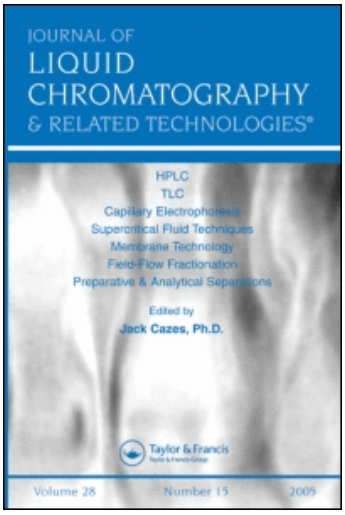

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Study of the Mechanism of Enantioseparation. Part XII. Comparison Study of Thermodynamic Parameters on Separation of Phenylcarbamic Acid Derivatives by HPLC using Macrocyclic Glycopeptide Chiral Stationary Phases

T. Rojkovičová[a]; J. Lehotay[a]; D. W. Armstrong[b]; J. Čižmárik[c]

[a] Department of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, Bratislava, Slovak Republic [b] Department of Chemistry, Gilman Hall, Iowa State University, Ames, Iowa, USA [c] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Bratislava, Slovak Republic

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Study of the Mechanism of Enantioseparation. Part XII. Comparison Study of Thermodynamic Parameters on Separation of Phenylcarbamic Acid Derivatives by HPLC using Macrocyclic Glycopeptide Chiral Stationary Phases

T. Rojkovičová and J. Lehotay
Department of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, Bratislava, Slovak Republic

D. W. Armstrong
Department of Chemistry, Gilman Hall, Iowa State University, Ames, Iowa, USA

J. Čižmárik
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Bratislava, Slovak Republic

Abstract: Four macrocyclic glycopeptide chiral stationary phases (CSPs) based on native teicoplanin (Chirobiotic T), methylated teicoplanin aglycone (Chirobiotic m-TAG), teicoplanin aglycone (Chirobiotic TAG), and vancomycin (Chirobiotic V) were compared for the high performance liquid chromatographic (HPLC) separation of enantiomers of 1-methyl-2-piperidinoethylesters of 2-, 3-and 4- alkoxyphenylcarbamic acid (potential local anaesthetic drugs). The enthalpies (ΔH_i), entropies (ΔS_i), and Gibbs energies (ΔG_i) of transfer were evaluated for the separation of these compounds. The enantiomers were separated isothermally in the range of 0–50°C with 10°C increments, in the polar organic mode. The thermodynamic parameters were calculated in order to gain an understanding of the driving forces for retention in this

Address correspondence to J. Lehotay, Department of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského 9, 812 37 Bratislava, Slovak Republic. E-mail: jozef.lehotay@stuba.sk

chromatographic system. From these results, it is evident that the elongation of the alkoxy-chain has major influence on the values of (ΔS_i) when using the vancomycin CSP and on the values of (ΔH_i) using the teicoplanin-type CSPs.

Keywords: Chiral separation, HPLC, Macrocyclic antibiotics, Thermodynamic study, Enthalpy-entropy compensation, Alkoxysubstituted esters of phenylcarbamic acid

INTRODUCTION

Over the past few years, it has been demonstrated that chiral stationary phases (CSPs) based on macrocyclic antibiotics are extremely useful for the enantiomeric separation of biological and synthetic amino acids,[1–4] food flavor components,[5] reagents, and catalysts advertised as being enantiomerically pure,[6,7] and a wide variety of compounds with various polarities.[8–11] More recently, it has emerged that teicoplanin and vancomycin molecules without the attached carbohydrate (sugar) moieties, consisting of only an aglycone peptide "basket", are more effective in the enantioseparation of certain types of analytes.[8,10–12]

The macrocyclic parts of the glycopeptides can even interact with solutes forming inclusion complexes. Furthermore, in liquid chromatography (HPLC), these CSPs are multimodal, i.e., they can work with polar hydro-organic mobile phases, (reversed phase mode or RPLC), as well as low polar alkane-alcohol mobile phases (normal phase mode) and polar organic mobile phases (non-aqueous polar organic solvents with traces of acetic acid and triethylamine or diethylamine to adjust the chiral selector ionization state). Indeed, it was observed that ionic interactions dominated in the chiral recognition mechanism of acid and/or base enantiomers.[13–16]

It was apparent from early observations, that temperature was an important parameter to control in HPLC. Most often, an increase of the column working temperature produces, at the same time, a decrease of solute retention times and an increase in peak efficiency.[17] The mobile phase viscosity also decreases so it may be possible to work at higher flow rates. Decreases in solute retention times due to an increase in the separation temperature can be viewed as being due to a higher elution strength mobile phase. It is then possible to work with less organic modifier in the mobile phase. The efficiency obtained with macrocyclic glycopeptide CSPs is not usually as high as can be observed with many standard achiral RPLC stationary phases. This is especially true for the second eluting enantiomer. Raising the temperature will increase the solute exchange rate, and hence, improve chromatographic efficiency.[18] Temperature changes also can adversely affect the enantioselectivity factor, which in turn affects the resolution factor, which combines both efficiency and retention factors.

The aim of the present paper is to compare the effect of temperature changes on the separation of chiral alkoxyphenylcarbamic acid derivates

using four commercially available macrocyclic glycopeptide CSPs. The thermodynamic data found from the linear dependencies of the natural logarithms of retention factors ($ln\ k_i$) with ($1/T$) are used to compare the separations obtained using vancomycin and teicoplanin-type CSPs.

EXPERIMENTAL

Materials

The structures of the 1-methyl-2-piperidinoethylesters of 2-, 3-, and 4-alkoxyphenylcarbamic acid are given in Figure 1. All derivates of phenylcarbamic acid used in this study are listed in Table 1, and were prepared according to Pokorná and co-workers.[19] HPLC grade solvent (methanol) was obtained from Merck (Germany). Diethylamine and acetic acid were of analytical grade and were obtained from Lachema (Czech Republic).

Equipment

The HPLC chromatographic system, Hewlett Packard (series 1100), consisted of a quaternary solvent 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 in a column temperature box (LCT 5100, INGOS, Czech Republic).

Methods

A teicoplanin (CHIROBIOTIC T), a teicoplanin aglycon (CHIROBIOTIC TAG) and a vancomycin (CHIROBIOTIC V) CSP (250 × 4.6 mm I.D., Astec, USA), and methylated teicoplanin aglycon (CHIROBIOTIC m-TAG) CSP (150 × 5 μm I.D., Astec, USA) were used for the separation of enantiomers of the alkoxysubstituted esters of phenylcarbamic acid. The analytes were dissolved in methanol (concentration 1 mg/mL). The analytes studied possess a UV absorption maximum at a wavelength of 240 nm that was used for detection. Mobile phases were prepared by mixing methanol with

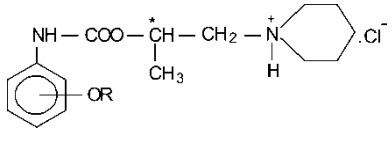

Figure 1. Structure of 1-methyl-2-piperidinoethylesters of 3- and 4-alkoxyphenylcarbamic acid.

Table 1. Description and numbering of the 1-methyl-2-piperidinoethylesters of 2-, 3- and 4-alkoxyphenylcarbamic acid derivates used in this study

2-Position		3-Position		4-Position	
Analyte	R	Analyte	R	Analyte	R
1_2	$-CH_3$	1_3	$-CH_3$	1_4	$-CH_3$
2_2	$-C_2H_5$	2_3	$-C_2H_5$	2_4	$-C_2H_5$
4_2	$-C_4H_9$	4_3	$-C_4H_9$	4_4	$-C_4H_9$
5_2	$-C_5H_{11}$	5_3	$-C_5H_{11}$	5_4	$-C_5H_{11}$
6_2	$-C_6H_{13}$	6_3	$-C_6H_{13}$	6_4	$-C_6H_{13}$
7_2	$-C_7H_{15}$	7_3	$-C_7H_{15}$	7_4	$-C_7H_{15}$

17.5 mmol/L acetic acid and 4.8 mmol/L diethylamine. Separations were carried out at a flow rate of 1.0 mL/min. Thermodynamic data were obtained using isothermal conditions over a temperature range of 0–50°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.

RESULTS AND DISCUSSION

In this work, the enantiomers of 1-methyl-2-piperidinoethylesters of 2-, 3-, and 4-alkoxyphenylcarbamic acid with different alkoxysubstituents (see Table 1) were separated isothermally, at successively different temperatures, using methanol containing 17.5 mmol/L acetic acid and 4.8 mmol/L diethylamine as mobile phase additives (polar organic mode). In all cases, the expected decrease in retention times associated with a rise in column temperature was observed. Results published previously show typical examples.[20–22] From a retention point of view, the elution of the second enantiomer of the 1-methyl-2-piperidinoethylesters of 4-methoxyphenylcarbamic acid on the Chirobiotic V CSP is 3- times quicker compared to the Chirobiotic T CSP, 10-times quicker than on the Chirobiotic TAG CSP and 15- times quicker than on the Chirobiotic m-TAG CSP (see Table 2). Also, the retention factors of these analytes decrease when the number of carbon atoms in the alkoxychain increases in the range of C_1–C_{10}. This decrease in k_i with a methanol mobile phase is the characteristic behaviour when solvophobic interactions between the analytes and the CSP are dominant.

The primary step in the chiral recognition process on teicoplanin and vancomycin containing CSPs are the strong charge-charge interaction between the protonated amine of the analyte molecules and the ammonium group of the teicoplanin and vancomycin chiral stationary phases. The structure of the teicoplanin molecule plays additional important roles in chiral recognition, by supplying appropriate hydrogen-bonding, solvophobic and steric interaction sites, while in the vancomycin molecule, hydrogen-bonding, anionic or

Table 2. Dependences of enantiomer of retention factors (k_a, k_b) for 3-alkoxyderivates of phenylcarbamic acid 1-methyl-2-piperidinoethylesters on chiral columns. (a-first eluted enantiomer, b-second eluted enantiomer, see Experimental for details)

	Chirobiotic V		Chirobiotic TAG		Chirobiotic m-TAG		Chirobiotic T	
Analyt	k_a	k_b	k_a	k_b	k_a	k_b	k_a	k_b
Temperature (293 K)								
1_3a	1.89	1.98	19.49	21.98	27.36	30.54	5.27	5.76
2_3a	1.70	1.82	18.17	20.29	24.02	26.64	4.70	5.08
4_3a	1.47	1.61	15.03	17.81	20.66	23.12	4.06	4.45
5_3a	1.40	1.54	15.64	17.46	19.23	21.72	3.86	4.24
6_3a	1.33	1.48	15.18	17.12	18.25	20.48	3.67	4.04
7_3a	1.28	1.43	14.44	16.28	18.01	20.45	3.53	3.88

(For n = 3, Chirobiotic V): $k_a \pm 0.12$, $k_b \pm 0.17$, (for n = 3, Chirobiotic TAG): $k_a \pm 0.24$, $k_b \pm 0.25$.

(For n = 3, Chirobiotic m-TAG): $k_a \pm 0.32$, $k_b \pm 0.35$, (for n = 3, Chirobiotic T): $k_a \pm 0.18$, $k_b \pm 0.20$.

cationic binding, and dipole stacking interactions are important. Any hindrance of these interactions weakens the chiral recognition. The bulkiness and rigidity of the molecule influence the secondary and tertiary interactions necessary for chiral recognition as well.[2,23] From previous studies it is known that the number of carbon atoms in the alkoxychain, as well as the position of alkoxy-substituents on the aromatic ring, play a significant role in the enantiomeric separation of the studied analytes.[20–22] This trend is probably related to the structure of the macrocyclic glycopeptide CSPs. The Chirobiotic T macromolecule also contains sugar units and a nonyl carbon chain, which likely leads to non-polar interactions between the Chirobiotic T CSP and these analytes. The Chirobiotic TAG does not contain any sugar units, the Chirobiotic m-TAG contains of 6 methyl groups per teicoplanin aglycon molecule, and the carboxy group is a methyl ester.

From Table 2, it is evident that the separation of enantiomers on the Chirobiotic m-TAG column is strongly influenced by the polar interactions of the enantiomers with the stationary phase (the highest retention factors), in contrast to the Chirobiotic V column, where the enantiomers have higher affinity to the mobile phase. The best resolution values for the separation of the alkoxyphenylcarbamic acid derivates[20–22] were observed on the Chirobiotic TAG column and the worst on the Chirobiotic V column. It is important to note, that there was no enantioseparation of the analytes with the alkoxy substitution in the 2- position when using the Chirobiotic T and Chirobiotic V CSPs, as opposed to using the Chirobiotic m-TAG and Chirobiotic TAG CSPs. This result may be due to the presence of the sugar units in the former two of these chiral stationary phases. Considering the

structure of the enantiomers, it was clear that the reason for this is the proximity of the 2-alkoxysubstituent to the stereogenic center. This indicates that steric interactions of the alkoxy chain influence chiral recognition only for the 2- alkoxysubstituted compounds.

The values of the thermodynamic parameters depend on the structure of the compounds and on the chromatographic system, respectively. The mobile phase composition has a critical effect on the mechanism of solute interaction with the stationary phase. This is supported by the thermodynamic parameters obtained through temperature studies. The effect of temperature on the retention of 1-methyl-2-piperidinethylesters of 3- and 4-alkoxyphenylcarbamic acid was studied. In the temperature range of 0–50°C, van't Hoff plots $[ln\ k_i = f(1/T)]$ were linear in all cases. Highly negative $\Delta(\Delta H_{2,1})$ values are indicative of remarkably temperature dependent chiral interactions.

Table 3 presents the thermodynamic data extracted from the separation data for the 3-alkoxyderivates of phenylcarbamic acid 1-methyl-2-piperidinoethylesters. Similar values of the thermodynamic data were observed for the separation of the 4-alkoxyderivates of phenylcarbamic acid. From Table 3, it is evident that for separations on the Chirobiotic T column, the values of enthalpy slightly decrease when the number of carbon atoms number in the alkoxychain increases. However, on the Chirobiotic m-TAG column, the values of enthalpy significantly decrease by increasing the carbon atom number in the alkoxy chain. When the Chirobiotic TAG and Chirobiotic V columns were used, the values of enthalpy increase with increasing numbers of carbon atoms in the alkoxy chain. As seen from the data listed in Table 3, the highest absolute ΔH_i values for these analytes were obtained on the Chirobiotic m-TAG CSP. When the Chirobiotic T, Chirobiotic TAG, Chirobiotic m-TAG columns were used for the separation of enantiomers, the changes of enthalpy are more important than for the Chirobiotic V column. It can be concluded, that the absolute magnitude of the enthalpic term (ΔH_i) is more significant than that of the entropic terms ($T\Delta S_i$) and the energetic changes probably have a greater influence on the separation of enantiomers than steric effects. When the Chirobiotic V column was used for the enantioseparation of the same analytes, the highest absolute ΔS_i values for these enantiomers were achieved. However, on teicoplanin type columns, the changes to entropies on the Chirobiotic TAG slightly increase (on the Chirobiotic m-TAG the values of entropy decrease slightly and on the Chirobiotic T are similar) with increasing numbers of carbon atoms in the alkoxy chain. The changes of entropy on the vancomycin column were more significant in comparison to the teicoplanin based columns. In this case, the steric effects may have a greater influence on the enantiomeric separations.

CONCLUSION

Macrocyclic glycopeptide chiral stationary phases (Chirobiotic T, Chirobiotic TAG, Chirobiotic m-TAG, and Chirobiotic V) were compared for their ability

Table 3. Dependences of enantiomer of slope (ΔH_i) and intercept (ΔS_i) for 3-alkoxyderivates of phenylcarbamic acid 1-methyl-2-piperidinoethylesters on chiral columns. (a-first eluted enantiomer, b-second eluted enantiomer, see Experimental for details)

Analyte	ΔH_1 ($J \cdot mol^{-1}$)	ΔS_1 ($J \cdot mol^{-1} \cdot K^{-1}$)	ΔH_2 ($J \cdot mol^{-1}$)	ΔS_2 ($J \cdot mol^{-1} \cdot K^{-1}$)	$\Delta(\Delta H_{2,1})$ ($J \cdot mol^{-1}$)	$\Delta(\Delta S_{2,1})$ ($J \cdot mol^{-1} \cdot K^{-1}$)	$\Delta(\Delta G_{2,1})_{0°C}$ ($J \cdot mol^{-1}$)
Chirobiotic V[a]							
1_3a	−8771	−24.5	−10475	−29.9	−1704	−5.4	−225
2_3a	−8153	−23.3	−10053	−29.3	−1901	−5.9	−278
4_3a	−8480	−25.6	−10550	−31.9	−2069	−6.3	−347
5_3a	−9228	−28.7	−10518	−32.2	−1290	−3.5	−325
6_3a	−9272	−29.2	−10506	−32.5	−1235	−3.3	−346
7_3a	−9138	−29.2	−10650	−33.3	−1512	−4.1	−384
Chirobiotic TAG[b]							
1_3a	−8143	−3.2	−9520	−7.1	−1377	−4.0	−296
2_3a	−8280	−4.2	−9634	−8.0	−1354	−3.8	−308
4_3a	−8901	−7.4	−9901	−10.2	−1000	−2.8	−236
5_3a	−9076	−8.1	−10123	−11.0	−1047	−2.9	−254
6_3a	−9259	−8.9	−10175	−11.4	−916	−2.5	−237
7_3a	−9346	−9.6	−10277	−12.2	−931	−2.6	−221
Chirobiotic m-TAG[c]							
1_3a	−10121	−6.9	−11216	−9.0	−1096	−2.8	−325
2_3a	−9487	−5.9	−10489	−8.5	−1002	−2.6	−305
4_3a	−8782	−5.0	−9858	−7.7	−1076	−2.7	−335
5_3a	−8228	−3.9	−9328	−6.7	−1100	−2.4	−353
6_3a	−7995	−2.7	−9023	−5.2	−1029	−2.5	−343
7_3a	−7483	−1.9	−8676	−4.9	−1192	−3.0	−372

(*continued*)

Table 3. Continued

Analyte	ΔH_1 ($J \cdot mol^{-1}$)	ΔS_1 ($J \cdot mol^{-1} \cdot K^{-1}$)	ΔH_2 ($J \cdot mol^{-1}$)	ΔS_2 ($J \cdot mol^{-1} \cdot K^{-1}$)	$\Delta(\Delta H_{2,1})$ ($J \cdot mol^{-1}$)	$\Delta(\Delta S_{2,1})$ ($J \cdot mol^{-1} \cdot K^{-1}$)	$\Delta(\Delta G_{2,1})_{0°C}$ ($J \cdot mol^{-1}$)
Chirobiotic T[d]							
1_3a	−7973	−13.4	−9425	−17.6	−1452	−4.2	−312
2_3a	−7911	−14.1	−9141	−17.6	−1230	−3.5	−274
4_3a	−7897	−15.3	−9882	−21.1	−1985	−5.8	−393
5_3a	−7878	−15.7	−8949	−18.5	−1071	−2.8	−306
6_3a	−5401	−7.7	−6711	−11.3	−1310	−3.6	−324
7_3a	−6581	−12.1	−7988	−16.0	−1407	−3.9	−343

[a] $\Delta H_1 \pm 185$ ($J \cdot mol^{-1}$); $\Delta H_2 \pm 250$ ($J \cdot mol^{-1}$); $\Delta S_1 \pm 0.30$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta S_2 \pm 0.35$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta(\Delta H_{2,1}) \pm 56$ ($J \cdot mol^{-1}$); $\Delta(\Delta S_{2,1}) \pm 0.3$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta(\Delta G_{2,1})_{0°C} \pm 30$ ($J \cdot mol^{-1}$).

[b] $\Delta H_1 \pm 193$ ($J \cdot mol^{-1}$); $\Delta H_2 \pm 220$ ($J \cdot mol^{-1}$); $\Delta S_1 \pm 0.18$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta S_2 \pm 0.16$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta(\Delta H_{2,1}) \pm 54$ ($J \cdot mol^{-1}$); $\Delta(\Delta S_{2,1}) \pm 0.2$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta(\Delta G_{2,1})_{0°C} \pm 29$ ($J \cdot mol^{-1}$).

[c] $\Delta H_1 \pm 155$ ($J \cdot mol^{-1}$); $\Delta H_2 \pm 170$ ($J \cdot mol^{-1}$); $\Delta S_1 \pm 0.18$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta S_2 \pm 0.23$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta(\Delta H_{2,1}) \pm 45$ ($J \cdot mol^{-1}$); $\Delta(\Delta S_{2,1}) \pm 0.19$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta(\Delta G_{2,1})_{0°C} \pm 32$ ($J \cdot mol^{-1}$).

[d] $\Delta(H_1 \pm 190$ ($J \cdot mol^{-1}$); $\Delta(H_2 \pm 210$ ($J \cdot mol^{-1}$); $\Delta(S_1 \pm 0.20$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta S_2 \pm 0.22$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta(\Delta H_{2,1}) \pm 58$ ($J \cdot mol^{-1}$); $\Delta(\Delta S_{2,1}) \pm 0.17$ ($J \cdot mol^{-1} \cdot K^{-1}$); $\Delta(\Delta G_{2,1})_{0°C} \pm 31$ ($J \cdot mol^{-1}$).

to separate enantiomers of alkoxyphenylcarbamic acid derivates by HPLC, and also to determine thermodynamic data, including the enthalpy (ΔH_i) and entropy (ΔS_i) of transfer. Enantioresolution is better at lower temperatures even though retention times are higher and the peak efficiencies lower. Once the separation is optimized, it may be possible to raise slowly the temperature in order to improve peak shapes and reduce retention times. The enantioresolution factors will be reduced as well. This study shows that the polar organic mobile phases can produce enthalpy as well as entropy driven separations. From these results, it can be concluded that the greatest influence on the separation of enantiomers of alkoxyphenylcarbamic acid derivates using the Chirobiotic m-TAG CSP is the enthalpy, while the entropy is more important for the Chirobiotic V CSP.

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