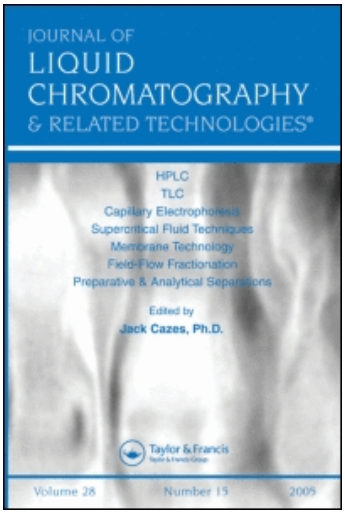

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Study of the Mechanism of Enantioseparation. VII. Effect of Temperature on Retention of Some Enantiomers of Phenylcarbamic Acid Derivates on a Teicoplanin Aglycone Chiral Stationary Phase

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Study of the Mechanism of Enantioseparation. VII. Effect of Temperature on Retention of Some Enantiomers of Phenylcarbamic Acid Derivates on a Teicoplanin Aglycone Chiral Stationary Phase

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ABSTRACT

It has been found that the teicoplanin aglycone (CHIROBIOTIC TAG) chiral stationary phase is a useful column for the high performance liquid

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chromatographic (HPLC) separation of enantiomers of 1-methyl-2-piperidinoethylesters of 2-, 3- and 4-alkoxy-phenylcarbamic acid (potential local anaesthetic drugs) in the polar organic mode. The enantiomers were separated on a CHIROBIOTIC TAG column, isothermally in the range of 0–50°C with 10°C increments, using methanol [100 mL (v)] containing 17.5 mmol L^{-1} acetic acid and 4.8 mmol L^{-1} diethylamine as a mobile phase. van't Hoff plots (dependence of $\ln k_i$ on $1/T$, where k is the retention factor of a solute i and T is the temperature) were linear in the studied temperature interval. This allowed the determination of interaction enthalpies (ΔH_i), entropy (ΔS_i), and Gibbs energies (ΔG_i). This thermodynamic information was used to evaluate the retention and resolution of enantiomers of studied analytes in this HPLC system.

Key Words: Enantiomeric separation; HPLC; CHIROBIOTIC TAG; Thermodynamic study; Enthalpy–entropy compensation; Local anaesthetic drugs; Alkoxysubstituted esters of phenylcarbamic acid.

INTRODUCTION

The search for new, effective, chiral selectors, capable of separating a wide variety of enantiomeric compounds, is an ongoing process. In the past few years, macrocyclic antibiotics have been shown to be an exceptionally useful class of chiral selectors for the separation of enantiomers of biological and pharmacological importance.[1–3] Teicoplanin aglycone (CHIROBIOTIC TAG) is one of the most recently introduced chiral selectors from this class. Teicoplanin aglycone chemically bonded on silica gel is now available commercially and has been successfully used for the separation of enantiomers of underivatized amino acids, carboxylic acids, phenylcarbamic acid derivatives, and many other compounds. Its excellent chiral discrimination capabilities are attributed to simultaneous stereospecific polar and ionic interactions with the substituents of its multiple chiral centers (more than 20), as well as binding sites, located in the cavities of a basket-like aglycone structure.[3–7]

The direct enantiomer separation is based on the formation of reversible diastereoisomeric complexes, which are created by intermolecular interactions of enantiomers with the chiral selector.[8] The formation process, for the R and S enantiomers, can be characterized by thermodynamic parameters (ΔG_i, ΔH_i, ΔS_i). These can be calculated for both enantiomers, according to the equation:

$$\Delta G_i = \Delta H_i - T\,\Delta S_i = -RT \ln K_i \tag{1}$$

where ΔG_i is the molar Gibbs free energy, K_i is the solute partition coefficient, R is the universal gas constant, and T is the temperature in K.[2,8–17]

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It is generally accepted that the temperature has a major impact on retention, enantioselectivity, resolution, and column efficiency.[10–13,17–21] The dependence of chromatographic retention on temperature is described by the following equation:

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

where k_i is the retention factor of a solute ($k_i = (t_R - t_M)/t_M$), ΔH_i is the interaction enthalpy of this solute in the chromatographic system, ΔS_i is the entropy of this solute, Φ is the phase ratio of the chromatographic column ($\Phi = V_M/V_s$, where V_M is the column hold up volume, and V_s is the volume of the chiral selector containing stationary phase).

Equation (2) shows that a plot of $\ln k_i$ on $1/T$ (van't Hoff plot) should be linear with a slope of $\Delta H_i/R$ and an intercept of $\Delta S_i/R + \ln \Phi$, if ΔH_i is invariant with temperature.[2,9,11] Non-linear plots are, however, often observed when the surface of the stationary phase is heterogeneous and the retention of a solute is influenced by mixed retention mechanisms, or if there are conformational (or other) changes in the stationary phase with temperature.[18]

The dependence of the natural logarithm of the selectivity factor ($\ln \alpha$) on the reciprocal temperature ($1/T$) is given by the following relationship:

$$\ln \alpha = \frac{-\Delta(\Delta H_{2,1})}{RT} + \frac{\Delta(\Delta S_{2,1})}{R} \tag{3}$$

where $\Delta(\Delta H_{2,1})$ and $\Delta(\Delta S_{2,1})$ are the enthalpy and entropy differences characterizing enantiomer-interactions with mobile and chiral stationary phases.

In high performance liquid chromatographic (HPLC), the enantioseparation is more influenced by the enthalpic term in most cases. This is, because, the experiment is usually performed at relatively low temperatures. The interaction of enantiomers with a chromatographic system then leads to negative $\Delta(\Delta H_{2,1})$ and $\Delta(\Delta S_{2,1})$ values. Since these thermodynamic parameters are easily accessible, they are frequently used to provide information on the separation system. If the dependence of $\ln \alpha$ on $1/T$ is linear with a slope $\Delta(\Delta H_{2,1})/R$ and a $\ln k_i$ is intercept $\Delta(\Delta S_{2,1})/R$, then it can be assumed that:

i. ΔH and ΔS are temperature independent.
ii. The enantiomers are interacting with a chiral selector by single associative mechanism.
iii. Solvation–desolvation equilibria do not obscure the association process of the enantiomers with the CSP.[18]

As stated above, enantioselectivity, expressed by $\Delta(\Delta G_{2,1})$, is mainly influenced by $\Delta(\Delta H_{2,1})$ at low temperatures. With increasing temperature,

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the enthalpic term will be more and more compensated by $T\Delta(\Delta S_{2,1})$. At a certain temperature, (the isoenantioselective temperature, T_{iso}) $\Delta(\Delta G_{2,1}) = 0$ and the enantiomers are not separated. Above the enantioselectivity temperature, the elution order of the enantiomers can be reversed and the enantioselectivity is dominantly influenced by the entropic term.[9]

The aim of the present paper was to investigate the effects of temperature on the enantioselective separations of 1-methyl-2-piperidinoethylesters of 2-, 3-, and 4-alkoxyphenylcarbamic acid on the CHIROBIOTIC TAG chiral stationary phase. Thermodynamic data found from the linear dependencies of the natural logarithms of retention and selectivity factors ($\ln k_i$ and $\ln \alpha$, respectively) with $(1/T)$ were used to study some mechanistic aspects of the chiral recognition process.[10–13,17,18,21]

EXPERIMENTAL

Materials

The structure of 1-methyl-2-piperidinoethylesters of 2-, 3-, and 4-alkoxyphenylcarbamic acid is given in Fig. 1. All derivates of phenylcarbamic acid used in this study are listed in Table 1, and were prepared according to Pokorna et al.[22] HPLC grade solvent (methanol) was obtained from Merck (Germany). Diethylamine and acetic acid were obtained from Lachema (Czech Republic).

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).

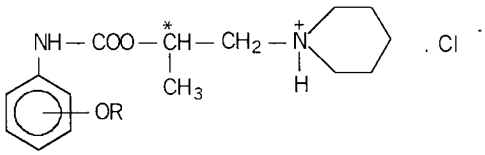

Figure 1. Structure of 1-methyl-2-piperidinoethylesters of 2-, 3-, and 4-alkoxyphenylcarbamic acid.

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

2-Position		3-Position		4-Position	
Analyte	R	Analyte	R	Analyte	R
1v	$-CH_3$	2v	$-CH_3$	3v	$-CH_3$
4v	$-C_2H_5$	5v	$-C_2H_5$	6v	$-C_2H_5$
10v	$-C_4H_9$	11v	$-C_4H_9$	12v	$-C_4H_9$
13v	$-C_5H_{11}$	14v	$-C_5H_{11}$	15v	$-C_5H_{11}$
16v	$-C_6H_{13}$	17v	$-C_6H_{13}$	18v	$-C_6H_{13}$
19v	$-C_7H_{15}$	20v	$-C_7H_{15}$	21v	$-C_7H_{15}$
28v	$-C_{10}H_{21}$	29v	$-C_{10}H_{21}$	30v	$-C_{10}H_{21}$

Methods

A CHIROBIOTIC TAG column (250 × 4.6 mm^2 I.D.) (Astec, USA) was used for the separation of enantiomers of the alkoxysubstituted esters of phenylcarbamic acid. The analytes were dissolved in methanol (concentration 1 $mg\,mL^{-1}$). 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 [100 mL (v)] with 17.5 $mmol\,L^{-1}$ acetic acid and 4.8 $mmol\,L^{-1}$ diethylamine. Separations were carried out at a flow rate of 1.0 $mL\,min^{-1}$. Thermodynamic data were measured under 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. The elution of enantiomers is, therefore, characterized in the text and tables with 1(−) and 2(+) labels, respectively (Fig. 2).

RESULTS AND DISCUSSION

Effect of Temperature on Retention, Selectivity, and Resolution Factors

It has been reported, that the teicoplanin aglycone chiral stationary phase is able to resolve enantiomers of alkoxyphenylcarbamic acid esters by HPLC in the polar organic mode, where hydrogen bonding, dipolar interactions, steric interactions, and $\pi-\pi$ interactions were dominant.[3]

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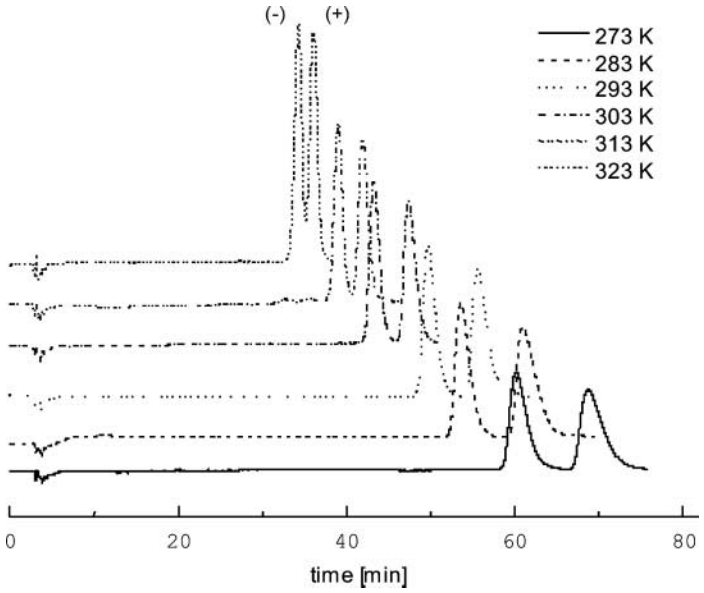

Figure 2. Temperature dependence of the enantiomeric separation of analyte 21v using the CHIROBIOTIC TAG column (see Experimental for details).

In this work, the enantiomers of alkoxyphenylcarbamic acid derivatives with different alkoxy substituents (see Table 1) were separated isothermally at various temperatures, using methanol [100 mL (v)] containing 17.5 mmol L^{-1} acetic acid and 4.8 mmol L^{-1} diethylamine as the mobile phase. Table 2 lists the retention factors (k_1, k_2) measured for these analytes, both of which increase with decreasing column temperature. The peak symmetry also deteriorates with decreasing column temperature. Moreover, from Table 2, it is evident that 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} (e.g., the k_1 and k_2 of the 4-alkoxyphenylcarbamic acids varied from ~32 to ~10). The lowest retention factors, were found for the 2-alkoxysubstituted esters of phenylcarbamic acid. (e.g., from ~23 to ~6).

In most cases, the selectivity (α) and the resolution (R_{21}) of the enantiomers decrease with an increase in temperature. The selectivity factor, however, does not adequately describe the separation of enantiomers, since it does not include information about peak widths. This is why we have used the resolution factor to describe the degree of enantiomeric separation. The data given in Table 2, shows that the magnitude of the decrease of R_{21} depends

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Table 2. Dependences of enantiomer retention factors (k_1, k_2) and resolutions (R_{21}) for 2-, 3-, and 4-alkoxy derivates of phenylcarbamic acid 1-methyl-2-piperidinoethylesters on temperature (see Experimental for details).

	Temperature (K)																	
	273			283			293			303			313			323		
Analyte	k_1	k_2	R_{21}	k_1	k_2	R_{21}	k_1	k_2	R_{21}	k_1	k_2	R_{21}	k_1	k_2	R_{21}	k_1	k_2	R_{21}
2-Alkoxy derivates[a]																		
1v	21.12	25.03	4.0	19.49	22.42	3.6	16.78	19.89	3.0	15.49	17.64	2.8	13.74	15.18	2.3	12.18	13.60	1.8
4v	17.99	20.70	3.4	16.61	18.54	3.2	14.15	16.12	2.4	12.94	13.87	1.4	11.59	12.81	1.7	10.38	11.25	1.6
10v	14.59	17.46	3.1	13.07	16.28	3.1	11.82	14.44	2.9	10.38	12.06	2.3	9.03	10.59	1.6	8.41	8.67	0.9
13v	13.87	15.80	2.1	13.05	14.59	2.0	11.59	12.81	1.8	10.07	10.59	1.4	9.12	9.68	1.0	7.92	8.67	0.4
16v	13.20	14.88	2.0	12.18	13.60	1.6	10.49	11.94	1.4	9.87	10.07	1.1	8.41	8.85	0.6	7.46	8.17	0.4
19v	13.46	14.73	1.8	12.43	13.20	1.7	11.13	11.82	1.4	9.68	10.38	1.1	8.25	8.85	0.7	7.61	7.77	0.4
28v	11.13	12.55	2.0	10.38	11.47	1.5	9.21	9.97	1.3	7.92	8.85	0.9	6.89	7.32	0.7	6.30	6.62	0.4
3-Alkoxy derivates[b]																		
2v	24.53	29.08	2.9	22.42	25.28	2.5	19.49	21.98	2.4	17.81	19.89	2.1	15.80	17.29	1.9	14.15	15.03	1.3
5v	22.42	27.39	2.5	20.29	23.10	2.4	18.17	20.29	2.2	15.96	17.99	1.9	14.44	15.96	1.6	12.81	14.01	1.2
11v	20.29	23.10	2.7	17.46	20.49	2.6	15.03	17.81	2.4	13.60	15.96	2.1	12.43	13.74	1.8	11.02	11.82	1.5
14v	19.49	22.65	2.9	17.12	19.69	2.7	15.64	17.46	2.5	13.60	15.33	2.2	12.06	13.20	1.8	10.70	11.47	1.1
17v	19.30	22.20	2.8	16.78	19.49	2.6	15.18	17.12	2.5	13.33	14.44	2.2	11.82	12.81	1.9	10.28	11.25	1.5
20v	18.54	21.54	2.9	16.12	18.36	2.7	14.44	16.28	2.6	12.55	14.15	2.3	11.13	12.43	1.9	9.68	10.59	1.5
29v	15.18	19.69	2.9	13.46	15.33	2.7	11.94	12.94	2.6	10.28	10.91	2.3	9.03	9.78	1.8	8.00	8.76	1.3

(*continued*)

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Table 2. Continued.

	Temperature (K)																	
	273			283			293			303			313			323		
Analyte	k_1	k_2	R_{21}	k_1	k_2	R_{21}	k_1	k_2	R_{21}	k_1	k_2	R_{21}	k_1	k_2	R_{21}	k_1	k_2	R_{21}
4-Alkoxy derivates[c]																		
3v	27.66	32.14	2.3	25.03	28.50	2.1	22.65	25.03	1.9	20.29	22.20	1.7	18.17	19.30	1.4	16.12	16.95	1.0
6v	25.28	29.37	2.4	22.87	25.53	2.2	20.49	23.34	2.0	18.17	20.09	1.7	16.28	17.29	1.4	14.73	15.18	1.0
12v	21.76	25.53	2.6	19.30	22.42	2.7	16.78	18.92	2.2	15.49	17.46	1.9	13.60	15.03	1.5	12.18	12.81	1.1
15v	21.12	24.53	2.6	18.45	21.54	2.1	17.12	18.54	2.2	14.73	16.44	1.9	13.20	14.44	1.5	11.59	12.30	1.1
18v	19.89	23.34	2.5	17.99	20.49	2.3	15.18	17.29	2.2	13.46	15.49	1.8	12.43	13.07	1.4	11.02	11.82	1.0
21v	20.09	23.57	2.5	17.99	19.89	2.3	15.96	18.17	2.2	13.87	15.33	1.8	12.43	13.46	1.5	11.02	11.47	1.1
30v	17.99	21.12	2.5	15.80	17.99	2.4	14.01	15.49	2.2	12.68	13.46	1.9	10.91	11.70	1.5	9.30	10.07	1.1

[a](For $n = 3$): $k_1 = \pm 0.27$, $k_2 = \pm 0.23$, $R_{21} = 0.1$.
[b](For $n = 3$): $k_1 = \pm 0.24$, $k_2 = \pm 0.25$, $R_{21} = 0.1$.
[c](For $n = 3$): $k_1 = \pm 0.28$, $k_2 = \pm 0.26$, $R_{21} = 0.1$.

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on the position of the alkoxy group on the phenyl ring (e.g., in the 2-position R_{21} varies from 4.0 to 0.3, in the 3-position R_{21} from 2.9 to 1.2, and in the 4-position R_{21} from 2.6 to 1.0). Studying the dependence of the resolution of enantiomers on the analyte structures, we have found that the length of the alkoxychain: (a) in the 2-position has a significant influence (higher values of R_{21} with shorter chain length), and (b) in the 3- and 4-positions has practically no influence.

This indicates that steric interactions of the alkoxy chain influences chiral recognition only for the 2-substituted compounds. Considering the structure of these compounds, it is clear that the reason for this is the proximity of the 2-alkoxy substituent to the stereogenic center.

Determination of Thermodynamic Parameters

The correlation coefficients of the van't Hoff plots (Eq. (2) for the enantiomers of all compounds in this study, indicated good linearity (correlation coefficients were higher than 0.993, see Table 3 and Fig. 3). Similar dependencies were obtained for all of the enantiomers in this study (see the $\Delta(\Delta H_{2,1})$, $\Delta(\Delta S_{2,1})$, $\Delta(G\Delta_{2,1})$ values listed in Table 3). From Eq. (1), it follows that the isoenantioselective temperature (T_{iso}) can be defined as the ratio:

$$T_{iso} = \frac{\Delta(\Delta H_{2,1})}{\Delta(\Delta S_{2,1})} \tag{4}$$

The isoenantioselective temperature determined in this work (370 ± 35 K see below) was higher than the working temperature range (0–50°C). It has been shown, that the (−)-enantiomers eluted prior to (+)-enantiomers in all cases. From the aforementioned data (Table 3), it has been concluded that the enantiomeric separation of 1-methyl-2-piperidinoethylesters of 2-, 3- and 4-alkoxysubstituted phenylcarbamic acid on the CHIROBIOTIC TAG column is enthalpy driven.

Enthalpy–Entropy Compensation

A further thermodynamic approach to the analysis of physicochemical data used in this work was enthalpy–entropy compensation,[2,11] that can be expressed by the formula:

$$\Delta H_i = \beta \Delta S_i + \Delta G_\beta \tag{5}$$

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Table 3. Thermodynamic data for the first eluted enantiomers, (−) form, and the second eluted enantiomers, (+) form, of 2-, 3-, and 4-alkoxyphenylcarbamic acid 1-methyl-2-piperidinoethyl esters (see Experimental for details).

Analyte	ΔH_1 ($J\,mol^{-1}$)	ΔS_1 ($J\,mol^{-1}\,K^{-1}$)	$\Delta G_{1.0^\circ C}$ ($J\,mol^{-1}$)	ΔH_2 ($J\,mol^{-1}$)	ΔS_2 ($J\,mol^{-1}\,K^{-1}$)	$\Delta G_{2.0^\circ C}$ ($J\,mol^{-1}$)	$\Delta(\Delta H_{2.1})$ ($J\,mol^{-1}$)	$\Delta(\Delta S_{2.1})$ ($J\,mol^{-1}\,K^{-1}$)	$\Delta(\Delta G_{2.1})_{0^\circ C}$ ($J\,mol^{-1}$)	T_{iso} (K)
2-Alkoxy derivates[a]										
1v	−8,723	−6.05	−7,071	−9,691	−8.93	−7,253	−968	−2.88	−182	336[b]
4v	−8,791	−7.03	−6,872	−9,719	−9.79	−7,046	−928	−2.76	−175	336[b]
10v	−8,930	−8.32	−6,659	−9,823	−10.95	−6,834	−893	−2.63	−175	340[b]
13v	−9,025	−9.26	−6,497	−9,927	−11.97	−6,659	−902	−2.71	−162	333[b]
16v	−9,146	−10.43	−6,299	−10,009	−12.96	−6,471	−863	−2.53	−172	341[b]
19v	−9,325	−11.41	−6,210	−10,140	−13.86	−6,356	−815	−2.45	−146	333[b]
28v	−9,509	−14.06	−5,671	−10,462	−16.88	−5,854	−953	−2.82	−183	338[b]
3-Alkoxy derivates[c]										
2v	−8,143	−3.15	−7,283	−9,520	−7.11	−7,579	−1,377	−3.96	−296	348[d]
5v	−8,280	−4.20	−7,133	−9,634	−8.03	−7,442	−1,354	−3.83	−308	354[d]
11v	−8,901	−7.36	−6,892	−9,901	−10.16	−7,127	−1,000	−2.80	−236	356[d]
14v	−9,076	−8.06	−6,874	−10,123	−10.97	−7,128	−1,047	−2.91	−254	360[d]
17v	−9,259	−8.88	−6,834	−10,175	−11.37	−7,071	−916	−2.49	−237	368[d]
20v	−9,346	−9.61	−6,722	−10,277	−12.21	−6,944	−931	−2.60	−221	358[d]
29v	−9,529	−10.86	−6,564	−10,545	−13.68	−6,810	−1,016	−2.82	−246	360[d]

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4-Alkoxy derivates[e]										
3v	−7,889	−1.10	−7,589	−9,403	−5.15	−7,997	−1,514	−4.05	−408	374[f]
6v	−8,033	−1.99	−7,490	−9,664	−6.46	−7,900	−1,631	−4.47	−410	365[f]
12v	−8,455	−4.28	−7,287	−9,905	−8.24	−7,656	−1,450	−3.96	−369	366[f]
15v	−8,722	−5.58	−7,199	−9,993	−8.95	−7,551	−1,271	−3.37	−352	378[f]
18v	−8,791	−6.26	−7,082	−10,186	−10.07	−7,437	−1,395	−3.81	−355	366[f]
21v	−8,909	−7.11	−6,968	−10,343	−10.85	−7,381	−1,434	−3.74	−413	383[f]
30v	−9,424	−9.08	−6,945	−10,756	−12.58	−7,322	−1,332	−3.50	−377	381[f]

[a]$\Delta H_1 = \pm 105$ ($J\,mol^{-1}$); $\Delta H_2 = \pm 150$ ($J\,mol^{-1}$); $\Delta S_1 = \pm 0.11$ ($J\,mol^{-1}\,K^{-1}$); $\Delta S_2 = \pm 0.13$ ($J\,mol^{-1}\,K^{-1}$); $\Delta(\Delta H_{2.1}) = \pm 32$ ($J\,mol^{-1}$); $\Delta(\Delta S_{2.1}) = \pm 0.12$ ($J\,mol^{-1}\,K^{-1}$). $\Delta G_1 = \pm 169$ ($J\,mol^{-1}$); $\Delta G_2 = \pm 171$ ($J\,mol^{-1}$); $\Delta(\Delta G_{2.1})_{0°C} = \pm 20$ ($J\,mol^{-1}$).
[b]Temperature reported to the nearest 7 K (for $n = 3$).
[c]$\Delta H_1 = \pm 193$ ($J\,mol^{-1}$); $\Delta H_2 = \pm 220$ ($J\,mol^{-1}$); $\Delta S_1 = \pm 0.18$ ($J\,mol^{-1}\,K^{-1}$); $\Delta S_2 = \pm 0.16$ ($J\,mol^{-1}\,K^{-1}$); $\Delta(\Delta H_{2.1}) = \pm 54$ ($J\,mol^{-1}$); $\Delta(\Delta S_{2.1}) = \pm 0.15$ ($J\,mol^{-1}\,K^{-1}$); $\Delta G_1 = \pm 192$ ($J\,mol^{-1}$); $\Delta G_2 = \pm 212$ ($J\,mol^{-1}$); $\Delta(\Delta G_{2.1})_{0°C} = \pm 29$ ($J\,mol^{-1}$).
[d]Temperature reported to the nearest 10 K (for $n = 3$).
[e]$\Delta H_1 = \pm 187$ ($J\,mol^{-1}$); $\Delta H_2 = \pm 159$ ($J\,mol^{-1}$); $\Delta S_1 = \pm 0.12$ ($J\,mol^{-1}\,K^{-1}$); $\Delta S_2 = \pm 0.16$ ($J\,mol^{-1}\,K^{-1}$); $\Delta(\Delta H_{2.1}) = \pm 55$ ($J\,mol^{-1}$); $\Delta(\Delta S_{2.1}) = \pm 0.14$ ($J\,mol^{-1}\,K^{-1}$); $\Delta G_1 = \pm 139$ ($J\,mol^{-1}$); $\Delta G_2 = \pm 164$ ($J\,mol^{-1}$); $\Delta(\Delta G_{2.1})_{0°C} = \pm 27$ ($J\,mol^{-1}$).
[f]Temperature reported to the nearest 9 K (for $n = 3$).

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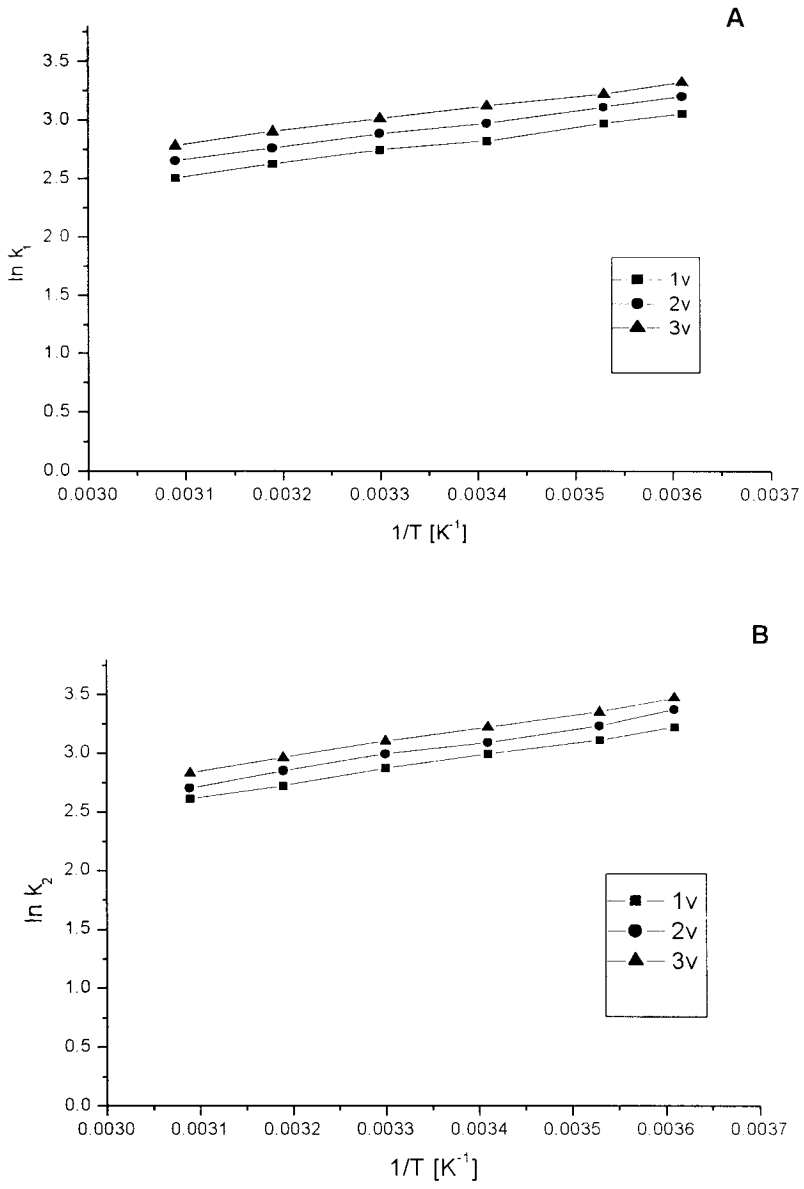

Figure 3. Dependence of natural logarithms of retention factors ($\ln k_i$) on the inverse of temperature ($1/T$) for 2-, 3-, and 4-methoxysubstituted esters of alkoxyphenylcarbamic acid (see Experimental for details).

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where ΔG_β is the Gibbs free energy of the enantiomeric interactions in the chromatographic system at the compensation temperature (β). The combination of Eqs. (2) and (5) leads to Eq. (6):

$$\ln k_i = \frac{-\Delta H_i}{R}\left(\frac{1}{T} - \frac{1}{\phi}\right) - \frac{\Delta G_\phi}{\phi R} + \ln \beta \tag{6}$$

which shows that plots of $\ln k_i$ on $-\Delta H_i$ can be used to determine the compensation temperature. If enthalpy-entropy compensation is observed, all compounds have the same free energy change, ΔG_β, at the compensation temperature β, and all compounds will have the same net retention at this temperature, although their temperature dependencies may differ.[11]

Figure 4 shows the enthalpy–entropy compensation plots ($\ln k_i$ vs. $-\Delta H_i$) for analytes with alkoxysubstitution in the 2-, 3-, and 4-positions ($T = 273$ K). Similar dependencies were observed at other studied temperatures. Figure 5 shows the dependence of $\Delta(\Delta H_{2,1})$ on $T\Delta(\Delta S_{2,1})$ for 4-alkoxy derivates of phenylcarbamic acid. The confidence interval at 90.0% probability shows no dependence of chiral recognition on the position of alkoxysubstituent on the phenyl ring, or the number of carbon atoms in the alkoxychain (C_1–C_{10}). Similar conclusions were obtained for 2- and 3-alkoxy derivatives of phenylcarbamic acid. Statistical treatment of the lines obtained for enantiomers of all the studied 1-methyl-2-piperidinoethylesters of 2-, 3- and 4-alkoxysubstituted phenylcarbamic acid shows the same compensation temperature, 370 ± 35 K.

Dependence of Enthalpy on the Alkoxy Chain Carbon Number, and Its Position in the Phenyl Ring

The plots in Fig. 6 show that the enthalpy values ($-\Delta H_i$) of these enantiomers decrease with increasing length of the alkoxychain. The dependence is linear for both enantiomers with alkoxy-substitution in the 2-position. Similar dependencies were also obtained for the 3- and 4-substituted analogues. The enantiomers with 10 carbon atoms in the alkoxychain (C_{10}) have very poor retention (see Table 2) as a consequence of very weak interactions with CSP (the absolute value of $-\Delta H_i$ was the lowest). On the other hand, enantiomers with a single carbon atom in the alkoxychain (C_1) had very high retention. In this case, the volume of molecule and, also, the space-configuration of molecule, may play an important role in retention. From data in Table 3, it is evident that both the enthalpy and entropy are negative, and their absolute values increase with the number of carbon atoms in the alkoxy group.

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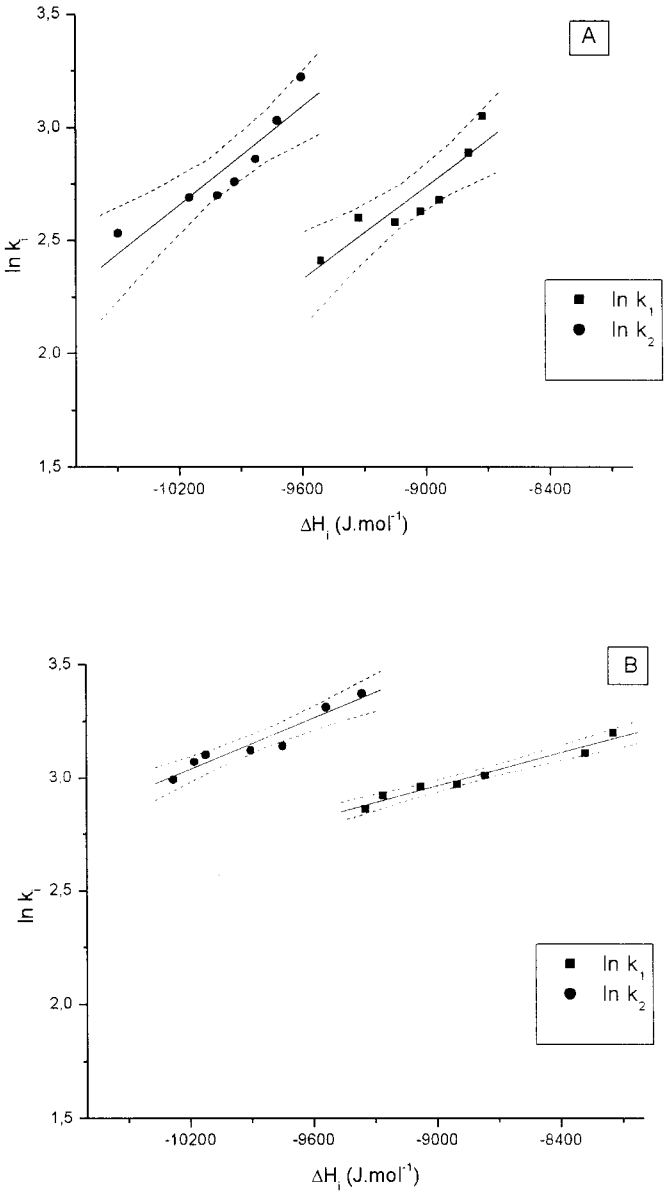

Figure 4. Plots of enthalpy–entropy compensation with the regression line and confidence intervals for the first (■) and second eluted (●) enantiomers of 1-methyl-2-piperidinoethyl esters of 2- (A), 3- (B), and 4- (C) alkoxyphenylcarbamic acid, at a temperature of 273 K (see Experimental for details).

(*continued*)

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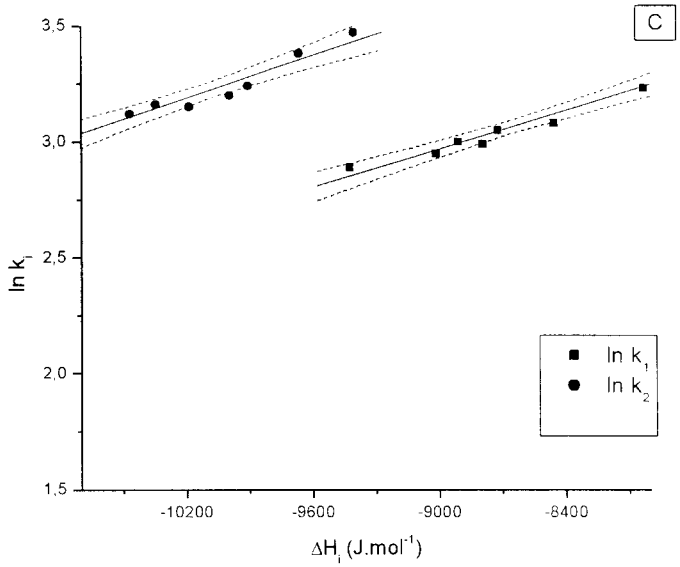

Figure 4. Continued.

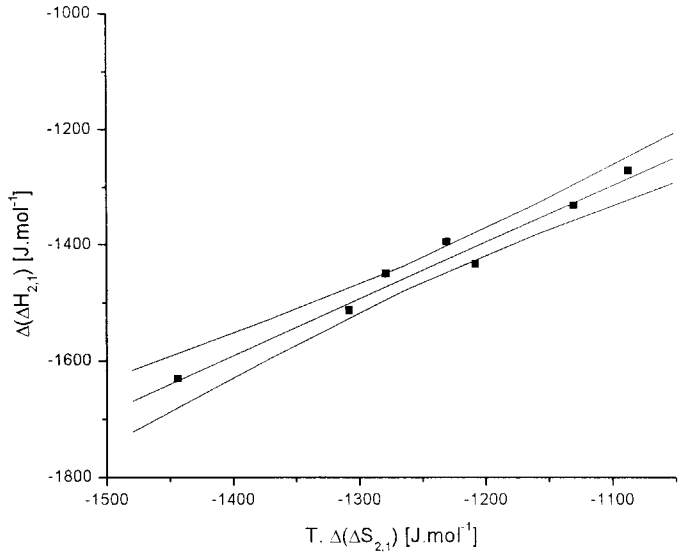

Figure 5. Dependence of $\Delta(\Delta H_{2.1})$ on $T\Delta(\Delta S_{2.1})$ for 4-alkoxy derivates of phenylcarbamic acid at 323 K (see Experimental for details).

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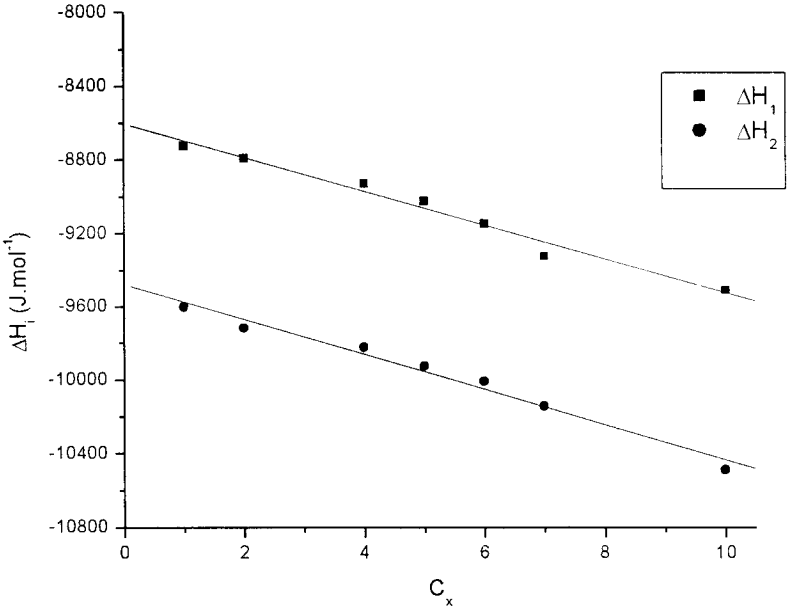

Figure 6. Dependence of the enthalpy (ΔH_i) on the number of carbon atoms (C_x) in the alkoxy chain attached to the 2-alkoxysubstituted esters of phenylcarbamic acid (for the first (■) and second eluted (●) enantiomers) (see Experimental for details).

CONCLUSION

The effect of temperature on the retention of 1-methyl-2-piperidinethyl-esters phenylcarbamic acid was studied. In the temperature range under study (0–50°C), van't Hoff plots [$\ln k_i = f(1/T)$] were linear. Changes in the enthalpies and entropies of solute transfer (MP to CSP) were determined. Values were calculated using the Gibbs–Helmholtz equation ΔG_i. The absolute values of ΔH_i and ΔS_i decrease with increasing length of the alkoxychain. Only when the alkoxy substituent was in the 2-position, did it have a significant effect on chiral recognition.

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