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Journal of Chromatography A, 846 (1999) 83–91

JOURNAL OF CHROMATOGRAPHY A

High-performance liquid chromatographic separation of novel atropic α,α-disubstituted-β-amino acids, either on different β-cyclodextrin-bonded phases or as their 1-fluoro-2,4-dinitrophenyl-5-L-alanine amide derivatives

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Abstract

The high-performance liquid chromatographic enantioresolution of free and N- and/or C-protected derivatives of (*R,S*)-2′,1′:1,2;1″,2″:3,4-dinaphthcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid (β^2-Bin) by direct and indirect methods is reported. The direct separation was carried out on native and different derivatized β-cyclodextrin-bonded phases. The indirect resolution was achieved by applying pre-column derivatization with 1-fluoro-2,4-dinitrophenyl-5-L-alanine amide. The effects of different parameters such as the mobile phase composition and the structures of the compounds on the enantiomeric resolution are discussed.

Keywords: Enantiomer separation; Mobile phase composition; Chiral stationary phases, LC; Amino acids

1. Introduction

The recent results of Gellman [1] and Seebach and Matthews [2] demonstrating that oligomers of β-amino acids can give rise to surprisingly stable helical conformations, different in nature from those adopted by oligomers of α-amino acids, have highlighted the interest in ''β-peptides'' in the search for synthetic foldamers. A new α,α-disubstituted-β-amino acid, 2′,1′:1,2;1″,2″:3,4-dinaphthcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid (β^2-Bin) which possesses only axial chirality, has recently been synthesized with a view to analysis of the conformational properties of its peptide oligomers [3]. We have been interested in the development of high-performance liquid chromatographic (HPLC) methods for the resolution and quantification of enantiomers of β^2-Bin, in connection with our earlier study of its α,α-disubstituted-α-amino acid analogue Bin [4].

In consequence of the availability of numerous new chiral stationary phases (CSPs), HPLC has become an attractive analytical tool for determination of the enantiomeric composition of mixtures of optical isomers from enantioselective syntheses, and a useful preparative method for enantiomerically pure compounds required for various applications involving the investigation of biological activities and interaction mechanisms.

Among these CSPs, cyclodextrins (CDs) (native or

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0021-9673/99/$ – see front matter
PII: S0021-9673(98)01081-4

derivatized) have been the subject of several reports [5–9]. Most of the studies involving CDs as CSPs in HPLC were accomplished either in the reversed-phase (RP) mode [8–10] or in the normal-phase (NP) mode [11,12]. Inclusion complexation and π-π/hydrogen-bonding forces are the driving forces of the enantioselective separation in the RP and NP modes, respectively. It has recently been established that separations are also possible with a new type of mobile phase, referred to as the polar-organic (PO) mode [13,14]. In this mode, a direct interaction occurs with the secondary hydroxyl groups of the CD. Acetonitrile is used as the dominant solvent (90–100%) with small amounts of methanol added to decrease retention if needed. The selectivity is due to the concentration and ratio of glacial acetic acid to anhydrous triethylamine (in the range 0.001–1.2%). Each mobile phase mode has distinct characteristics; thus each displays different selectivities towards the chiral analytes. As an example, although atropic compounds, containing an axis of asymmetry, have been resolved with CD phases [15] but to date have not been successfully resolved on racemically derivatized CD phases [10,11].

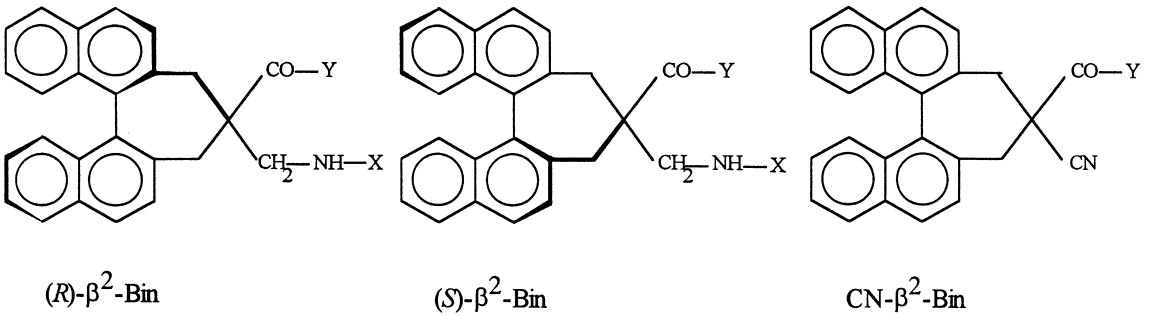
In the present study, several different CD-bonded phases, among them a racemically derivatized one, were used in the RP and the PO modes for the direct resolution of the enantiomers of β^2-Bin (Fig. 1). The indirect separation of the compounds containing the free amino group was carried out as their 1-fluoro-2,4-dinitrophenyl-5-L-alanine amide (FDAA) derivatives. The effects of the structural features of the compounds and of the mobile phase composition on the enantioselectivity are discussed, including the similarities and differences of the different modes applied.

2. Experimental

2.1. Apparatus

The HPLC system consisted of two instruments, a Waters system including an M-600 low-pressure gradient pump, equipped with an M-996 photodiode array detector and a MILLENIUM 2010 chromatography manager data system (Waters Chromatography, Milford, MA, USA) and an L-6000 Merck-Hitachi pump (Tokyo, Japan) with a Shimadzu SPD-6AV variable-wavelength UV–Vis detector. For data processing, a Hewlett-Packard, HP 3395 integrator (Waldbronn, Germany) was applied.

The columns used for chiral separations were Cyclobond I 2000 (β-CD-bonded), Cyclobond I 2000 RSP (*R,S*-2-hydroxypropyl ether-derivatized β-CD-bonded), Cyclobond I 2000 SN (*S*-naphthylethylcarbamate-derivatized β-CD-bonded) 250× 4.6 mm I.D., 5 μm particle size (Astec, Advanced



(*R*)-β^2-Bin (*S*)-β^2-Bin CN-β^2-Bin

1a-d **2**

Fig. 1. Structures of (*R,S*)-2′,1′:1,2;1″,2″:3,4-dinaphthcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid (β^2-Bin) compounds **1a**: X=H, Y=OH, H-β^2-Bin-OH; **1b**: X=H, Y=OEt, H-β^2-Bin-OEt; **1c**: X=Boc, Y=OH, Boc-β^2-Bin-OH; **1d**: X=Boc, Y=OEt, Boc-β^2-Bin-OEt; **2**: Y=OEt, CN-β^2-Bin-OEt.

Separation Technologies, Whippany, NJ, USA) and ChiraDex (β-CD-bonded) 250×4.0 mm I.D., 5 μm particle size (Merck, Darmstadt, Germany).

For indirect separation, a Vydac 218TP54 C_{18} 250×4.6 mm I.D., 5 μm particle size (The Separations Group, Hesperia, CA, USA) column was utilized.

A Radelkis OP/20811 pH meter (Budapest, Hungary) equipped with a combined glass-calomel electrode was employed for pH measurements.

2.2. Chemicals and reagents

The amino esters of racemic (*R*,*S*)- and optically pure (*R*)-β²-Bin were synthetized by bis-alkylation of ethyl cyanoacetate with (*R*,*S*)- and (*R*)-2,2′-bis-(bromomethyl)-1,1′-binaphthyl, respectively, followed by selective reduction of the cyano group with $CoCl_2$–$NaBH_4$. The corresponding free amino acids and their N-*tert*-butoxycarbonyl (N-Boc)-protected derivatives were prepared by standard methods [3].

1-Fluoro-2,4-dinitrophenyl-5-L-alanine amide (FDAA or Marfey's reagent) and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) were purchased from Sigma (St. Louis, MO, USA) and Aldrich (Steinheim, Germany), respectively. Trifluoroacetic acid (TFA), sodium acetate (NaOAc), potassium dihydrogenphosphate (KH_2PO_4), glacial acetic acid (AcOH) and triethylamine (TEA) of analytical reagent grade and HPLC grade acetonitrile (CH_3CN) and methanol (CH_3OH), were obtained from Merck.

2.3. Procedures

Solutions (1 mg/ml) of H-(*R*,*S*)-β²-Bin-OH, H-(*R*)-β²-Bin-OH, H-(*R*,*S*)-β²-Bin-OEt and H-(*R*)-β²-Bin-OEt were used for derivatization with GITC by the method of Nimura et al. [16], and with FDAA by a slight modification of the method of Marfey [17]. In the latter case the reagent solution was more concentrated, 16 mg/ml instead of the 10 mg/ml suggested by Marfey, and the reaction mixture was directly diluted with the mobile phase after a 1-h incubation at 40°C. The GITC and FDAA derivatives were detected at wavelengths of 250 and 340 nm, respectively.

For direct separation, solutions of the free and protected amino acids were prepared by dissolution in eluent to give a concentration of 1 mg/ml. Compounds were detected at 230 nm.

A 20 μl volume of each sample solution was injected with a Model 7125 injector (Rheodyne, Cotati, CA, USA).

Phosphate buffer was prepared by dissolving 0.01 *M* KH_2PO_4 in ~950 ml Milli-Q water, adjusting the pH with 5.0 *M* phosphoric acid to pH 3.0 and diluting to a final volume of 1000 ml in a volumetric flask. Acetate buffer, 1% triethylammonium acetate (TEAA) buffer and a 0.1% aqueous solution of TFA were prepared in the same manner, by dissolving 0.01 *M* NaOAc, 10 ml TEA and 1 ml TFA, respectively, in water and adjusting the pH with glacial acetic acid to pH 3.0 in the case of the acetate buffer and to pH 4.1 and/or 6.8 in the case of the TEAA buffer. The buffers were filtered on a 0.45-μm Millipore filter, type HV (Molsheim, France).

The mobile phases were prepared by mixing the eluent components volume by volume.

The void volume of the Vydac column was determined by injecting 20 μl of a 0.01 *M* methanolic solution of KBr. Although a graphical method has been proposed [18] for determination of CD column void volumes, in which the retention times or volumes of low molecular mass alcohols are plotted against their binding constants to the CD, we used CH_3CN as a relative retention marker because of the non-availability of these binding constants for derivatized CD-bonded phases.

3. Results and discussion

3.1. Indirect separation of enantiomers

For indirect separation, compounds derivatized on the amino group of the compounds were prepared with FDAA and GITC as chiral derivatization reagents. Since some compounds, (N-Boc-protected Boc-β²-Bin-OH, Boc-β²-Bin-OEt and CN-β²-Bin-OEt) were not suitable for further derivatization, they were analysed by direct methods. The GITC derivatives of the samples could not be resolved (results not presented), which was unexpected because the enantiomers of the α,α-disubstituted-α-amino acid

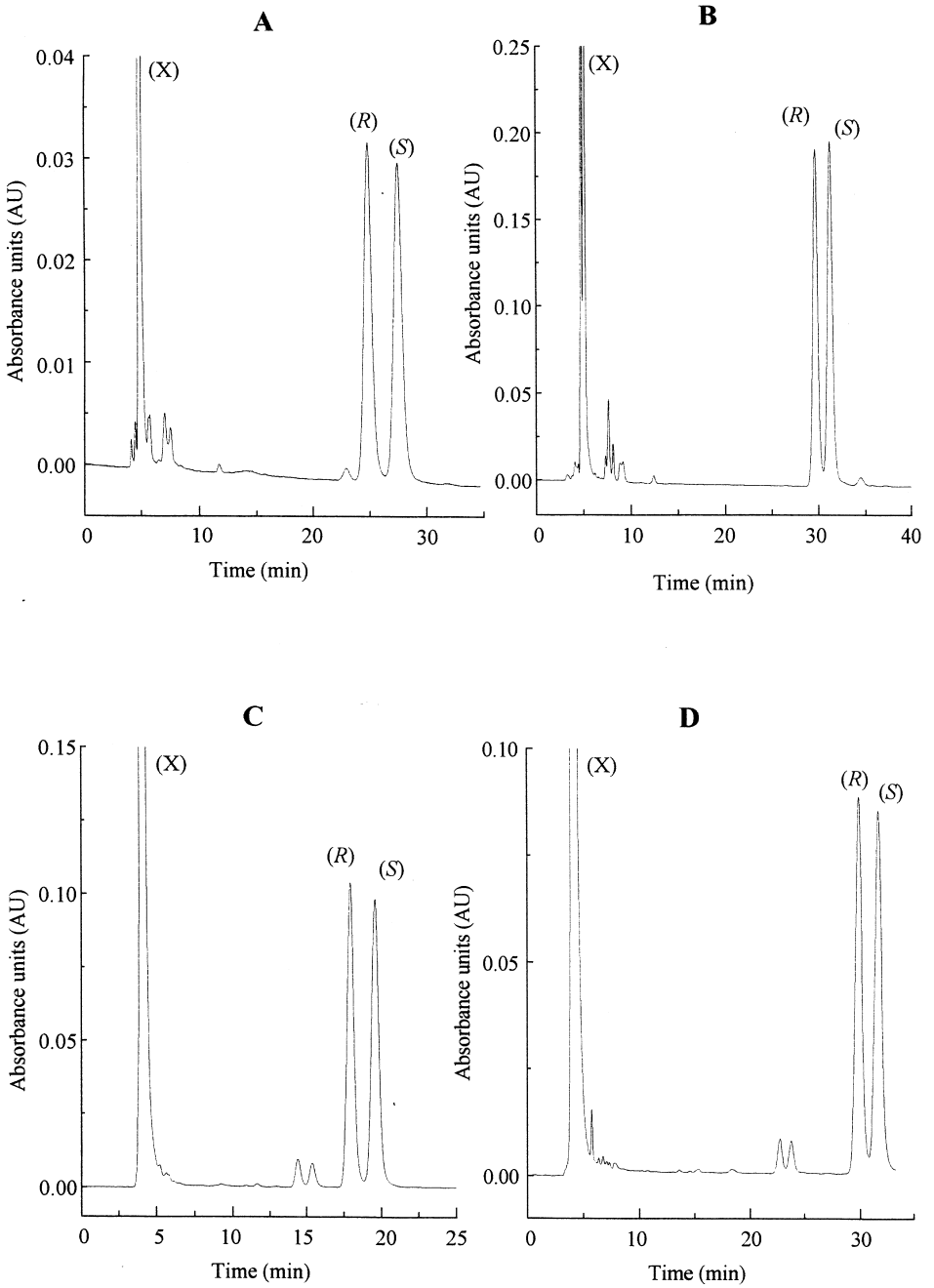


Fig. 2. Representative chromatograms of the separation of FDAA derivatives. Column, Vydac 218TP54 C_{18}; flow-rate, 0.8 ml/min; detection, 340 nm; at room temperature; eluent composition: (A) TFA–CH_3OH (25:75, v/v), (B) TFA–CH_3CN (50:50, v/v), (C) NaOAc–CH_3OH (20:80, v/v), (D) NaOAc–CH_3CN (40:60, v/v); A and B for FDAA-β^2-Bin-OH, C and D for FDAA-β^2-Bin-OEt; X is the excess of Marfey's reagent; TFA, 0.1% aqueous solution of trifluoroacetic acid; NaOAc, 0.01 *M* aqueous solution of sodium acetate (pH 3.0).

Table 1
Separation data for H-β²-Bin-OH as FDAA derivative

Eluent composition (v/v)	k_R	k_S	α	R_S
TFA–CH_3OH				
15:85	1.23	1.34	1.09	0.63
20:80	2.25	2.49	1.11	1.16
25:75	6.29	7.06	1.12	1.86
NaOAc–CH_3OH				
15:85	0.77	0.84	1.09	<0.40
20:80	2.07	2.27	1.10	1.18
25:75	4.02	4.66	1.16	1.52
TFA–CH_3CN				
35:65	1.51	1.62	1.07	0.71
40:60	2.73	2.91	1.07	1.20
50:50	7.71	8.16	1.06	1.60
NaOAc–CH_3CN				
35:65	1.30	1.39	1.07	0.50
40:60	2.04	2.18	1.07	0.78
50:50	7.20	7.79	1.08	1.19

Column, Vydac 218TP54 C_{18}; flow-rate, 0.8 ml/min; detection, 340 nm; TFA, 0.1% aqueous solution of trifluoroacetic acid; NaOAc, 0.01 *M* aqueous solution of sodium acetate (pH 3.0); t_0, 3.41 min.

analogue Bin had been reported to have been separated successfully as their GITC derivatives [4].

The chromatograms of FDAA derivatives are shown in Fig. 2. The results of the separation are given in Tables 1 and 2. For each derivatized compound, different organic (CH_3OH and CH_3CN) and aqueous (0.1% TFA, 0.01 *M* NaOAc pH 3.0) eluent components were used at different volume/volume ratios (v/v). On decrease of the organic modifier content, retention factors (k) increased, the resolution (R_S) improved and the separation factor (α) either did not change or slightly improved. At all mobile phase compositions, the more hydrophobic FDAA-β²-Bin-OEt eluted later than FDAA-β²-Bin-OH and gave larger k values. The difference between the k values of the FDAA derivatives of β²-Bin-OH and β²-Bin-OEt was significantly larger in CH_3CN-containing mobile phases. A further comparison of the organic modifiers revealed that a separation with better resolution (with similar k values) can be achieved in CH_3OH-containing mobile phases.

A comparison of the effects of the two different aqueous eluent components at the same composition with both organic modifiers revealed that similar or slightly smaller retention factors with similar resolutions were achieved for the NaOAc-containing systems with both organic modifiers.

Overall the use of CH_3OH as organic modifier in the mobile phase, combined with 0.01 *M* NaOAc with a pH of 3.0, ensures that the FDAA derivatives can be effectively resolved within a short analysis time.

The elution sequence was determined by standard addition. For both compounds, the derivatives of the (*R*) isomers eluted first. The same elution sequence was reported for the GITC derivatives of Bin [4].

Table 2
Separation data for H-β²-Bin-OEt as FDAA derivative

Eluent composition (v/v)	k_R	k_S	α	R_S
TFA–CH_3OH				
15:85	2.19	2.42	1.10	1.26
20:80	4.89	5.42	1.11	1.73
NaOAc–CH_3OH				
15:85	1.90	2.11	1.11	1.05
20:80	4.27	4.75	1.11	1.53
TFA–CH_3CN				
35:65	5.08	5.44	1.07	0.89
40:60	9.70	10.34	1.06	1.42
NaOAc–CH_3CN				
35:65	4.90	5.24	1.07	0.88
40:60	7.77	8.30	1.07	1.44

Column, Vydac 218TP54 C_{18}; flow-rate, 0.8 ml/min; detection, 340 nm; TFA, 0.1% aqueous solution of trifluoroacetic acid; NaOAc, 0.01 *M* aqueous solution of sodium acetate (pH 3.0); t_0, 3.41 min.

3.2. Direct separation of the enantiomers

Since three of the five investigated compounds, **1c**, **1d** and **2**, were not suitable for indirect separations, it was essential to find an appropriate direct method for the enantioresolution of these compounds. Table 3 summarizes the results concerning the optical resolution of the β²-Bin compounds when four different β-CD-bonded phases were used in different operating modes. Representative chromatograms are presented in Fig. 3. The elution sequence was determined by standard addition, and in all cases the (*R*) enantiomer was found to elute earlier. The results of the present study are discussed below in terms of different parameters, such as the structural features of the analyte and the chiral selector, the effects of

Table 3
Separation data for the enantiomers of β²-Bin compounds on different β-CD phases

Compound	k_R	k_S	α	R_S	Column	Conditions
1a	0.45	0.78	1.90	0.45	ChiraDex	RP[a]
H-β²-Bin-OH	0.67	1.24	1.85	0.75		RP[b]
	4.26	8.66	2.03	3.40		RP[c+]
	0.95	1.37	1.44	2.36	Cyclobond I 2000	RP[a]
	1.51	2.04	1.35	2.72		RP[b]
	1.76	2.67	1.52	3.14	Cyclobond I 2000 RSP	RP[a]
	2.02	3.06	1.51	3.25		RP[b]
1b	0.49	1.05	2.14	1.46	ChiraDex	RP[c+]
H-β²-Bin-OEt	0.31	0.44	1.42	1.06	Cyclobond I 2000	RP[a]
	1.87	2.18	1.17	0.62		RP[b]
	1.30	1.78	1.37	1.62	Cyclobond I 2000 RSP	RP[a]
	2.84	4.02	1.41	1.40		RP[b]
1c	5.16	7.30	1.41	1.34	ChiraDex	RP[a]
Boc-β²-Bin-OH	6.55	8.78	1.34	1.36		RP[b]
	2.36	2.55	1.08	1.00	Cyclobond I 2000	PO[d]
	3.10	3.34	1.08	1.22		PO[e]
	2.27	2.47	1.09	0.60	Cyclobond I 2000 SN	PO[d]
	2.50	2.76	1.11	0.82		PO[e]
1d Boc-β²-Bin-OEt	6.15	7.17	1.16	<0.40	Cyclobond I 2000 RSP	RP[a]
2	3.48	3.80	1.09	<0.40	Cyclobond I 2000 RSP	RP[a]
CN-β²-Bin-OEt	4.48	4.85	1.08	<0.40		RP[b]

CH_3COOH, glacial acetic acid; TEA, triethylamine; 1% TEAA, aqueous solution of triethylammonium acetate; RP, reversed-phase mode; PO, polar organic mode; flow-rate, 1 ml/min, [+]0.75 ml/min; detection, 230 nm; void volumes, ChiraDex, t_0=2.56 min, $^+t_0$=3.16 min, Cyclobond I 2000, t_0=3.16 min, Cyclobond I 2000 RSP, t_0=3.13 min, Cyclobond I 2000 SN, t_0=3.19 min.
[a] 1% TEAA (pH 4.1)–CH_3CN (75:25, v/v).
[b] 1% TEAA (pH 6.8)–CH_3CN (75:25, v/v).
[c] 0.01 *M* KH_2PO_4 (pH 3.0)–CH_3OH (75:25, v/v).
[d] CH_3CN–CH_3COOH–TEA (100:0.5:0.5, v/v/v).
[e] CH_3CN–CH_3COOH–TEA (100:0.5:0.4, v/v/v).

the organic modifier and of pH, as regards chiral recognition and separation on the applied β-CD-bonded phases.

3.2.1. Structural factors affecting chiral recognition

The results of this study, listed in Table 3, confirm the fact that so far the same compounds have not been effectively resolved by the same CD-bonded phase, operated in different modes, RP, NP and PO. This is due to the different separation mechanisms and different types of interactions in the different modes.

It is interesting that three of the investigated β²-Bin compounds, **1a**, **1b** and **1c**, were resolved not merely by one of the β-CD phases, but by three of them. Enantioseparation of **1a** and **1b** was achieved with the ChiraDex, Cyclobond I 2000 and Cyclobond I 2000 RSP phases in the RP-HPLC. This means that in these cases the formation of an inclusion complex, due to the hydrophobic effect and hydrogen-bonding interactions between the guest molecule and the hydroxyl groups of the native β-CD or the hydroxypropyl (HP) groups of the derivatized β-CD, is responsible for the chiral recognition. To the best of our knowledge, a racemically derivatized HP-β-CD phase has not been found suitable for the resolution of enantiomers of atropic compounds. Our results on the separation with this phase are in contradiction of earlier observations [8].

Chiral recognition on the derivatized CD phases is probably the sum of total of the interactions arising

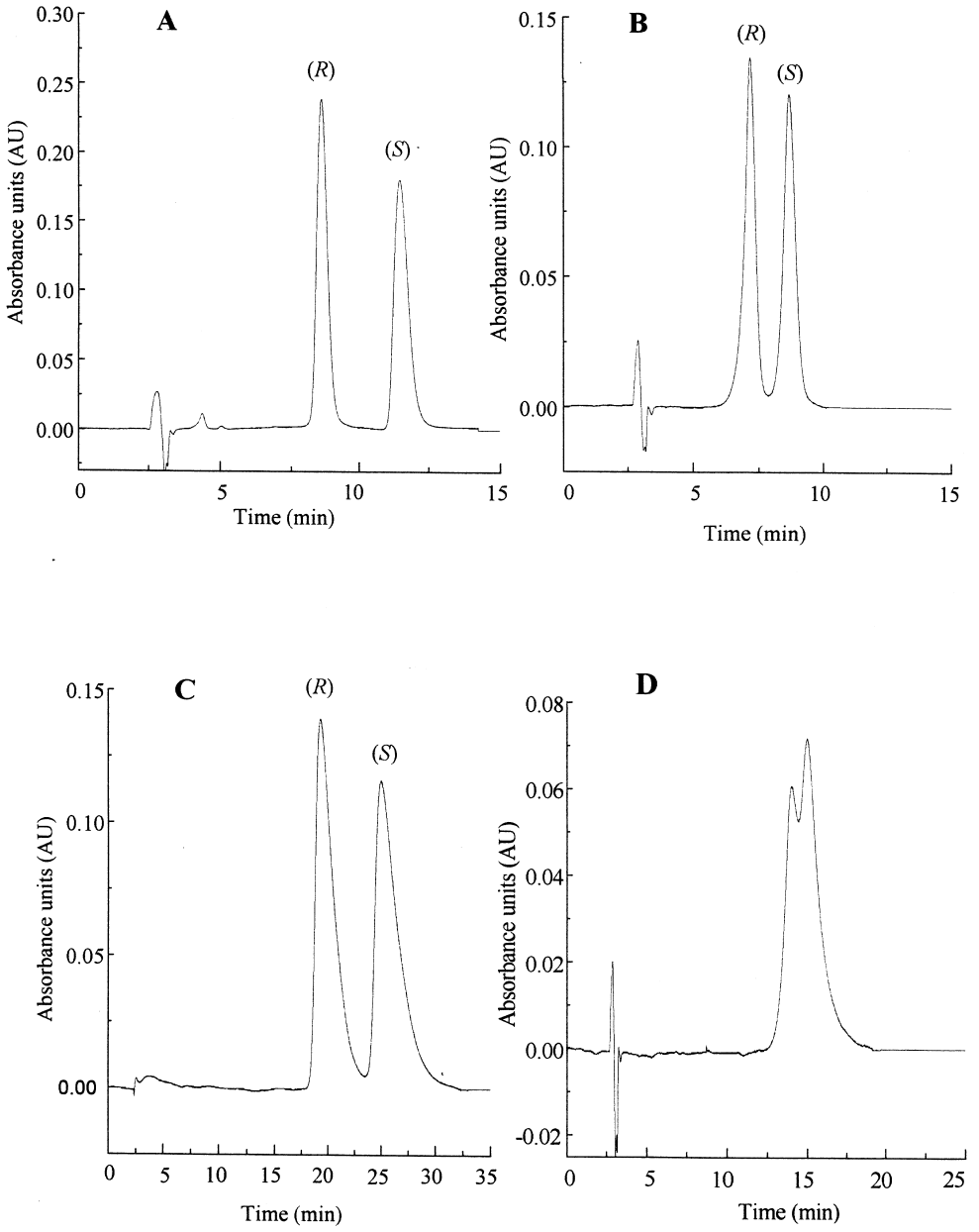


Fig. 3. Illustrative chromatograms of direct separation of the enantiomers of β^2-Bin compounds. Flow-rate, 1 ml/min; detection, 230 nm; at room temperature; chromatographic conditions: column (A, B and D) Cyclobond I 2000 RSP, (C) ChiraDex; eluent composition, (A, B and D) 1% TEAA (pH 4.1)–CH_3CN (75:25, v/v), (C) 1% TEAA (pH 6.8)–CH_3CN (75:25, v/v), A for H-β^2-Bin-OH, B for Boc-β^2-Bin-OH, C for H-β^2-Bin-OEt, D for CN-β^2-Bin-OEt; 1% TEAA, 1% aqueous solution of triethylammonium acetate.

from two sources: the base CD or the chiral substituent [19]. Furthermore, it can be stated that the configuration of the HP groups here is less important than the fact that they provide additional, but probably nonstereospecific sites. These groups might allow the analyte to form a stronger inclusion complex with the CD. This is a possible explanation for the partial enantioseparation of **1d** and **2** by the HP-

derivatized β-CD phase in the RP-HPLC. Although the resolution of the enantiomers of these compounds was very poor, the HP-β-CD phase, operated in the RP-HPLC, was the only one that exhibited some enantioselectivity towards these compounds.

Among the applied β-CD-bonded phases, only the naphthylethylcarbamate (NEC) derivative (Cyclobond I 2000 SN) is said to be a highly effective multimodal CSP [9] that can be operated in all three modes, thereby expanding the types of analytes to be resolved. Due to this fact, it was expected to be a very successful tool in the separation of the enantiomers of the β^2-Bin compounds, especially in the NP-HPLC, in consequence of the presence of aromatic rings, capable of π–π interactions, involving both the analytes and the substituent on the CD. Carbamoylation of the CD moiety introduces not only new π–π interaction sites into the CSP, but also additional hydrogen-bonding sites and the potential for dipole stacking interactions [20]. The aromatic substituents on the CD did not result in enantioselective separation in the NP-HPLC; the solutes eluted at or near the void volume of the column. Surprisingly, on this phase we observed enantioselectivity only for **1c** in the PO mode, which may be explained by the possibility for the base CD moiety to dominate in the chiral recognition via the greater contribution of hydrogen bonding to the separation mechanism, and hence by the formation of a more strongly complexed solute in the CD cavity.

3.2.2. Effects of organic modifier nature and content

It is known from CD-binding studies that an increase of the organic content in the mobile phase will weaken the strength of inclusion complexation between guest molecules and the CD, resulting in a decreased retention and a decreased resolution [21]. CH_3OH, as a hydrogen-bond donor, unlike CH_3CN, is believed to compete with the analyte for the specific hydrogen-bonding sites on the CD. Accordingly in our experiments we used CH_3CN in RP-HPLC in most cases. Only the ChiraDex column was successfully operated with CH_3OH in the enantioresolution of **1a** and **1b**, which may be explained by the fact that the columns were manufactured by different methods and the operating conditions may therefore differ.

3.2.3. Effect of pH

In this investigation, the influence of pH on the retention and resolution of β^2-Bin enantiomers was studied by using 1% TEAA buffer. When the pH was increased from 4.1 to 6.8, the retention (*k*) increased. These results are in contrast with those reported so far [22,23]. A likely explanation for this appears to be that at higher pH each investigated compound (either contains ionizable groups **1a**, **1b** and **1c** or not **2**) forms stronger inclusion complexes with the CD cavity itself resulting in an increased retention.

4. Conclusions

In summary, it can be stated that not merely one chiral separation technique, indirect or direct, can be used for the separation of enantiomers of β^2-Bin compounds. The analytes can be effectively separated indirectly as their FDAA derivatives. Concerning the results of direct separation, two interesting observations must be mentioned: a racemically derivatized β-CD-bonded phase was successfully applied for the enantioresolution of atropic molecules, and increase of the pH of the applied buffer led to an increased retention.

Acknowledgements

This work was supported by grants OTKA T 14898 and FKFP 0087/97. D.W.A. acknowledges the support of the National Institutes of Health, NIH ROI GM 53825-01.

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