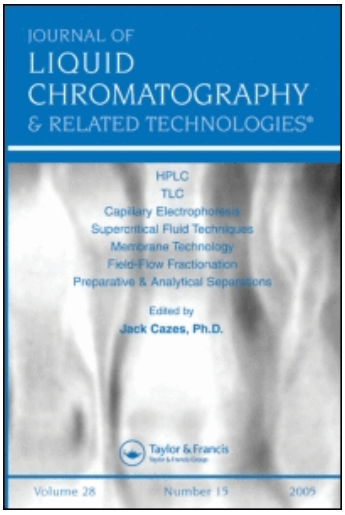


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# Separation and Thermodynamic Studies of Chiral Sulfoxides on Teicoplanin-Based Stationary Phase

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# Separation and Thermodynamic Studies of Chiral Sulfoxides on Teicoplanin-Based Stationary Phase

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**Abstract:** Three different teicoplanin chiral stationary phases (CSPs) (native teicoplanin, teicoplanin aglycon, and methylated teicoplanin aglycon) were used to study the enantioseparation and temperature behaviour of a set of chiral sulfoxides. The chiral analytes studied were 2-, 3-, 4- toluyl methyl sulfoxides and phenyl methyl sulfoxides with different 2-, 3-, 4-halogen substituents on the aromatic ring. The effect of temperature on the LC separation of racemic aromatic sulfoxides was studied between 10 and 50°C in a methanol mobile phase. The van't Hoff plots were constructed and thermodynamic data were determined from the slope and the intercept of linear van't Hoff plots. The van't Hoff plots (ln k versus 1/T and ln $\alpha$ versus 1/T) were linear for all enantiomers. Given the linearity of the van't Hoff plots, thermodynamic parameters, such as the change in enthalpies $\Delta(\Delta H_{2,1})$ and the entropies $\Delta(\Delta S_{2,1})$ for the sulfoxide enantiomers could be calculated. In addition, the elution order did not reverse in the temperature range of this study and the mechanism of enantioseparation did not vary.

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

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## INTRODUCTION

A wide range of biological and physical functions are controlled through precise molecular recognition. Thus, molecular chirality is a fundamental phenomenon that plays an important role in biological processes. Without doubt, enzymes, receptors, and other natural binding sites within biological systems interact with different enantiomers in decisively different ways. As a consequence of such chiral recognition, drug enantiomers may differ in their pharmacological and/or toxicological profiles.[1] 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 adverse effects.[2,3] Because of the different biological activities of enantiomers, the preparation of highly enantiopure compounds is of utmost importance.[4]

The increasing demands for the separation of chiral compounds and the production of enantiomerically pure compounds in the field of pharmacology, chemistry, biotechnology, chemical engineering, etc., have led to enantioselective separation becoming one of the most important analytical tasks.[5] So far, macrocyclic antibiotics, as suitable chiral selectors, are most promising in this respect. The most successful and most extensively used macrocyclic antibiotic CSPs are the glycopeptides.[2,6,7] These chiral macrocyclic phases based on the macrocyclic antibiotics can be operated in reversed phase, normal phase, and polar organic mode conditions.[4]

By changing the glycopeptide antibiotic used for the separation, the enantioselectivity of the separations can be significantly altered. While the glycopeptide antibiotics have similar structures, they often exhibit different but complementary enantioselectivities. This suggests that the mechanism of separation is similar though not identical. Consequently, if only a partial separation is obtained using one of the glycopeptides, there is an excellent probability that a baseline or better separation may be obtained with one of the other glycopeptides.[2,6,8]

Thus far, macrocyclic antibiotics, especially teicoplanin glycopeptides, have become suitable chiral selectors for the separation of not only amino acids, carboxylate compounds,[9–11] but also chiral sulfoxides[12] and many other compounds due to their excellent chiral recognition capabilities. This is attributed to their ability to form simultaneous polar and ionic interactions via the substituents from their multiple chiral centres and binding sites that are located in and about the cavities of the glycopeptide's basket like structure.[11,13]

The enantioseparation power of the teicoplanin aglycone is documented by many papers, which have published comparison studies of the enantioseparation of various compounds using teicoplanin or another glycopeptide with or without their sugar moieties.[2,4,14,15] Considerable work has been done to modify teicoplanin-based chiral stationary phases or in preparing the new ones with similar properties but potential higher resolving power.

As is clear from Figure 1, the glycopeptide chiral selectors possess many functional groups (for example hydroxyl, amine, amide linkages, carboxylic acid, aromatic moieties) and hydrophobic pockets that offer different molecular interactions, including hydrophobic, ionic, hydrogen bonding, dipole–dipole, π-π, and steric interactions.[16] The glycopeptide teicoplanin (T) (Figure 1A) consists of a macrocyclic peptide aglycon with three attached carbohydrate moieties. The aglycon peptide "basket" is in general regarded as hydrophobic. In many cases, the bulky saccharide moieties are responsible for restriction of access to the hydrophobic "basket," which contains several interaction sites. On the other hand, the size and mobility of attached carbohydrate moieties allow steric repulsive interactions and their hydroxyl groups provide hydrogen binding sites. Unlike the native teicoplanin selector (T), which has three sugar moieties bonded to the hydrophobic "basket" through other linkages, the teicoplanin aglycon (TAG) (Figure1B) does not contain any saccharides or the associated nonpolar alkyl chain. Thus, teicoplanin aglycon may become more accessible for some analyte "basket" interactions. In addition, three new OH-groups are produced on the aglycone where the three saccharides are removed. The separation efficiency could be improved by methylation of teicoplanin aglycon to block the hydrogen bonding groups.



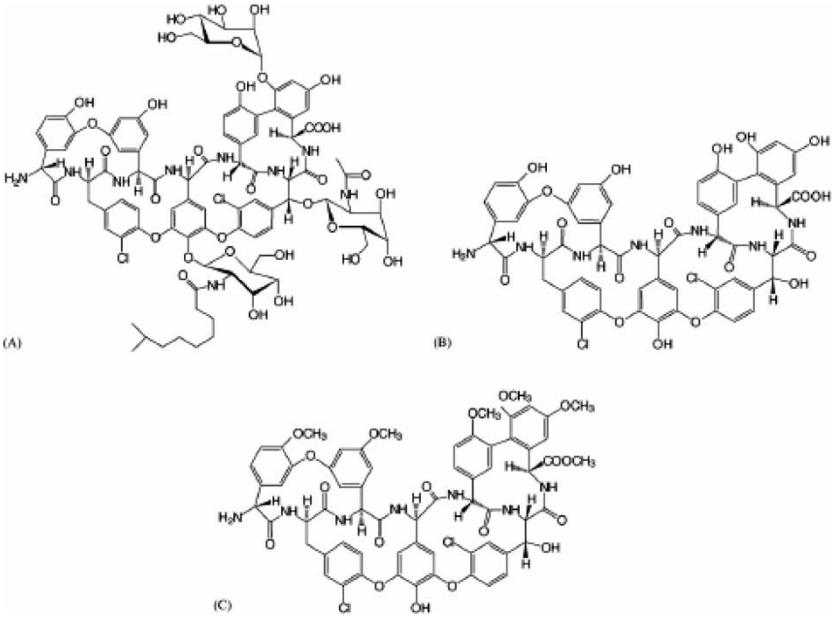



***Figure 1.*** Structures of the macrocyclic antibiotics: (A) teicoplanin, (B) teicoplanin aglycone, and (C) proposed structure of methylated teicoplanin aglycon.[15]

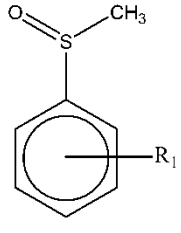
In the case of the recently prepared methylated teicoplanin aglycon (MTAG), the strong hydrogen bonding interactions can be thereby reduced (Figure 1C).[16,17]

The importance of facile separations for enantiomeric compounds, including chiral sulfoxides can not be emphasized enough. Since the first synthesis of chiral sulfoxides in 1926[18] to the present time, chiral sulfoxides have become widely used as important bioactive compounds[19,20] in asymmetric synthesis,[21,22] as valuable reagents for drug synthesis,[23] and as extensively used intermediates in synthetic reactions.[24,25] In addition, thermodynamic studies and the evaluation of temperature effects during the separation of chiral sulfoxides, can serve as a suitable approach to acquire some insight into the enantioseparation process.

## EXPERIMENTAL

### Materials

The names and structures of the chiral sulfoxides used in this study are given in Figure 2. All 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 a method previously described in the literature.[26,27] HPLC grade solvent (methanol) was obtained from Merck (Germany).




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 2.*** Description and numbering of the sulfoxides used in this study.

## 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

Three teicoplanin-based chiral stationary phases, teicoplanin aglycon column (Chirobiotic TAG) (250 × 4, 6 mm I.D.) (Astec, USA), teicoplanin (Chirobiotic T) (250 × 4, 6 mm I.D.) (Astec, USA), and methylated teicoplanin aglycon column (15O × 4, 6 mm I.D.) (Astec, USA) were used for the study. The analytes were dissolved in methanol (concentration 1 mg/mL). UV absorption at a wavelength of 254 nm was used for detection. The teicoplanin-based chiral stationary phases were used in a polar organic mode, i.e., 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.[28] The elution order was confirmed with pure standards and for all the chiral sulfoxides separated using teicoplanin-based columns the (S)-(+)-enantiomer eluted first.[12]



## RESULTS AND DISCUSSION

Systematically changing the temperature in a chromatographic study is one way to control the retention and selectivity of selected analytes. In addition, it could provide information in regard to the factors that affect and control chiral recognition. Temperature dependent chromatographic data, including retention factors, $\alpha$- values, and resolutions for triplicate analysis of the studied racemic chiral sulfoxides, are summarized in Tables 1, 2, and 3 (see Experimental for details). In all cases, as the temperature of the enantioseparation increased, the retention factors as well as enantioselectivities, and resolutions decreased. The teicoplanin aglycon (TAG) chiral stationary phase seemed to be most suitable for the separation of aromatic substituted chiral sulfoxide compounds. In comparison to the other related chiral stationary phases, all analytes had higher selectivities and resolutions on the TAG CSP at all temperatures. This was true even though the methylated-teicoplanin chiral stationary phase produced greater retention factors for the chiral sulfoxides under identical separation conditions. All chiral sulfoxides were least

***Table 1.*** Dependences of enantiomer retention factors ($k_1$), enantioselectivity factors ($\alpha$) and resolutions ($R_{12}$) for sulfoxides with substituents in 2-position, 3-position and 4-position on temperature using teicoplanin aglycon CSP (250 × 4,6 mm I.D), 1 mL/min methanol mobile phase, UV detection at 254 nm (See Experimental for details)

| | Temperature | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 283 K | | | 293 K | | | 303 K | | | 313 K | | | 323 K | | |
| TAG analyte | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ |
| 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 (triplicate analyzes), the ± values of $k_1$, $\alpha$, $R_{12}$ for all analytes are below: $k_1 \pm 0.01$, $\alpha \pm 0.07$, $R_{12} \pm 0.1$.

***Table 2.*** Dependences of enantiomer retention factors ($k_1$), enantioselectivity factors ($\alpha$) and resolutions ($R_{12}$) for sulfoxides with substituents in 2-position, 3-position and 4-position on temperature using methylated teicoplanin aglycon CSP (150 × 4,6 mm I.D), 1 mL/min methanol mobile phase, UV detection at 254 nm. (See Experimental for details)

| | Temperature | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 283 K | | | 293 K | | | 303 K | | | 313 K | | | 323 K | | |
| p-TAG analyte | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ |
| 1 | 0.82 | 1.26 | 1.14 | 0.72 | 1.24 | 0.95 | 0.64 | 1.20 | 0.78 | 0.55 | 1.19 | 0.66 | 0.47 | 1.17 | 0.64 |
| 2 | 0.61 | 1.43 | 1.66 | 0.55 | 1.41 | 1.52 | 0.49 | 1.39 | 1.38 | 0.43 | 1.36 | 1.18 | 0.38 | 1.35 | 1.05 |
| 3 | 0.87 | 1.25 | 1.15 | 0.78 | 1.23 | 1.08 | 0.68 | 1.20 | 0.89 | 0.60 | 1.18 | 0.75 | 0.52 | 1.16 | 0.72 |
| 4 | 0.87 | 1.46 | 2.15 | 0.78 | 1.42 | 1.9 | 0.70 | 1.37 | 1.68 | 0.61 | 1.34 | 1.40 | 0.53 | 1.31 | 1.25 |
| 5 | 0.68 | 1.56 | 2.27 | 0.62 | 1.51 | 2.06 | 0.56 | 1.46 | 1.80 | 0.50 | 1.41 | 1.60 | 0.43 | 1.38 | 1.31 |
| 6 | 0.96 | 1.47 | 2.41 | 0.86 | 1.41 | 2.16 | 0.77 | 1.36 | 1.84 | 0.68 | 1.32 | 1.55 | 0.58 | 1.27 | 1.24 |
| 7 | 0.79 | 1.53 | 2.47 | 0.71 | 1.49 | 2.12 | 0.63 | 1.43 | 1.87 | 0.55 | 1.39 | 1.50 | 0.48 | 1.36 | 1.31 |
| 8 | 0.63 | 1.51 | 2.12 | 0.57 | 1.47 | 1.88 | 0.51 | 1.42 | 1.52 | 0.44 | 1.39 | 1.33 | 0.38 | 1.37 | 1.16 |
| 9 | 0.84 | 1.42 | 2.12 | 0.74 | 1.38 | 1.79 | 0.67 | 1.33 | 1.48 | 0.58 | 1.29 | 1.19 | 0.51 | 1.25 | 0.99 |
| 10 | 0.68 | 1.65 | 2.77 | 0.61 | 1.61 | 2.51 | 0.55 | 1.54 | 2.08 | 0.48 | 1.49 | 1.77 | 0.41 | 1.46 | 1.55 |

For n = 3 (triplicate analyzes), the ± values of $k_1$, $\alpha$, $R_{12}$ for all analytes are below: $k_1 \pm 0.01$, $\alpha \pm 0.03$, $R_{12} \pm 0.1$.

***Table 3.*** Dependences of enantiomer retention factors ($k_1$), enantioselectivity factors ($\alpha$) and resolutions ($R_{12}$) for sulfoxides with substituents in 2-position, 3-position and 4-position on temperature using native teicoplanin CSP (250 × 4,6 mm I.D), 1 mL/min methanol mobile phase, UV detection at 254 nm (See Experimental for details)

| | Temperature | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | 283 K | | | 293 K | | | 303 K | | | 313 K | | | 323 K | | |
| analyte | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ | $k_1$ | $\alpha$ | $R_{12}$ |
| 1 | 0.39 | 1 | 0 | 0.35 | 1 | 0 | 0.32 | 1 | 0 | 0.27 | 1 | 0 | 0.23 | 1 | 0 |
| 2 | 0.29 | 1.42 | 1.54 | 0.26 | 1.41 | 1.43 | 0.24 | 1.38 | 1.28 | 0.21 | 1.35 | 1.09 | 0.18 | 1.37 | 1.06 |
| 3 | 0.40 | 1.17 | 0.84 | 0.35 | 1.17 | 0.72 | 0.33 | 1.12 | 0.63 | 0.29 | 1.10 | 0.50 | 0.27 | 1 | 0 |
| 4 | 0.38 | 1.27 | 1.25 | 0.33 | 1.24 | 1.03 | 0.31 | 1.22 | 0.94 | 0.28 | 1.21 | 0.83 | 0.24 | 1.19 | 0.72 |
| 5 | 0.31 | 1.39 | 1.55 | 0.28 | 1.37 | 1.39 | 0.25 | 1.34 | 1.22 | 0.23 | 1.31 | 1.02 | 0.20 | 1.29 | 0.84 |
| 6 | 0.40 | 1.50 | 2.47 | 0.35 | 1.45 | 2.14 | 0.33 | 1.39 | 1.77 | 0.29 | 1.34 | 1.45 | 0.25 | 1.30 | 1.13 |
| 7 | 0.35 | 1.32 | 1.38 | 0.31 | 1.30 | 1.21 | 0.29 | 1.27 | 1.06 | 0.26 | 1.26 | 0.90 | 0.22 | 1.24 | 0.71 |
| 8 | 0.28 | 1.39 | 1.49 | 0.25 | 1.38 | 1.34 | 0.24 | 1.34 | 1.18 | 0.21 | 1.32 | 0.98 | 0.18 | 1.31 | 0.83 |
| 9 | 0.36 | 1.40 | 1.79 | 0.32 | 1.38 | 1.64 | 0.29 | 1.34 | 1.35 | 0.26 | 1.29 | 1.07 | 0.23 | 1.27 | 0.85 |
| 10 | 0.33 | 1.40 | 1.73 | 0.29 | 1.38 | 1.50 | 0.27 | 1.35 | 1.3 | 0.24 | 1.30 | 1.09 | 0.21 | 1.29 | 0.89 |

For n = 3 (triplicate analyzes), the ± values of $k_1$, $\alpha$, $R_{12}$ for all analytes are below: $k_1 \pm 0.01$, $\alpha \pm 0.04$, $R_{12} \pm 0.1$.

retained on the teicoplanin chiral stationary phase (which has the attached saccharide moieties). The native teicoplanin CSP also produced the worst resolution of all racemic sulfoxides. All of the teicoplanin- based chiral stationary phases have the same aglycone "basket," but they differ in types of functional groups thereon, and this influences the enantioseparation. Thus, modification of the teicoplanin-based chiral stationary phase not only affects its polarity, but also changes the analyte-aglycone "basket" interactions. Clearly, the factors that lead to increased retention do not necessarily contribute to better chiral recognition and enantioseparation. The sulfoxide compounds with halogen atoms on the aromatic ring are better separated in comparison with toluyl sulfoxides. In addition, analyte 10, (racemic 4-fluorophenyl methyl sulfoxide) is the best separated analyte within this group of studied sulfoxides. Even when the temperature of the enantioseparation was about 50°C and the retention factors were relatively small, the resolution factors were $R_{12} = 2{,}2$ for the TAG-CSP, $R_{12} = 1{,}6$ for p-TAG-CSP, and $R_{12} = 0{,}9$ for the T-CSP.



It is well known that the enantioselectivity factor ($\alpha$) is related to the differences in the enantiomeric enthalpy and entropy of transfer as shown in Equation (1), where $\alpha$, $R$, *and* $T$ are the enantioselective factor for the enantiomeric mixture, the gas constant, and the absolute temperature respectively.

$$\ln \alpha = -\frac{\Delta(\Delta H)}{RT} + \frac{\Delta(\Delta S)}{R} \tag{1}$$

Thus, ln $\alpha$ may be plotted as a function of $1/\mathrm{T}$ and using linear regression the $\Delta(\Delta H)$ is obtained from the slope of the line, and the $\Delta(\Delta S)$ from the intercept. This was determined for each set of enantiomers using the three teicoplanin-based chiral stationary phases. The thermodynamic parameters obtained from the van´t Hoff plot (ln $\alpha$ as a function of $1/\mathrm{T}$, Eq. (1) are summarized in Tables 8, 9, and 10 and will be discussed later.

Another widely used version of the van't Hoff expression uses the logarithm of the retention factors ($\ln k_i$) versus the inverse of absolute temperature ($1/\mathrm{T}$) in the form of equation (2),

$$\ln k_i = \frac{-\Delta H_i}{RT} + \frac{\Delta S_i}{R} + \ln \phi \tag{2}$$

where $k$, $\Delta H_i$, $\Delta S_i$ $R$, $T$, and $\phi$ are the retention factor for the solute, partial molar enthalpy of transfer, partial molar entropy of transfer, the gas constant, the absolute temperature, and the phase ratio (that, is the volume of the stationary phase, $V_s$, divided by the volume of the mobile phase, $V_m$,), respectively. The procedure involves plotting ln k against $1/\mathrm{T}$, then setting the slope equal to $-\Delta H_i/R$ and solving for $\Delta H_i$, and enable to determine $\Delta S_i$, from the intercept ($\Delta S_i + \ln \phi$) of the plot (see Table 4, 5 and 6). Chromatographic retention is often used to calculate the partial molar enthalpy ($\Delta H_i$) of transfer of a solute from the mobile phase to the stationary phase. The transfer enthalpy can be used to characterize or

***Table 4.*** The results of linear regression (ln k vs. 1/T) for the first eluted enantiomers, S (+) form, and the second eluted enantiomers, R (−) form, of all studied sulfoxides on TAG-CSP. (See Experimental for details)

| | TAG | | | | | |
|---|---|---|---|---|---|---|
| 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 |

***Table 5.*** The results of linear regression (ln k vs. 1/T) for the first eluted enantiomers, S (+) form, and the second eluted enantiomers, R (−) form, of all studied sulfoxides on p-TAG-CSP. (See Experimental for details)

| | p-TAG | | | | | |
|---|---|---|---|---|---|---|
| Analyte | $-(\Delta H_1/\mathrm{R})$ | $\Delta S_1/\mathrm{R} + \ln \varphi$ | Correlation coefficient, r | $-(\Delta H_2/\mathrm{R})$ | $\Delta S_2/\mathrm{R} + \ln \varphi$ | Correlation coefficient, r |
| 4-position | | | | | | |
| 1 | 1260 ± 64 | −4.63 ± 0.21 | 0.996 | 1370 ± 49 | −4.81 ± 0.16 | 0.998 |
| 4 | 1106 ± 55 | −4.03 ± 0.18 | 0.996 | 1361 ± 51 | −4.55 ± 0.17 | 0.998 |
| 7 | 1124 ± 58 | −4.19 ± 0.19 | 0.996 | 1406 ± 65 | −4.75 ± 0.22 | 0.997 |
| 10 | 1123 ± 83 | −4.33 ± 0.27 | 0.992 | 1468 ± 89 | −5.04 ± 0.29 | 0.995 |
| 3-position | | | | | | |
| 2 | 1089 ± 46 | −4.32 ± 0.15 | 0.997 | 1153 ± 35 | −4.21 ± 0.12 | 0.999 |
| 5 | 1005 ± 78 | −3.92 ± 0.26 | 0.991 | 1278 ± 65 | −4.44 ± 0.21 | 0.996 |
| 8 | 1159 ± 83 | −4.53 ± 0.28 | 0.992 | 1297 ± 66 | −4.62 ± 0.22 | 0.996 |
| 2-position | | | | | | |
| 3 | 1161 ± 45 | −4.23 ± 0.15 | 0.998 | 1361 ± 57 | −4.70 ± 0.19 | 0.997 |
| 6 | 1124 ± 65 | −3.99 ± 0.22 | 0.995 | 1442 ± 58 | −4.74 ± 0.19 | 0.998 |
| 9 | 1126 ± 44 | −4.13 ± 0.14 | 0.998 | 1433 ± 54 | −4.87 ± 0.18 | 0.998 |

***Table 6.*** The results of linear regression (ln k vs. 1/T) for the first eluted enantiomers, S (+) form, and the second eluted enantiomers, R (−) form, of all studied sulfoxides on T-CSP. (See Experimental for details)

| | T | | | | | |
|---|---|---|---|---|---|---|
| Analyte | $-(\Delta H_1/\mathrm{R})$ | $\Delta S_1/\mathrm{R} + \ln \varphi$ | Correlation coefficient, r | $-(\Delta H_2/\mathrm{R})$ | $\Delta S_2/\mathrm{R} + \ln \varphi$ | Correlation coefficient, r |
| 4-position | | | | | | |
| 1 | 1191 ± 108 | −5.12 ± 0.36 | 0.988 | 1191 ± 108 | −5.12 ± 0.36 | 0.988 |
| 4 | 983 ± 85 | −4.44 ± 0.28 | 0.989 | 1106 ± 64 | −4.63 ± 0.21 | 0.995 |
| 7 | 1000 ± 98 | −4.57 ± 0.32 | 0.986 | 1125 ± 58 | −4.73 ± 0.19 | 0.996 |
| 10 | 992 ± 61 | −4.61 ± 0.20 | 0.994 | 1169 ± 70 | −4.89 ± 0.23 | 0.994 |
| 3-position | | | | | | |
| 2 | 1057 ± 88 | −4.95 ± 0.29 | 0.990 | 1189 ± 108 | −5.06 ± 0.36 | 0.988 |
| 5 | 973 ± 53 | −4.60 ± 0.18 | 0.996 | 1096 ± 81 | −4.70 ± 0.27 | 0.992 |
| 8 | 957 ± 115 | −4.64 ± 0.38 | 0.979 | 1082 ± 83 | −4.74 ± 0.27 | 0.991 |
| 2-position | | | | | | |
| 3 | 887 ± 52 | −4.05 ± 0.17 | 0.994 | 1230 ± 78 | −5.08 ± 0.26 | 0.994 |
| 6 | 1023 ± 87 | −4.52 ± 0.29 | 0.989 | 1297 ± 78 | −5.09 ± 0.26 | 0.995 |
| 9 | 1002 ± 32 | −4.55 ± 0.11 | 0.998 | 1312 ± 78 | −5.30 ± 0.26 | 0.995 |

compare various stationary phases using a particular mobile phase. In order to use the van´t Hoff models, and acquire the values of enthalpy and entropy contributions, it is necessary to observe linear dependence. Otherwise, if linear dependence is not observed, there is some possibility that the stationary phase in HPLC may undergo a change in conformation at a certain temperature (transition temperature) and the enthalpy and entropy of the retention process changes (e.g., not constant) over the range of temperatures used. In the case of the chiral sulfoxides in this study, linear dependences were observed with correlation coefficients in the range of 0.979–0.998 for T-CSP; 0,991–0.998 for p-TAG-CSP, and 0.997–0.999 for TAG-CSP. This shows the linear dependence of the retention factors on temperature within the range studied. The results also revealed some differences in the energy contributions as well as the entropy contributions for each separation system. Obviously, differences in the enthalpy and entropy contributions for each CSP were expected, given the differences in the structure of these CSPs. According to the obtained results (Table 4, 5, and 6), the energy contributions on the p-TAG seem to be, in the case of all sulfoxides, bigger in comparison with those calculated for T-CSP and TAG-CSP. Despite very similar values of energy contributions, there are some differences between the entropy contributions calculated for T-CSP and TAG-CSP (Table 4, 6). In all cases, the absolute value of the entropy terms for T-CSP are greater than those calculated for the TAG-CSP, and in some cases, even bigger than values calculated for p-TAG-CSP. The presence of sugar moieties in T-CSP likely contributes to the higher entropy contribution of solute transfer between the mobile phase and stationary phase (Table 6). The larger entropy changes indicate that the sulfoxide molecules are more restricted in this stationary phase, as it is in the case of TAG-CSP and p-TAG-CSP. This loss of freedom is responsible for a reduced distribution of the sulfoxide analytes in the stationary phase, which results in lower values of retention factors of studied sulfoxides. The change of entropy is also probably controlled by the number of solvent molecules released from solvating the CSP. In the case of p-TAG (Table 5), the biggest changes in temperature dependence were observed for studied sulfoxides within the compared teicoplanin-based CSPs. The methylation of the teicoplanin aglycon results in bigger values of the energy contribution for solute transfer (contributions from intermolecular forces increase), therefore, retention of the sulfoxides increases.

Table 7 lists the $\Delta(\Delta H)$ and $\Delta(\Delta S)$ values obtained by plotting selectivity data in Table 1 using Eq. (1) for the three teicoplanin based chiral stationary phases. The main difference in the structure of T-CSP in comparison with p-TAG-CSP and TAG-CSP can also be seen in the values of $\Delta(\Delta H)$ and $\Delta(\Delta S)$ and values of $\Delta(\Delta G)$ (Tables 8, 9, and 10). In the case of analytes 1 and 3 separated on the T-CSP, there was either an inadequate enantioseparation at higher temperatures or no separation in some cases. That explains missing values of $\Delta(\Delta H)$ and $\Delta(\Delta S)$ for these analytes in these cases. The sugar moieties of the T-CSP also contain stereogenic centers and, in this

***Table 7.*** Comparison of the thermodynamic data for the first eluted enantiomers, S (+) form, and the second eluted enantiomers, R (−) form, of all studied sulfoxides using TAG-CSP, p-TAG-CSP and T-CSP. (See Experimental for details)

| | TAG | | | *p*-TAG | | | T | | |
|---|---|---|---|---|---|---|---|---|---|
| Analyte | $\Delta(\Delta H_{2,1})$ (J/mol) | $\Delta(\Delta S_{2,1})$ (J/mol/K) | Correlation coefficient, r | $\Delta(\Delta H_{2,1})$ (J/mol) | $\Delta(\Delta S_{2,1})$ (J/mol/K) | Correlation coefficient,r | $\Delta(\Delta H_{2,1})$ (J/mol) | $\Delta(\Delta S_{2,1})$ (J/mol/K) | Correlation coefficient, r |
| 4-position | | | | | | | | | |
| 1 | −1355 | −2.16 | 0.990 | −1438 | −3.16 | 0.967 | — | — | — |
| 4 | −2187 | −4.07 | 0.992 | −2120 | −4.32 | 0.993 | −1289 | −2.58 | 0.995 |
| 7 | −2336 | −4.16 | 0.992 | −2345 | −4.74 | 0.996 | −1139 | −1.75 | 0.989 |
| 10 | −2569 | −4.49 | 0.993 | −2419 | −4.32 | 0.989 | −1812 | −3.58 | 0.987 |
| 3-position | | | | | | | | | |
| 2 | −1355 | −1.33 | 0.990 | −1139 | −1.00 | 0.995 | −915 | −0.33 | 0.885 |
| 5 | −2037 | −3.08 | 0.981 | −2345 | −4.57 | 0.997 | −1513 | −2.58 | 0.999 |
| 8 | −1962 | −3.08 | 0.997 | −1962 | −3.49 | 0.992 | −1214 | −1.50 | 0.979 |
| 2-position | | | | | | | | | |
| 3 | −1505 | −2.99 | 0.999 | −1355 | −2.91 | 0.986 | — | — | — |
| 6 | −2935 | −6.48 | 0.991 | −2719 | −6.40 | 0.996 | −2877 | −6.73 | 0.999 |
| 9 | −2794 | −6.24 | 0.992 | −2494 | −5.82 | 0.998 | −2045 | −4.32 | 0.988 |

***Table 8.*** Thermodynamic data for the first eluted enantiomers, S (+) form, and the second eluted enantiomers, R (−) form, of all studied sulfoxides using TAG-CSP. (See Experimental for details)

| | Teicoplanin- TAG | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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) | $\alpha$(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 |

***Table 9.*** Thermodynamic data for the first eluted enantiomers, S (+) form, and the second eluted enantiomers, R (−) form, of all studied sulfoxides using p-TAG-CSP. (See Experimental for details)

| | TAG permethylated | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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) | $\alpha$(293 K) | $\Delta(\Delta G_{2,1})_{293\ K}$ (J/mol) | $T_{iso}$ (K) |
| 4-position | | | | | | | | |
| 1 | 173 ± 26 | −0.38 ± 0.09 | 0.967 | −1438 | −3.16 | 1.24 | −513 | 455 |
| 4 | 255 ± 18 | −0.52 ± 0.06 | 0.993 | −2120 | −4.32 | 1.42 | −853 | 490 |
| 7 | 282 ± 14 | −0.57 ± 0.05 | 0.996 | −2345 | −4.74 | 1.49 | −956 | 495 |
| 10 | 291 ± 25 | −0.52 ± 0.08 | 0.989 | −2419 | −4.32 | 1.61 | −1153 | 560 |
| 3-position | | | | | | | | |
| 2 | 137 ± 8 | −0.12 ± 0.03 | 0.995 | −1139 | −1.00 | 1.41 | −847 | 1142 |
| 5 | 282 ± 13 | −0.55 ± 0.04 | 0.997 | −2345 | −4.57 | 1.51 | −1005 | 513 |
| 8 | 236 ± 17 | −0.42 ± 0.06 | 0.992 | −1962 | −3.49 | 1.47 | −939 | 562 |
| 2-position | | | | | | | | |
| 3 | 163 ± 16 | −0.35 ± 0.05 | 0.986 | −1355 | −2.91 | 1.23 | −503 | 466 |
| 6 | 327 ± 16 | −0.77 ± 0.05 | 0.996 | −2719 | −6.40 | 1.41 | −843 | 425 |
| 9 | 300 ± 12 | −0.70 ± 0.04 | 0.998 | −2494 | −5.82 | 1.38 | −789 | 429 |

***Table 10.*** Thermodynamic data for the first eluted enantiomers, S (+) form, and the second eluted enantiomers, R (−) form, of all studied sulfoxides using T-CSP. (See Experimental for details)

| | Teicoplanin-T | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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) | $\alpha$(293 K) | $\Delta(\Delta G_{2,1})_{293\ K}$ (J/mol) | $T_{iso}$ (K) |
| 4-position | | | | | | | | |
| 1 | — | — | — | — | — | 1 | 0 | — |
| 4 | 155 ± 9 | −0.31 ± 0.03 | 0.995 | −1289 | −2.58 | 1.24 | −534 | 500 |
| 7 | 137 ± 12 | −0.21 ± 0.04 | 0.989 | −1139 | −1.75 | 1.3 | −627 | 652 |
| 10 | 218 ± 20 | −0.43 ± 0.07 | 0.987 | −1812 | −3.58 | 1.38 | −765 | 507 |
| 3-position | | | | | | | | |
| 2 | 110 ± 33 | −0.04 ± 0.11 | 0.885 | −915 | −0.33 | 1.41 | −817 | 2750 |
| 5 | 182 ± 3 | −0.31 ± 0.01 | 0.999 | −1513 | −2.58 | 1.37 | −758 | 587 |
| 8 | 146 ± 18 | −0.18 ± 0.06 | 0.979 | −1214 | −1.50 | 1.38 | −775 | 811 |
| 2-position | | | | | | | | |
| 3 | — | — | — | — | — | 1.17 | 0 | — |
| 6 | 346 ± 6 | −0.81 ± 0.02 | 0.999 | −2877 | −6.73 | 1.45 | −903 | 427 |
| 9 | 246 ± 22 | −0.52 ± 0.07 | 0.988 | −2045 | −4.32 | 1.38 | −779 | 473 |

way, present other possible interaction sites for the chiral sulfoxides. In the case of analytes 1 and 3, no enantiomeric separation was observed, while in the case of the related analyte 2 (3-toluyl methyl sulfoxide) separations were observed at all temperatures with resolution factors in the range of 1.06–1.54 (see Table 3). Thus, the position of methyl groups on the aromatic ring of the sulfoxides is of paramount importance.

The similarity in the values of $\Delta(\Delta H)$ and $\Delta(\Delta S)$ for p-TAG and TAG-CSP (Table 7) reveals the possibility of the similar enantioselective mechanism of the studied sulfoxides. For analytes with halogen substituents in the 4-position there is a characteristic increase of the energy contribution to the enantioseparation with increasing electronegativity of the halogen atoms (Tables 8, 9, and 10). This was not observed in the case of the T-CSP. Clearly, the difference in both the enthalpic and entropic contributions for the enantiomeric pairs (Table 7) is less for the T-CSP, except for those sulfoxides with 2-substituted phenyl groups (which have comparable values). Indeed, even though the retention is less on the T-CSP, its enantioselectivity approaches that of the p-TAG- CSP for the 2-substituted compounds. The coelution or changing of the elution order was not observed and enantioselective temperature ($T_{iso}$) calculated for each enantiomeric pair (Table 8, 9, and 10) is over the temperature range of study.



## CONCLUSION

The vańt Hoff plots were linear in all cases, indicating that the mechanism of enantioseparation of the aryl-methyl sulfoxides did not change in the temperature range 10°C–50°C. On the other hand, significant differences in the enantioseparation mechanism were observed for T-CSP in comparison with p-TAG and TAG-CSP. These enantioseparations are enthalpy driven but the extent of the enthalpy and entropy contributions are different for each CSP. In addition, the retention of the studied sulfoxides is also mainly dominated by the molecular forces. The differences in the transfer enthalpy and entropy contributions for each CSP were expected given the differences in the structure of these CSPs. The coelution or changing of the elution order, in the range of the study temperatures, was not observed.

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