Short Communication

GC Separation of Enantiomers of Alkyl Esters of 2-Bromo Substituted Carboxylic Acids Enantiomers on 6-TBDMS-2,3-di-alkyl- β- and γ-Cyclodextrin Stationary Phases

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ABSTRACT The gas chromatographic separation of enantiomers of 2-Br carboxylic acid derivatives was studied on four different 6-TBDMS-2,3-di-O-alkyl- β- and -γ-CD stationary phases. The differences in thermodynamic data {*ΔH and –ΔS*} for the 15 structurally related racemates were evaluated. The influence of structure differences in the alkyl substituents covalently attached to the stereogenic carbon atom, as well as in the ester group of the homologous analytes, and the selectivity of modified β- and γ- cyclodextrin derivatives was studied in detail. The cyclodextrin cavity size, as well as elongation of alkyl substituents in positions 2 and 3 of 6-TBDMS-β-CD, also affected their selectivity. The quality of enantiomeric separations is influenced mainly by alkyl chains of the ester group of the molecule and this appears to be independent of the CD stationary phase used. In some cases the separations occur as the result of external adsorption rather than inclusion complexations with the chiral selector. It was found that the temperature dependencies of the selectivity factor were nonlinear. *Chirality 26:279–285, 2014.* © 2014 Wiley Periodicals, Inc.

KEY WORDS: capillary GC; chiral recognition; 6-TBDMS-2,3-alkyl- β- and γ-cyclodextrins; enantiomer separation

INTRODUCTION

The native cyclodextrins are cyclic glucose oligomers in which each glucose unit contains three hydroxyl groups bonded to the 2, 3, and 6 carbon atoms. They were introduced as stationary phases in gas chromatography by Smolková-Keulemansová and Soják for separation of xylene isomers.[1] Since that time, various substituents such as alkyl, acyl, or *tert*-butyldimethylsilyl were introduced into CD molecule by substitution of hydrogen atoms in hydroxyl groups.[2–8] Cyclodextrin derivatives (CDs) are currently the most frequently used stationary phases for separation of enantiomers in gas chromatography (GC) and other separation methods. However, in many cases the chiral recognition process is still not fully understood.[9–11] The GC separation of enantiomers is generally influenced by several parameters. Apart from the nonspecific ones, which generally influence the GC separation (i.e., column characteristics, mobile phase flow rate, and working conditions), the enantiomer separation depends particularly on the nature of the immobilized chiral selector and its immediate environment.[12–14] The type of CD and its substituents, the degree of substitution and location of the substituents, as well as the concentration of a given CD derivative and the polarity of an achiral solvent,[15] belong to the basic parameters which determine the quality of enantiomeric separations. It is assumed that inclusion into the CD cavity, interactions with inner or outer CD surface, as well as substituents attached to CD derivatives by hydrogen-bonding, dispersion forces, dipole–dipole interactions, and electrostatic interactions are a prerequisite for a successful chiral recognition process.[9] The types of interactions involved in chiral discrimination are affected by functional groups in CD substituents and also by structure of the functional groups of the separated enantiomers.[9,16]

Indeed, in one of the first articles dealing with studies of the chiral separation mechanism, Venema et al.[17] reported that the enantioselectivity of alkylated CDs is not influenced by the permanent dipole of the chiral compounds (which depends on the electronegativity of the X substituent) in 2-X-alkyl derivatives (where X = Cl, Br, I, OH, O-CH_3, CN and NH_2), but rather by the alkyl chain length of the substituent bonded to the stereogenic carbon atom. Similar conclusions have been reached using 2-alkanoic acids esters that have α-substituted with Cl or Br atoms.[18] In another work, Špánik et al. studied interactions of ethyl esters of α-substituted propionic acid derivatives substituted by Cl, Br, I, CN, OH, O-C_2H_5, O-C_6H_5, and NH-$COCF_3$ on alkylated β- and γ-CDs.[19] It was found that the contribution of particular substituents to the overall chemical interaction (*ΔH*) varies from 10% to 43%, depending mostly on the polarity of the substituent. The highest contribution was observed for phenoxy and the lowest for the Cl substituent on all of the evaluated alkylated cyclodextrin stationary phases. The contribution of a particular substituent to inclusion into the CD cavity (*ΔS*)

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varies from 0.5% to 33%. From the presented data, it followed that the 2-NHCOCF3 derivative would create the most stable inclusion complexes on all studied CD derivatives.[19] The role of alkyl chain in the chiral recognition process on permethylated-β-CD was studied by separation of N-TFA-O-alkyl amino acid derivatives with linear, branched, and cyclic alkyl chains attached at the stereogenic center, as well as the ester part of the molecule. The separation of enantiomers was influenced mainly by the type of the substituent at the stereogenic center. Short and linear alkyl groups bonded to the stereogenic center were found to be favorable for the separation of enantiomers, while branching of the alkyl chain caused a change in the elution order.[20] In a further study, the GC separation of enantiomers of seven amino acid N-TFA-O-alkyl derivatives on four capillary columns coated with 2,3,6-tri-O-methyl-, and 2,6-di-O-methyl-3-O-pentyl-β- and γ-CD stationary phases was examined. The influence of the alkyl substituents bonded to the stereogenic center (R_1) and/or the ester group (R_2) of the N-TFA-O-alkyl amino acid derivatives showed that the enantioselectivity was mainly influenced by the alkyl substituents attached to the stereogenic carbon atom R_1.[21] The effect of cavity size, as well as the 3-O-alkyl chain length of 2,6-di-O-methyl-3-O-alkyl-β- and γ-cyclodextrins, also had an impact on the resolution of enantiomers.[21] In contrast, the resolution of N-trifluoroacetyl-O-alkyl nipecotic acid ester enantiomers on the permethylated-β-CD stationary phase is influenced by structure of alkyl chain in the ester part of molecule. The n-alkyl esters provided stronger interactions with permethylated-CD than esters containing branched alkyl groups. Despite having weaker interactions with the CD chiral selectors, esters containing branched alkyl groups exhibited higher enantioselectivity than the corresponding n-alkyl esters. This indicated that there were different types of enantioselective interactions for the linear alkyl chain and branched alkyl chain esters.[22] As can be seen, most studies were performed on alkylated cyclodextrins, but there are limited data for other substituted CD derivatives.

In this work, the enantiomers of alkyl esters of 2-Br-carboxylic acids were separated by GC on four capillary columns coated with 6-TBDMS-2,3-di-O-alkyl-β-CD and 6-TBDMS-2,3-di-O-ethyl-γ-CD stationary phases. The separation of enantiomers was evaluated in terms of the nonpolar interactions of the alkyl substituents bonded to the stereogenic carbon (R_1) and/or the ester group (R_2) as well as the 2,3-O-alkyl chain length of 6-TBDMS-2,3-di-O-alkyl-β-CD.

MATERIALS AND METHODS

Instruments

Agilent 7890 gas chromatograph and Chemstation software were used for recording and evaluating signals for all separations. The split-splitless injector and flame ionization detector (FID) were utilized, both with temperatures of 250°C. Helium was used as a carrier gas with an optimal flow rate of 25–30 cm s^{-1}. Methane was used to determine the hold time. Sample volumes of 1 μl were injected into the column by split injection with a ratio of 100:1. The measurements were performed at isothermal conditions in the temperature range 30–160°C at 10°C increments. All measurements were repeated three times and statistically evaluated.

Columns

Column A. A 25-m capillary column with 0.25 mm i.d. was coated with a 0.25 μm film thickness of 6-TBDMS-2,3-di-O-methyl-β-CD dissolved in a polysiloxane matrix (6-TBDMS-2,3-DiMe-β-CD). The column was obtained from MEGA (Capillary Column Laboratory, Legnano, Italy).

Column B. A 25-m capillary column with 0.25 mm i.d. was coated with a 0.25 μm film thickness of a 6-TBDMS-2,3-di-O-ethyl-β-CD dissolved in a polysiloxane matrix (6-TBDMS-2,3-DiEt-β-CD). The column was obtained from MEGA.

Column C. A 30-m capillary column with 0.25 mm i.d. was coated with a 0.25 μm film thickness of a 6-TBDMS-2,3-di-O-propyl-β-CD dissolved in a polysiloxane matrix (6-TBDMS-2,3-DiPr-β-CD). The column was obtained from RESTEK (Bellefonte, PA) .

Column D. A 25-m capillary column with 0.25 mm i.d. was coated with a 0.25 μm film thickness of a 6-TBDMS-2,3-di-O-ethyl-γ-CD dissolved in a polysiloxane matrix (6-TBDMS-2,3-DiEt-γ-CD). The column was obtained from MEGA.

Chemicals

Racemic mixtures of 2-Br-propionic acid, 2-Br-butyric acid, 2-Br-pentanoic acid, and 2-Br-hexanoic acid were purchased from Sigma-Aldriche; Chemie (Munich, Germany). Methanol, ethanol, propanol, butanol, and n-hexane for chromatography was purchased from Merck (Darmstadt, Germany).

Analytes

The methyl, ethyl, n-propyl, and n-butyl esters of all racemic mixtures of 2-bromo carboxylic acids were prepared by esterification of the corresponding 2-bromo carboxylic acid with 20% (v/v) solution of acetylchloride in the corresponding alcohol at elevated temperature (from 90–120 °C depending on the type of alcohol used) in a vial with a Teflon cap. After a 30-min reaction the excess reagent was removed with a stream of nitrogen. The general chemical structure of prepared derivatives is shown in Figure 1.

RESULTS AND DISCUSSION

The overall free energy of transfer (ΔG) of the chiral molecule to the cyclodextrin stationary phase can be represented as a sum of partial interaction energies (δG_i) proportional to individual partial interactions:[23]

$$\Delta G = \sum_{i=1}^{n} \delta G_i \tag{1}$$

where n is the number of individual interactions of a selectand with a selector. This energy is related to the thermodynamic parameters enthalpy (ΔH) and entropy (ΔS):

$$\Delta G = \frac{-\Delta H}{RT} + \frac{\Delta S}{R} \tag{2}$$

where R is a universal gas constant and T is the absolute temperature in Kelvin.

An overall interaction energy of a selectand with a selector in a chromatographic column can be calculated from the chromatographic experiment by:

$$\Delta G = -RT \ln k - RT \ln \beta \tag{3}$$

where k is the retention factor and β is the ratio of volumes (V) in the column ($\beta = V_m/V_s$ where m denotes mobile and s stationary phase).

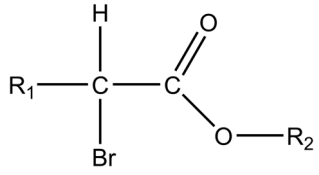

Fig. 1. General formula of studied esters of 2-Br-carboxylic acid.

A combination of eqs. 2 and 3 leads to:

$$ln\ k = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} - ln\ \beta \qquad (4)$$

which indicates a linear dependence of *ln k* on the inverse of temperature ($1/T$).

Esters of 2-Br-carboxylic acid used in this study can be illustrated as follows:

$$R_1 - CBrH - CO - OR_2$$

where R_1 and R_2 are the alkyl substituents bonded to the stereogenic carbon or to the carboxylate group, respectively. Since the 2-Br carboxylic acid moiety is identical for all of the studied 2-Br carboxylic acid derivatives, the contribution of interactions of the alkyl substituents R_1 and R_2 with a cyclodextrin stationary phase can be studied independently. Van't Hoff plots (semilogarithmic dependencies of the retention factor on the inverse of absolute temperature) constructed for the first eluted enantiomer using the data obtained from the separation of the studied racemates on 6-TBDMS-2,3-di-O-alkyl cyclodextrin stationary phases are shown in Figure 2. The linear van't Hoff dependencies (correlation coefficient higher than 0.99) also were obtained for the second eluted enantiomer. The obtained linear dependencies confirm the validity of eq. 4, thus the slopes of these plots can be used to determine enthalpies ($-\Delta H/R$) terms and the intercepts for the entropic ($\Delta S/R$) contributions. The comparison of the retention behavior of 2-Br carboxylic acid derivatives with equal molecular weight shows that enantiomers of ethyl ester of 2-Br-propionic acid has weaker interactions than methyl ester of 2-Br-butanoic acid on all studied CD derivatives. The smallest differences in ΔH and ΔS values between those two studied molecules were observed on 6-TBDMS-2,3-DiEt-γ-CD. This indicates that a similar retention and separation mechanism is employed in separation of the studied γ-CD derivative independently on position of the alkyl substituents in the studied molecule. This is also confirmed by the obtained similar selectivity factors α, ($\alpha = k_2/k_1$ and k is the retention factor of the first and second eluted enantiomer, respectively) obtained for enantiomers of the 2-Br-carboxylic acid derivatives on all studied CD stationary phases. Table 1 gives the obtained enthalpies and entropies that characterize interactions of enantiomers with the cyclodextrin-based chiral stationary phase derivatives. It must be noted that the obtained enthalpies and entropies are assumed to be independent of T in the ranges used in GC experiments. The ethyl ester of 2-Br-propionic acid had the weakest interaction which resulted in the least retention of all studied CD derivatives. As discussed previously, selected compounds represent homologous series that differ by one methylene group either in the alkyl chain attached on asymmetric the carbon atom or in the ester group of the molecule. The methyl esters represent the smallest molecule of all the compounds studied in this work. From the data given in Figure 2 it follows that methyl esters always show the smallest retention on all studied CD derivatives. Elongation of the alkyl chain in both R_1 and R_2 groups increases the retention on all studied CD derivatives in the order Methyl, Ethyl, Propyl, and Butyl independently of their position in the molecule. This is also supported by

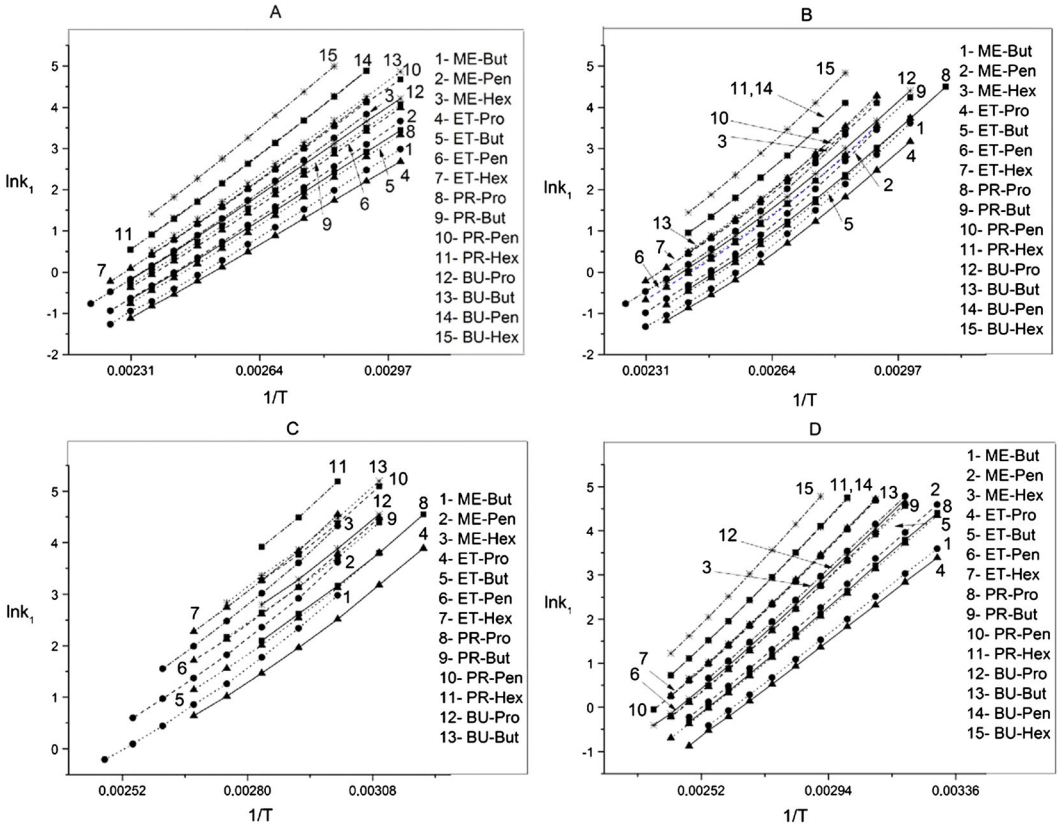

Fig. 2. van't Hoff plots for the first eluted enantiomer found from data obtained by the separation of the studied compounds on 6-TBDMS-2,3-DiMe-β-CD (**A**), 6-TBDMS-2,3-DiEt-β-CD (**B**), 6-TBDMS-2,3-DiPr-β-CD (**C**), and 6-TBDMS-2,3-DiEt-γ-CD (**D**) columns.

TABLE 1. ΔH values in kJ mol^{-1} and $-\Delta S$ in J mol^{-1} K^{-1} found for enantiomers of all studied compounds from of van´t Hoff plots

Compound*	Molecular weight	6-TBDMS-2,3-DiMe-β-CD		6-TBDMS-2,3-DiEt-β-CD		6-TBDMS-2,3-DiEt-γ-CD		6-TBDMS-2,3-DiPr-β-CD	
		ΔH	$-\Delta S$	ΔH	$-\Delta S$	ΔH	$-\Delta S$	ΔH	$-\Delta S$
ET-Pro 1	181.03	44.87	112.70	56.72	145.19	42.53	112.44	46.40	118.00
2		48.07	119.93	63.59	161.55	43.75	115.32	51.94	131.73
PR-Pro 1	195.05	48.59	117.62	60.78	151.83	47.48	120.46	48.42	118.72
2		50.72	122.41	64.62	161.13	48.64	123.25	50.12	122.97
BU-Pro 1	209.08	52.38	122.47	60.60	146.3	51.74	126.73	50.15	118.45
2		54.18	126.54	63.65	153.67	52.05	127.52	51.51	121.83
ME-But 1	181.03	47.11	117.00	59.27	149.75	43.07	112.59	47.09	118.23
2		50.19	123.61	70.21	175.41	43.95	114.70	57.57	143.59
ET-But 1	195.05	48.21	117.47	58.74	146.80	47.25	120.24	47.07	115.72
2		51.53	125.07	68.35	169.93	48.90	124.15	53.59	131.84
PR-But 1	209.08	51.70	121.83	60.53	147.50	50.62	124.40	48.68	115.43
2		54.00	127.10	67.26	164.05	52.47	128.83	51.82	123.23
BU-But 1	223.11	56.21	128.59	62.26	147.21	53.71	127.75	52.57	120.65
2		57.42	131.04	67.03	158.89	54.73	130.20	54.99	126.68
ME-Pen 1	195.05	50.85	122.77	60.23	148.53	48.26	121.50	49.59	120.48
2		54.44	130.80	70.64	172.85	49.07	123.41	59.03	143.41
ET-Pen 1	209.08	51.43	121.85	57.56	139.66	51.59	127.04	49.92	118.82
2		54.80	129.58	65.48	158.45	53.46	131.51	55.78	133.34
PR-Pen 1	223.11	54.68	125.57	61.50	145.93	53.52	127.51	51.96	119.66
2		57.00	130.92	67.08	159.63	55.61	132.48	54.68	126.46
BU-Pen 1	237.14	58.55	130.51	63.90	147.33	56.38	130.54	54.57	121.72
2		60.02	133.89	67.43	155.94	58.00	134.43	55.13	123.09
ME-Hex 1	209.08	54.18	126.58	58.90	140.54	51.56	125.37	52.71	123.82
2		57.88	134.76	66.93	159.04	52.29	127.16	59.75	140.98
ET-Hex 1	223.11	55.02	126.28	61.38	144.69	54.28	129.42	52.03	119.78
2		58.16	133.37	68.36	144.69	55.69	132.79	55.61	128.59
PR-Hex 1	237.14	58.59	130.73	64.02	147.64	56.83	131.65	54.91	122.61
2		60.64	135.44	67.68	156.56	58.37	135.37	55.87	124.98
BU-Hex 1	251.16	66.14	145.66	68.47	154.27	59.20	133.24	58.72	127.74
2		67.15	147.87	71.21	160.95	60.32	135.93	58.89	128.15

*First two letters express the abbreviation for an ester part: ME - Methyl, ET- Ethyl, PR - Propyl and BU - Butyl; the second three letters express the abbreviation for 2-Br-carboxylic acid: Pro - 2-Br propionic acid, But - 2-Br butyric acid, Pen- 2-Br pentanoic acid and Hex - 2-Br hexanoic acid.

the data in Table 2 (ΔH) obtained on 6-TBDMS-2,3-DiMe-β-CD 6-TBDMS-2,3-DiEt-γ-CD. However, the data in Table 2 shows that the methyl ester of the studied 2-Br carboxylic acids provide stronger interactions than the corresponding ethyl derivatives on 6-TBDMS-β-CD derivatives with ethyl and propyl attached in positions 2 and 3. McGachy et al. explain this behavior by a higher number of interactions inside the CD cavity and suggest that the chiral molecule gains additional interactions from other parts of the CD derivative.[22] Indeed, the CD moiety in 6-TBDMS-2,3-alkyl-β-CD derivatives decreases with elongation of alkyl substituents in positions 2 and 3 from methyl to propyl. Considering the fact that the chiral recognition process includes inclusion of molecules into the CD cavity, the chiral molecules would be faced with a stronger interaction with substituents at position 3 in the CD derivative since those are oriented into the CD cavity. The 6-TBDMS-2,3-DiEt-γ-CD derivative has a larger cavity size due to higher number of glucopyranose units compared to corresponding β-CD derivative.

The calculated enthalpies are higher on (6-TBDMS-2,3-DiEt)-β-CD in comparison to the corresponding γ-CD derivative. An interesting behavior was observed on the 6-TBDMS-2,3-DiPr-β-CD, where the calculated entropies for all studied esters of 2-Br-propionic acid, 2-Br-butyric acid, and methyl and ethyl esters of 2-Br-pentanoic acid showed similar values. This indicates that interactions on the outer surface of this CD derivative are preferred in chiral recognition and separation for the columns studied under those conditions. From the data in Table 1 it follows that the decrease of enthalpic terms is compensated for by an increase in the entropic term on all studied CD derivatives except for 6-TBDMS-2,3-DiPr-β-CD. This compensation, however, is not proportional, since inclusion as well as interactions of enantiomers with the CD derivative surface affect the overall entropic term. It is supposed that the chiral recognition process is not driven by one only type of separation mechanism, but involves many types of intramolecular interactions such as hydrogen bonding, nonpolar interactions, dipole–dipole interactions, or electrostatic interactions (generally, the sum of those interactions is expressed by the enthalpic term[23]) and inclusion phenomena connected with loss of freedom in molecular motion (generally, expressed as entropic part[23]).

Figure 3 shows the dependencies of $ln\alpha = f(1/T)$. It was expected that the dependencies in Figure 3 would be linear; however, all the dependencies are nonlinear, which indicates that the chiral recognition mechanism on the 6-TBDMS-2,3-di-O-alkyl-β and γ-CD stationary phases probably shows nonadditive contributions of the individual interactions of solute enantiomers. Table 2 shows selectivity factors obtained for the racemic analytes evaluated at 80 °C on all CD stationary phases studied. The highest α values were observed on the 6-TBDMS-2,3-DiEt-β-CD phase for all analytes. The smallest α values were obtained on the CD derivative with the largest

TABLE 2. The selectivity factors (α) obtained for compounds studied evaluated at 80 °C on all CDs stationary phases used in this study

Compound*	6-TBDMS-2,3-DiMe-β-CD	6-TBDMS-2,3-DiEt-β-CD	6-TBDMS-2,3-DiEt-γ-CD	6-TBDMS-2,3-DiPr-β-CD
ET-Pro	1.24	1.45	1.07	1.16
PR-Pro	1.16	1.19	1.05	1.04
BU-Pro	1.13	1.17	1.00	1.03
ME-But	1.29	1.93	1.05	1.65
ET-But	1.24	1.62	1.09	1.23
PR-But	1.16	1.32	1.08	1.08
BU-But	1.12	1.25	1.05	1.04
ME-Pen	1.29	1.91	1.04	1.54
ET-Pen	1.24	1.60	1.09	1.18
PR-Pen	1.15	1.29	1.10	1.03
BU-Pen	1.10	1.21	1.08	1.00
ME-Hex	1.34	1.79	1.03	1.38
ET-Hex	1.25	1.50	1.07	1.11
PR- Hex	1.15	1.22	1.08	1.02
BU- Hex	1.10	1.16	1.06	1.00

*See footnote to Table 1.

cavity size (6-TBDMS-2,3-DiEt-γ-CD) for a smaller methyl and ethyl esters of the studied 2-Br carboxylic acids and BU-Pro. On the contrary, propyl and butyl esters (except for BU-Pro) showed the lowest α values on a CD derivative with the smallest cavity size (6-TBDMS-2,3-DiPr-β-CD). Figure 4 shows the dependencies of α-values on the carbon atom number of the alkyl chains R_1 (Fig. 4A) and R_2 (Fig. 4B) obtained on all of the studied stationary phases at 80°C. The resolution of enantiomers decreases with an increase in the number of carbon atoms in the alkyl chain of the ester part of the molecule R_2 on all β-CD stationary phases used in this study. The opposite effect was observed on the γ-CD stationary phase, where elongation of the R_2 alkyl chain from methyl to ethyl either slightly improved or had little effect on the enantiomeric separation of 2-Br-carboxylic acid derivatives. The further elongation of the alkyl chain in the ester part of molecule from ethyl to butyl decreased the enantiomeric resolution. Table 2 and Figure 4 show that methyl esters provide the highest selectivity factors regardless of the type of CD stationary phase. A further increase from methyl to ethyl in the ester group caused a significant loss of enantioselectivity on almost all studied CD derivatives. However, the most evident decrease in enantioselectivity was observed on 6-TBDMS-2,3-DiPr-β-CD. This CD derivative has the smallest cavity from all studied CD derivatives that are sufficient to form the most stable inclusion complexes with methyl esters. The small cavity size, however, will prevent deeper inclusion of a molecule into the CD cavity and interactions with outer the CD surface must also be considered in the chiral recognition process. This conclusion is supported also by similar entropic terms obtained on this CD derivative presented in Table 1.

A further increase of alkyl chain length to propyl and butyl causes another significant drop in α values or complete loss of enantioselectivity. The elongation of the alkyl chain attached to the stereogenic center, R_1 did not influence the enantioselectivity as dramatically as the alkyl chain in the ester group. This may lead to the conclusion that the quality of enantiomer separation alkyl esters of 2-Br carboxylic acids on the studied 6-TBDMS-2,3-Di-alkyl-CD is mostly affected

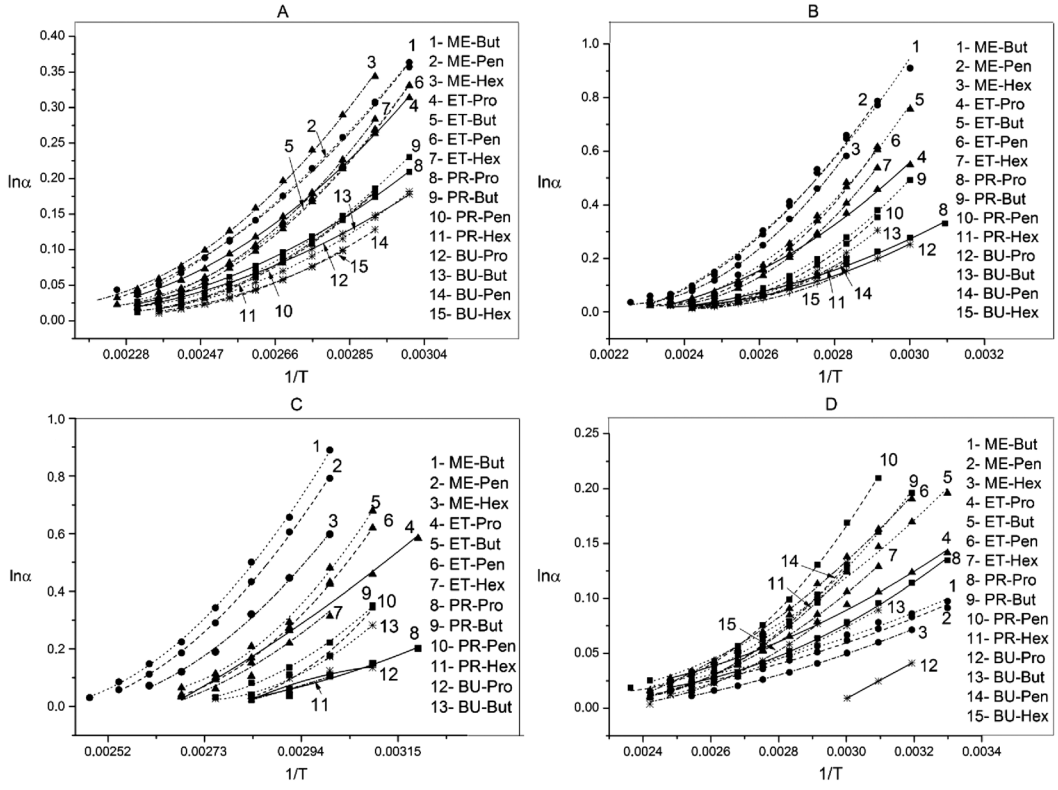

Fig. 3. Dependencies of *ln α* on the reverse of temperature (1/*T*) found from data obtained by the separation of the studied compounds on 6-TBDMS-2,3-DiMe-β-CD (**A**), 6-TBDMS-2,3-DiEt-β-CD (**B**), 6-TBDMS-2,3-DiPr-β-CD (**C**), and 6-TBDMS-2,3-DiEt-γ-CD (**D**) columns.

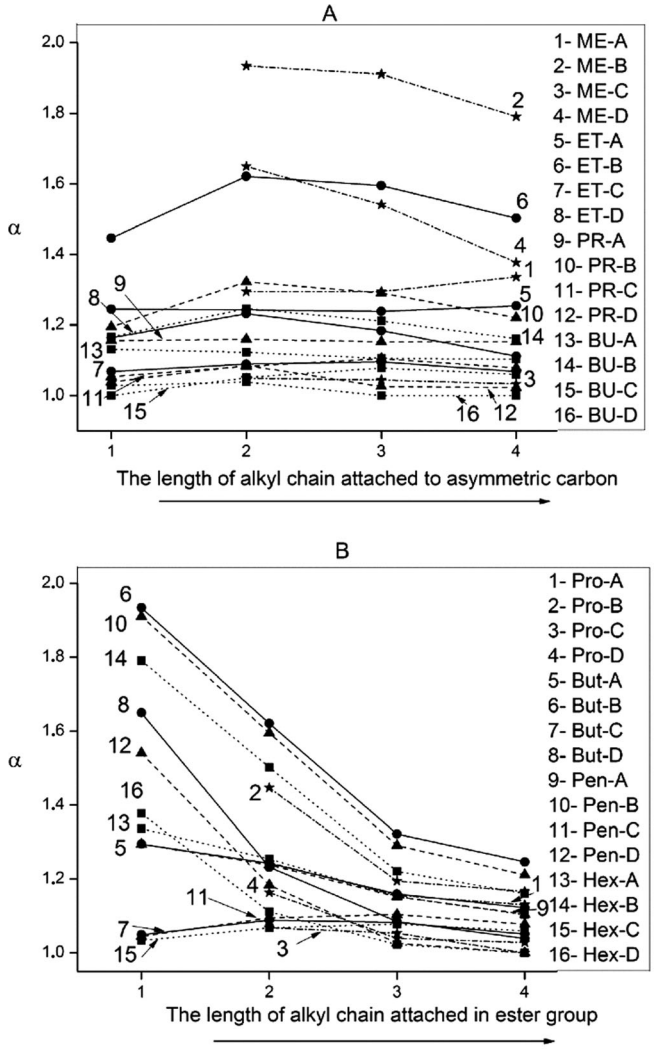

Fig. 4. Dependencies of α on the carbon atom number of the alkyl chains R_1 (**A**) and R_2 (**B**) obtained on all studied stationary phases at 80°C. The first letters of abbreviations correspond to the abbreviations in Table 1, while the second part expresses the column used in the experimental part.

by the length of the alkyl chain in the ester group of the molecule. This is in contrast with observations obtained on alkylated cyclodextrins for N-TFA-O-alkyl amino acid derivatives, where resolution of the enantiomers was mostly affected by the alkyl chain attached to the stereogenic center.[21]

A suitable selection of CD derivatives allowed us to study the effect of alkyl chain elongation in positions 2 and 3 of the 6-TBDMS-2,3-alkyl-β-CD derivative on the resolution of the enantiomers of the studied compounds. The change of alkyl substituents from methyl to ethyl improved enantiomer separation, but further elongation has a negative impact on the resolution of the enantiomers of 2-Br-carboxylic acid esters. The cyclodextrin cavity size also influences the separation of these racemates. A decrease of α values was observed with an increase of CD cavity size, while the most significant influence was observed for the separation of the enantiomers of the methyl esters of 2-Br-carboxylic acid.

CONCLUSION

Thermodynamic studies were performed on enantiomer pairs of alkyl esters of 2-Br carboxylic acid derivatives on four different 6-TBDMS-2,3-di-O-alkyl- β- and -γ-CD stationary phases. The linear temperature dependencies of the retention factors ($ln\ k$ on $1/T$) of enantiomers of all the studied compounds on all of the studied CD stationary phases allowed us to compare the basic thermodynamic data {ΔH and −ΔS} in order to characterize the overall interactions of the studied enantiomers with the stationary phases. On the contrary, the temperature dependencies of selectivity factors, $ln\ \alpha$ on $1/T$, were nonlinear as a consequence of the nonadditive contributions of the individual interactions in the chiral recognition process. The chiral recognition process of alkyl esters of 2-Br-carboxylic acid derivatives on 6-TBDMS-2,3-alkyl-β and 6-TBDMS-2,3-ethyl-γ-CD derivatives is substantially affected by both properties of the chiral stationary phase (CD cavity size, alkyl chain length in position 2 and 3 in the CD derivative) as well as the structure of the separated enantiomers. It was shown that the alkyl chain in ester group 2-Br carboxylic acids influences the overall retention and also plays a more significant role in the chiral recognition process on 6-TBDMS-2,3-di-O-alkyl-CD derivatives. The length of the alkyl chain attached to the asymmetric carbon did not have a significant influence on the quality of enantiomer separation. In some cases, chiral recognition and separation is the result of external adsorption on the chiral selector rather than inclusion complex formation. The prolongation of the alkyl chain in 6-TBDMS-2,3-di-O-alkyl-β-CD influences obtained α values, while the best separation was achieved on 6-TBDMS-2,3-di-O-ethyl-β-CD. The cyclodextrin cavity size, as well as elongation of alkyl substituents in positions 2 and 3 of 6-TBDMS-β-CD, also strongly influenced the separation of enantiomers.

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