delta G_2{}^b$ KJ/(mol. K)
4-position								
1	1569 ± 136	−2.01 ± 0,45	0,989	13,045	3,2	−11,6	13,983	9,646
4	1520 ± 65	−1.92 ± 0,22	0,997	12,637	4,0	−10,8	13,809	9,473
7	1711 ± 52	−2.32 ± 0,17	0,999	14,225	0,6	−14,2	14,401	10,064
3-position								
2	1638 ± 62	−2.44 ± 0,21	0,998	13,618	−0,4	−15,2	13,501	9,164
5	1526 ± 33	−2.18 ± 0,11	0,999	12,687	1,8	−13,0	13,214	8,878
2-position								
3	1571 ± 113	−2.67 ± 0.37	0,993	13,061	−2,3	−17,1	12,387	8,051
6	1735 ± 52	−3.28 ± 0,18	0,999	14,425	−7,3	−22,1	12,286	7,950

$\Delta S_2{}^a$ calculated with a phase ratio, $\phi = 0{,}091$, taken from reference [41].
$\Delta S_2{}^b$ calculated with a phase ratio, $\phi = 0{,}540$, obtained from equation 2.
$\Delta G_2{}^a$ calculated with $\Delta S_2{}^a$, $T = 293$ K.
$\Delta G_2{}^b$ calculated with $\Delta S_2{}^b$, $T = 293$ K.

Table 4. Thermodynamic parameters for the first eluted enantiomers, S (+) form, and the second eluted enantiomers, R (−) form, of all studied sulfoxides on CHIROBTIOTIC TAG-CSP. (See Experimental for details)

Analyte	$-\Delta(\Delta H_{2,1})/R$	$\Delta(\Delta S_{2,1})/R$	Correlation coefficient,r	$\Delta(\Delta H_{2,1})$ (kJ/mol)	$\Delta(\Delta S_{2,1})$ (J/mol/K)	$\Delta(\Delta H_{2,1})^*$ (kJ/mol)	$\Delta(\Delta S_{2,1})^*$ (J/mol/K)	$\Delta(\Delta G_{2,1})$ (J/mol)	T_{iso} (K)
4-position									
1	244 ± 37	$-0{,}46 \pm 0{,}12$	0,967	−2,029	−3,7	−2,037	−3,7	−971	544
4	200 ± 28	$-0{,}30 \pm 0{,}09$	0,973	−1,662	−2,5	−1,580	−2,2	−938	704
7	291 ± 6	$-0{,}58 \pm 0{,}02$	0,999	−2,420	−4,8	−2,270	−4,5	−1004	409
3-position									
2	248 ± 55	$-0{,}40 \pm 0{,}18$	0,935	−2,062	−3,2	−1,904	−2,7	−1052	694
5	139 ± 154	$-0{,}01 \pm 0{,}51$	0,461	−1,152	−0,1	−1,297	−0,6	−1099	2229
2-position									
3	276 ± 106	$-0{,}65 \pm 0{,}35$	0,834	−2,295	−5,4	−2,145	−4,9	−731	437
6	263 ± 23	$-0{,}63 \pm 0{,}08$	0,988	−2,190	−5,2	−2,403	−6,0	−658	401

$\Delta(\Delta H_{2,1})^*$ and $\Delta(\Delta S_{2,1})^*$ represent thermodynamic parameters obtained as differences $\Delta H_2 - \Delta H_1$ and $\Delta S_2 - \Delta S_1$, (the subscripts 2 and 1 refer to the second and first eluted enantiomer, respectively). T_{iso}, theoretical temperature for coelution calculated from thermodynamic parameters $\Delta(\Delta H_{2,1})^*$ and $\Delta(\Delta S_{2,1})^*$; $\Delta(\Delta G_{2,1})$ calculated with α–values for $T = 293\,K$ according to equation 5.

Given the relationship between the distribution coefficient (K) and the retention factor (k), the equation 3 can be also expressed as:

$$-RT[\ln k_i - \ln \phi] = \Delta G_i \tag{4}$$

Table 1 reveals that all α-values (α) were greater than 1.19, which is the value obtained for 2-chlorophenyl methyl sulfoxide at the highest temperature. Thus all values of $\Delta(\Delta G_{2,1})$ must be negative according to equation 5.

$$-\Delta(\Delta G_{2,1}) = RT \ln \alpha \tag{5}$$

In this case, the value of $\Delta(\Delta G_{2,1})$ would be negative only if both the ΔG_i values are negative. Since both of ΔG_i values are negative it means that the process of retention is spontaneous. In addition, if ΔH_i values are negative, (positive slope of the van't Hoff dependence ($ln\ k_i$ vs. $1/T$) then, according to the Gibbs-Helmholtz equation (6):

$$\Delta G_i = \Delta H_i - T\Delta S_i \tag{6}$$

the value of ΔS_i could be either positive or a small negative value. A positive ΔS_i value with a $(-\Delta H_i)$ value increases the value of $(-\Delta G_i)$, whereas a small negative value of ΔS_i has the opposite effect. That is why inaccurate phase ratios may leads to different interpretations of the entropy contribution and results in wrong conclusions.

Using van't Hoff plots of the logarithm of the enantioselectivity factor ($\ln \alpha$) versus reciprocal absolute temperature ($1/T$) (eq. 7; where α, R, and T are the enantioselectivity factor, for the enantiomeric mixture, the gas constant, and the absolute temperature, respectively) does not require the phase ratio for the determination of thermodynamic parameters.

$$\ln \alpha = -\frac{\Delta(\Delta H_{2,1})}{RT} + \frac{\Delta(\Delta S_{2,1})}{R} \tag{7}$$

In general, the corresponding $\Delta(\Delta H_{2,1})$ and $\Delta(\Delta S_{2,1})$ values can be also obtained as the differences $\Delta H_2 - \Delta H_1$ and $\Delta S_2 - \Delta S_1$, (2, 1-terms for second and first eluted enantiomers, respectively). The values of $\Delta(\Delta H_{2,1})$ and $\Delta(\Delta S_{2,1})$ obtained by these two different methods should be identical within experimental error (Figure 3). Naturally, this need not be true if some aberrations from linearity are observed. Even in some cases when van't Hoff dependences ($\ln k_i$ vs. $1/T$) are not linear, due to changing of the phase ratio within studied temperature range, using van't Hoff equation ($\ln \alpha$ *vs.* $1/T$) shows linear behavior.[42] The linearity/nonlinearity of enantioselectivity van't Hoff plot helps us to make some conclusions and decide whether the enthalpy and entropy of transfer for

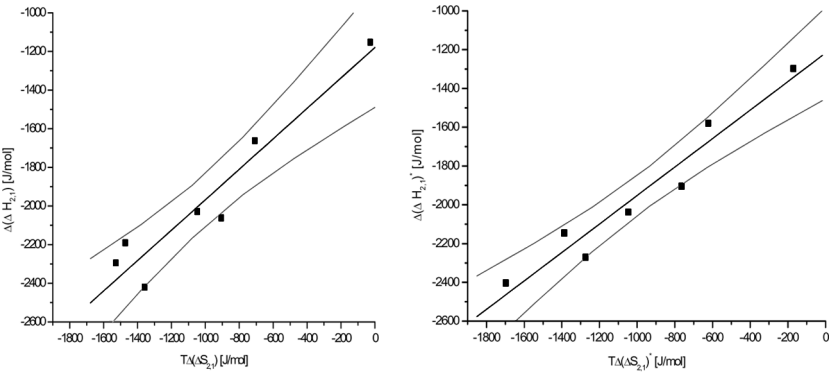


Figure 3. Comparison of $\Delta(\Delta H_{2,1})$ and $\Delta(\Delta S_{2,1})$ values obtained from vaňt Hoff dependences (ln α vs.$1/T$) with values of $\Delta(\Delta H_{2,1})^*$ and $\Delta(\Delta S_{2,1})^*$ obtained as the differences $\Delta H_2 - \Delta H_1$ and $\Delta S_2 - \Delta S_1$, (2, 1-terms for second and first eluted enantiomers, respectively), $T = 283$ K.

the enantiomers are independent of the temperature within the range studied. The accuracy of the correct determination of the thermodynamic parameters from the van't Hoff plots relates with the linearity of these van't Hoff plots. On the other hand, in some cases, especially in cases of bigger retention factors, the Equation 7 van't Hoff plot need not be linear despite the fact that van't Hoff dependences (ln k_i vs. $1/T$) for each enantiomer are linear. This may occur as a result of the monotonic dependence or weak linear dependence of the enantioselectivity factor on the temperature. In Figure 4, the changing $-\Delta(\Delta G_{2,1})$ values for the studied analytes with the increasing temperature is shown. The biggest deviation from the linearity can be seen for analytes 3 and 5. That is why, in the case of these two enantiomer couples, the lowest values of correlation coefficient (r) for enantioselectivity van't Hoff plots were observed. Despite some deviations from the linearity, there are probably no changes in enantioseparation mechanism within the studied range of temperatures, since clearly linear vaň Hoff plots (ln k vs. $1/T$) were observed for both of enantiomers (Tables 2 and 3).

As mentioned previously, larger differences in the corresponding $(-\Delta G_i)$ for each enantiomer results in a greater absolute value of $\Delta(\Delta G)$. Tables 2 and 3 list values of ΔS_1 and ΔS_2 calculated with using different phase ratio values. Using a phase ratio equal to 0.540 always results in negative values for the entropy change. In comparison, a phase ratio of 0.091 produces mostly positive values for the entropy change of the first eluted enantiomer (Table 2) and the second eluted enantiomer

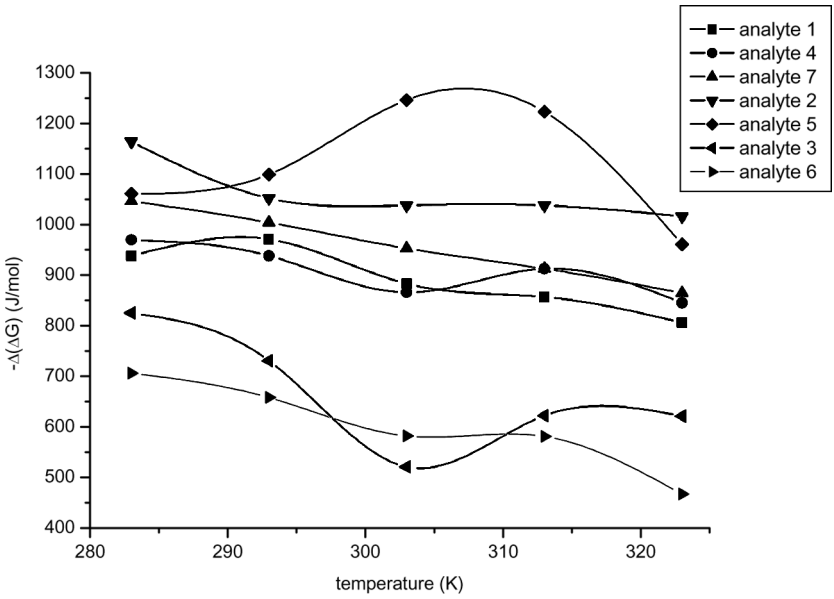


Figure 4. Dependence of $-\Delta(\Delta G_{2,1})$ values on temperature for set of studied aryl-methyl sulfoxides.

(Table 3). The entropy values for the second enantiomer are always either lower (phase ratio of 0,091) or more negative (phase ratio of 0.540). Despite the fact that lower or more negative entropy contributions decreases the $(-\Delta G_2)$, the value of $(-\Delta G_2)$ is always bigger than $(-\Delta G_1)$. Naturally this can be possible only if enthalpy contribution for the second eluted enantiomer is much bigger as enthalpy contribution for first eluted enantiomer (Tables 2, 3). Thus, the enantioseparations of aryl-methyl sulfoxides in normal phase mode are probably enthalpy driven. There were no coelutions, nor changes in the elution order observed within the temperature range of study. In the case of all studied chiral sulfoxides separated using teicoplanin based columns, the (S)-(+)-enantiomer eluted first.

In comparison with results obtained on the same column but with pure methanol as a mobile phase,[40] sulfoxides are much more retained on the stationary phase, the change of retention factors is bigger with increasing temperature than in case of polar organic mode, which results in higher values of transfer enthalpy. The values for entropy of transfer in this study are smaller than in the previous case of the methanol mobile phase owing to bigger retention factors. The entropy contribution has little influence on the retention of the studied aryl-methyl sulfoxides.

CONCLUSION

The interpretation of chromatographic data, from a thermodynamic point of view, can sometimes depend on an accurate knowledge of the stationary phase volume, and/or possible changes of the phase ratio within the temperature range studied. It is usually more important, for the interpretation of thermodynamic data, to know whether the phase ratio is constant within a given temperature range than to know the exact value of the phase ratio.

Using the van't Hoff expression for the logarithm of the enantioselectivity factors versus reciprocal temperature for determination of thermodynamic parameters (Equation 7) may partially solve the problem of correct interpretation, but only in the cases of linear van't Hoff dependences. It is necessary to determine whether or not any curvature for van't Hoff plots has its origin in retention behaviour of studied enantiomers.

Despite the fact that using normal phase mode for aryl sulfoxides produced increased values of resolution factors both at lower temperatures as well at higher temperatures, the use of pure methanol as the mobile phase is still recommended since it produces lower retention times. In the case of aryl-methyl sulfoxides used in this study, the dominant influence of the enthalpy contribution to retention and enantioseparation can be clearly observed. The enthalpies of transfer values for all sulfoxides were larger than those obtained in the polar organic mode. On the other hand, in the normal mobile phase mode, a decrease in the entropy values were observed for all analytes in comparison with those obtained in the polar organic mode, regardless the character and position of the substituent on the aromatic ring of the studied sulfoxides.

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