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Journal of Chromatography A, 752 (1996) 77–84

JOURNAL OF CHROMATOGRAPHY A

Chiral recognition models for the liquid chromatographic resolution of π-acidic racemates on a chiral stationary phase derived from N-phenyl-N-alkylamide of (*S*)-naproxen

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Received 5 March 1996; accepted 23 May 1996

Abstract

To elucidate the chiral recognition mechanism exerted by an (*S*)-naproxen-derived chiral stationary phase (CSP) containing a long tether consisting of a tertiary N-phenyl-N-undecyl amide linkage, a CSP with a short tether consisting of N-phenyl-N-propyl amide linkage was prepared and homologous series of N-(3,5-dinitrobenzoyl)-α-amino alkyl esters and N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines were resolved on the two CSPs. Based on the chiral recognition trends for resolving homologous series of π-acidic racemates on the two CSPs which differ only in the tether length and from the study of CPK space filling molecular models, chiral recognition models utilizing the intercalation of the alkyl substituent of the analyte between the adjacent strands of bonded phase in rationalizing the dependence of the separation factors on the length of the alkyl substituent of the analyte and the tether length of the CSP were proposed.

Keywords: Chiral stationary phases, LC; Chiral recognition mechanisms; Enantiomer separation

1. Introduction

Among various chiral stationary phases (CSPs) for the liquid chromatographic separation of enantiomers, Pirkle-type CSPs have been known to separate two enantiomers through the enantioselective π-donor -acceptor interaction between the CSP and racemic analytes [1,2]. For the effective separation of enantiomers, therefore, Pirkle-type CSPs have been generally designed to contain π-acidic and/or π-basic aromatic rings [3–5]. In this context, (*S*)-naproxen, an optically active anti-inflammatory drug, is an attractive candidate as a chiral selector in chiral liquid chromatography because it contains a strong π-basic aromatic ring such as 6-methoxy-2-naphthyl group. Indeed, various CSPs based on (*S*)-naproxen have been reported [6–12]. Among others, CSP 1 Fig. 1, which was recently reported by us, has been known to separate various racemates quite effectively and found to show greater enantioselectivities than any other (*S*)-naproxen-derived CSPs reported so far in resolving various π-acidic racemates [13]. However, the chiral recognition mechanism exerted by CSP 1 has not been systematically studied yet.

A homologous series of analytes has been often utilized to investigate the origins of enantioselectivity exerted by certain Pirkle-type CSPs. For example, increasing or decreasing trends in the separation factors of a homologous series of analytes and the dependence of the enantioselectivity of a

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0021-9673/96/$15.00
PII S0021-9673(96)00508-0

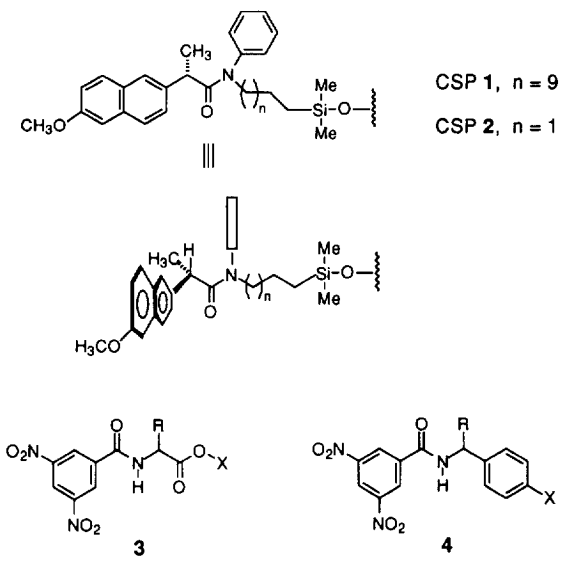

Fig. 1. Structures of CSP 1, CSP 2, analyte 3 and 4.

homologous series of analytes upon the length of the connecting tether of CSPs have been used as evidences for the intercalation of the alkyl substituent of analytes between the adjacent strands of bonded phase [12,14,15]. In this context, to explore the chiral recognition mechanism exerted by CSP 1, we prepared a new CSP (CSP 2), which is the short tethered version of CSP 1, and compared the chiral recognition trends for resolving a homologous series of π-acidic racemates on CSP 1 and 2. On the basis of the chiral recognition trends for resolving π-acidic racemates on CSP 1 and 2 and from the study of CPK space filling molecular models, we herein propose chiral recognition mechanisms exerted by CSP 1 and/or 2.

2. Experimental

2.1. Chromatography

Chromatography was performed with a HPLC system consisting of a Waters Model 510 pump, a Waters Model U6k universal liquid chromatograph injector with a 20 μl sample loop, a Waters Model 441 absorbance detector with a 254 nm UV filter and a Waters Model 740 data module recorder. All chromatographic data were obtained using 2-propanol–hexane (10:90) as a mobile phase at a flow-rate of 2 ml/min at 21 °C. The column void volumes were determined using 1,3,5-tri-*tert.*-butylbenzene [16]. The analytes used in this study were available from previous studies [12]. Solvents for HPLC analysis were of HPLC grade.

2.2. Preparation of CSP 2.

CSP 2 was prepared as outlined in Fig. 2 according to the method described for the preparation of CSP 1 [13]. Elemental analysis of CSP 2 (C 8.76, H 0.88, N 0.52%) showed a loading of 0.29 mmole (based on C) or 0.37 mmole (based on N) of chiral selector per gram of stationary phase. The physical and spectroscopic properties of intermediates are as follows [^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer (200 MHz). Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as the internal standard. IR spectra were obtained with a Mattson Polaris Fourier transform (FT) IR spectrometer].

2.2.1. N-phenyl-N-(2-propenyl)-(S)-α-(6-methoxy-2-naphthyl)propionamide

This compound was obtained as a viscous oily material. The enantiomeric purity of this compound was greater than 98% ee by HPLC analysis on a commercial chiral column (Regis, Morton Grove, IL, USA) derived from (*S*)-N-(3,5-dinitrobenzoyl)-

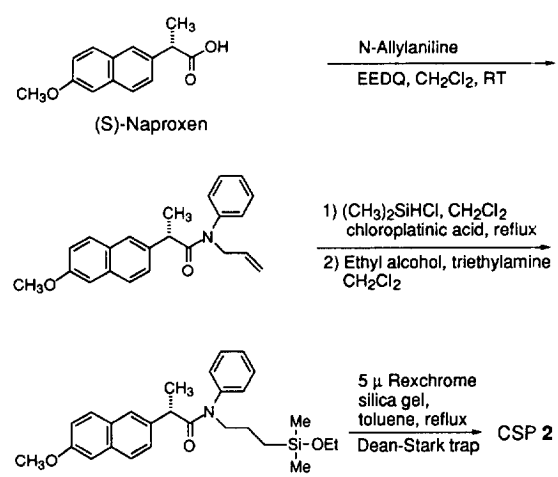

Fig. 2. Scheme for the preparation of CSP 2.

leucine. ^{1}H NMR (C^2HCl_3), δ 1.48(d, 3H), 3.75(q, 1H), 3.91(s, 3H), 4.29(d, 2H), 4.96–5.08(m, 2H), 5.77–5.91(m, 1H), 6.95–7.64(m, 11H). IR (NaCl window) cm^{-1} 3059, 2971, 1648, 1605, 1450.

2.2.2. N-phenyl-N-(3-ethoxydimethylsilylpropyl)-(S)-α-(6-methoxy-2-naphthyl)propionamide

This compound was obtained as a viscous oily material. The enantiomeric purity of this compound was greater than 98% ee by the HPLC analysis on a chiral column derived from (*S*)-N-(3,5-dinitrobenzoyl)leucine. ^{1}H NMR (C^2HCl_3), δ −0.12(s, 6H), 0.34–0.40(m, 2H), 1.24(t, 3H), 1.48(d, 3H), 1.35–1.52(m, 2H), 3.55–3.75(m, 3H), 3.90(s, 3H), 6.85–7.61(m, 11H). IR (NaCl window) cm^{-1} 3059, 2955, 1656, 1607, 1494.

3. Results and discussion

To explore the chiral recognition mechanism exerted by CSP 1 for resolving π-acidic racemates, we resolved homologous series of racemic N-(3,5-dinitrobenzoyl)-α-amino alkyl esters 3 and racemic N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines 4 on CSP 1 and compared the chromatographic resolution results with those on CSP 2.

The chromatographic results for resolving homologous series of racemic N-(3,5-dinitrobenzoyl)leucine alkyl esters (3, R=isobutyl and X=alkyl) and racemic N-(3,5-dinitrobenzoyl)alkylglycine ethyl esters (3, R=alkyl and X=ethyl) on CSP 1 and 2 are summarized in Table 1 and the trends in the separation factors, α, are graphically presented in Fig. 3. The elution orders noted in Table 1 have been established by injecting configurationally known samples. As shown in Table 1 and Fig. 3, the separation factors, α, generally increase as the ester alkyl chain (X of 3) of the analyte increases in length (Fig. 3a) whereas those decreases as the α-alkyl chain (R of 3) at the chiral center of the analyte increases in length (Fig. 3b) and all of these trends are much more significant on CSP 2 than on CSP 1. The discrepancy in the continuous decrease in the separation factor at $n=3$ noted in Fig. 3b might be a consequence of conformational factors as described previously [12,15].

In our previous study concerning the resolution of N-(3,5-dinitrobenzoyl)-α-alkylamino alkyl esters on a CSP derived from 3,5-dimethylanilide derivative of (*S*)-naproxen [13], we have proposed that the amide

Table 1
Resolution of N-(3,5-dinitrobenzoyl)-α-amino acid alkyl esters (3) on CSP 1 and 2[a]

Analyte	R	X	CSP 1			CSP 2		
			k_1'[b]	α[c]	Configuration[d]	k_1'[b]	α[c]	Configuration[d]
3	$CH_2CH(CH_3)_2$	CH_3	5.83	3.88	R	8.59	2.94	R
	$CH_2CH(CH_3)_2$	CH_2CH_3	4.66	3.91	R	5.83	3.34	R
	$CH_2CH(CH_3)_2$	$(CH_2)_2CH_3$	4.29	3.85	R	4.81	3.70	R
	$CH_2CH(CH_3)_2$	$(CH_2)_3CH_3$	4.03	3.87	R	4.10	4.09	R
	$CH_2CH(CH_3)_2$	$(CH_2)_5CH_3$	3.71	3.92	R	3.39	4.59	R
	$CH_2CH(CH_3)_2$	$(CH_2)_7CH_3$	3.36	4.04	R	3.05	4.72	R
	$CH_2CH(CH_3)_2$	$(CH_2)_9CH_3$	3.07	4.10	R	2.78	4.82	R
	$CH_2CH(CH_3)_2$	$(CH_2)_{11}CH_3$	2.89	4.16	R	2.69	4.85	R
	$CH_2CH(CH_3)_2$	$(CH_2)_{13}CH_3$	2.69	4.24	R	2.61	4.80	R
	$CH_2CH(CH_3)_2$	$(CH_2)_{15}CH_3$	2.43	4.21	R	2.47	4.86	R
	CH_3	CH_2CH_3	5.14	3.08	R	9.73	3.19	R
	$(CH_2)_2CH_3$	CH_2CH_3	4.90	3.89		7.00	3.46	
	$(CH_2)_4CH_3$	CH_2CH_3	4.54	3.57		5.61	2.49	
	$(CH_2)_6CH_3$	CH_2CH_3	4.14	3.50		4.59	1.86	
	$(CH_2)_7CH_3$	CH_2CH_3	4.00	3.45		4.28	1.68	

[a] See Section 2 for the chromatographic conditions.
[b] Capacity factor of the first eluted enantiomers.
[c] Separation factor.
[d] Absolute configuration of the second eluted enantiomer.

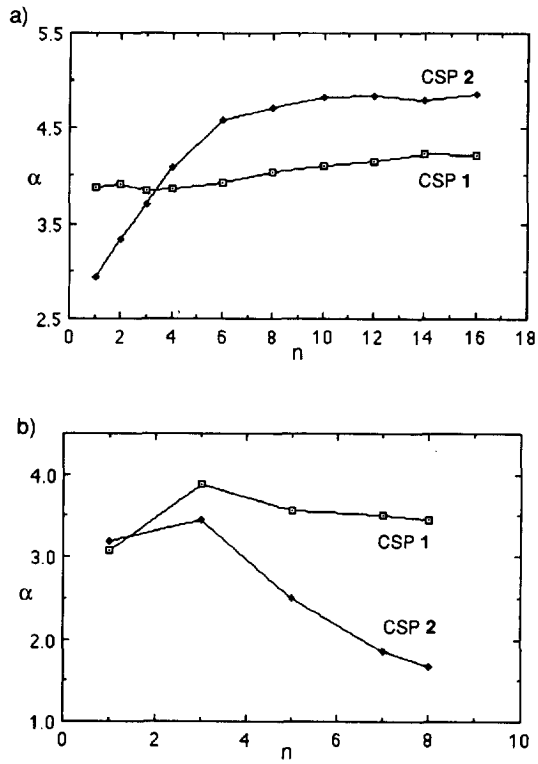

Fig. 3. Trends in the enantioselectivity, α, for resolving (a) N-(3,5-dinitrobenzoyl)leucine alkyl esters [3, R=isobutyl and X=$(CH_2)_n$-H] and (b) N-(3,5-dinitrobenzoyl)-α-alkylglycine ethyl esters [3, R=$(CH_2)_n$-H and X=ethyl] on CSP 1 and 2. The length [-$(CH_2)_n$-H] of the ester alkyl group or the α-alkyl substituent of the analyte is denoted by n on the abscissa.

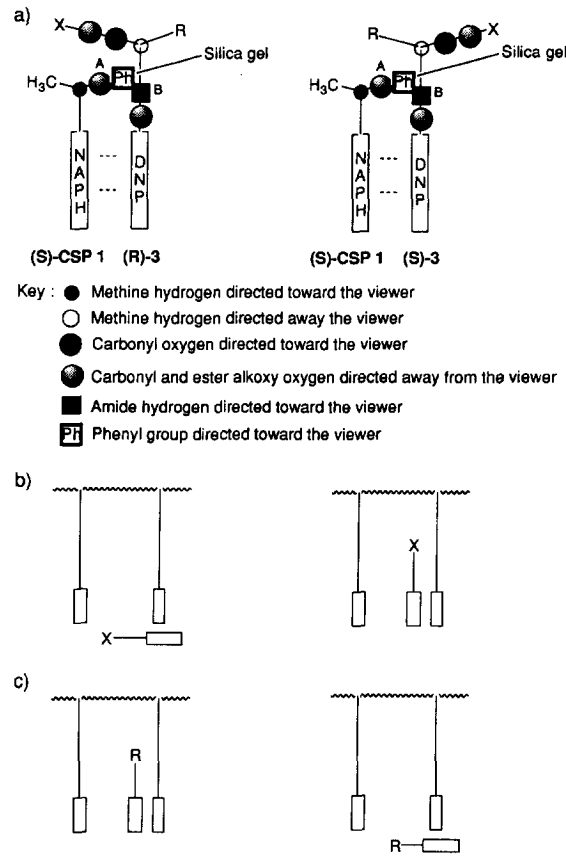

Fig. 4. (a) Proposed chiral recognition model for resolving N-(3,5-dinitrobenzoyl)-α-amino alkyl esters (3) on CSP 1 or 2. (b) Schematic presentation of the proposed chiral recognition model indicating the intercalation of the ester alkyl group between the adjacent strands of bonded phase. (c) Schematic presentation of the proposed chiral recognition model indicating the intercalation of the α-alkyl substituent of the analyte between the adjacent strands of bonded phase.

N-H hydrogen of the CSP participates in the chiral recognition by hydrogen bonding with the carbonyl oxygen of the 3,5-dinitrobenzoyl amide group of the analyte. However, CSP 1 (or 2) does not contain the amide N-H hydrogen but resolves racemic N-(3,5-dinitrobenzoyl)-α-alkylamino alkyl esters with greater separation factors than the CSP derived from 3,5-dimethylanilide derivative of (*S*)-naproxen [13]. Therefore, the chiral recognition models for the resolution of N-(3,5-dinitrobenzoyl)-α-alkylamino alkyl esters on CSP 1 (or 2) should be different from those proposed previously for the CSP derived from 3,5-dimethylanilide derivative of (*S*)-naproxen [13].

Based on the chiral recognition trends shown in Table 1 and Fig. 3 and from the study of CPK space filling molecular models, we propose a chiral recognition model such as shown in Fig. 4a. In the model, CSP 1 (or CSP 2) and the analyte are presumed to be in their lowest energy conformations and hence preferentially populated [8,14]. One thing to note is that the exact geometrical structure of the tertiary amide part of the CSP is not confirmed yet. However, the *cis* orientation of the N-phenyl ring and the chiral moiety of the CSP shown in Fig. 1 is speculated to seem plausible due to steric hindrance between the N-alkyl chain and the chiral moiety and to electronic repulsion between the carbonyl lone-pair electrons and the phenyl π-electrons as described previously [13,17]. In addition, the N-phenyl

ring of the anilide part of the CSP is assumed to take a perpendicular conformation with respect to the plane of the amide part of the CSP as shown in Fig. 1, based on the ab initio molecular orbital calculation concerning the conformational preference of the phenyl ring of N-methylacetanilide [17] and on the CPK molecular model study.

In the proposed chiral recognition model shown in Fig. 4a, the CSP interacts with the analyte through the face to face π-π interaction between the 6-methoxy-2-naphthyl group (NAPH in the model) of the CSP and the 3,5-dinitrophenyl group (DNP in the model) of the analyte and through the hydrogen bonding interaction between the carbonyl oxygen (A in the model) of the CSP and the amide N-H hydrogen (B in the model) of the analyte. Between the two transient diastereomeric complexes shown in the model, the (*S*,*R*)-complex is presumed to be more stable based on the elution orders than the (*S*,*S*)-complex and this might be originated from the fact that the carboalkoxy group is sterically less demanding than the alkyl substituent (α-alkyl group, R, in the model) [18]. In this instance, the ester alkyl chain (X in the model) of the less retained (*S*)-enantiomer is intercalated between the adjacent strands of bonded phase and eventually directed toward the silica support whereas that of the more retained (*R*)-enantiomer is directed away from the tether. These are schematically illustrated in Fig. 4b. The intercalation of the ester alkyl chain of the less retained (*S*)-enantiomer between the adjacent strands of bonded phase becomes increasingly unfavorable as the ester alkyl chain increases in length and this is more significant on the short tethered CSP. Consequently the separation factors increase gradually as the ester alkyl chain increases in length and the increasing trends in the separation factors should be more significant on CSP 2.

In contrast to this, the α-alkyl chain (R in the model) at the chiral center of the more retained (*R*)-enantiomer is intercalated between the adjacent strands of bonded phase and directed toward the silica support whereas that of the less retained (*S*)-enantiomer is directed away from the tether and the silica support as shown schematically in Fig. 4c. The intercalation of the α-alkyl chain (R in the model) at the chiral center of the more retained (*R*)-enantiomer between the adjacent strands of bonded phase encounters difficulty more and more as the α-alkyl chain increases in length and this is again more significant on the short tethered CSP. In consequence, the separation factors decrease as the α-alkyl chain increases in length and these trends should be more significant on CSP 2.

The chromatographic results for resolving homologous series of N-(3,5-dinitrobenzoyl)-α-phenylalkylamines (4, R=alkyl, X=H) and N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)ethylamines (4, R=methyl, X=alkyl) on CSP 1 are compared to those on CSP 2 in Table 2 and the trends of the separation factors are graphically presented in Fig. 5. The elution orders shown in Table 2 were established from the configurationally known samples or inferred from the TRAC (tracking of absolute configuration) technique [18]. The inversion of the elution orders for resolving N-(3,5-dinitrobenzoyl)-α-phenylalkylamines (4, R=alkyl, X=H) on CSP 2 shown in Table 2 and Fig. 5a were checked by collecting chromatographic fractions of each enantiomer eluting from one CSP and then injecting collected and concentrated fractions of each enantiomer into another CSP. As shown in Table 2 and Fig. 5, the separation factors for resolving homologous series of N-(3,5-dinitrobenzoyl)-α-phenylalkylamines (4, R=alkyl, X=H) on CSP 1 decrease gradually as the alkyl substituent at the chiral center of the analyte increases in length (Fig. 5a) whereas those for resolving N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)ethylamines (4, R=methyl, X=alkyl) on CSP 1 increase continuously as the 4-alkyl substituent at the phenyl group of the analyte increases in length (Fig. 5b). All of these trends are much more significant on CSP 2 and, consequently, the elution orders of the two enantiomers of N-(3,5-dinitrobenzoyl)-α-phenylalkylamines (4, R=alkyl, X=H) on CSP 2 are even reversed when the length of the alkyl substituent at the chiral center of the analyte reaches at a certain distance as shown in Fig. 5a.

Fig. 6a shows one possible chiral recognition model, which can rationalize the chiral recognition trends shown in Table 2 and Fig. 5. In the model, the analyte is again presumed to be in its lowest energy conformation and hence preferentially populated [18]. As shown in Fig. 6a, the CSP interacts with the analyte in a very similar fashion to that presented in

Table 2
Resolution of N-(3,5-dinitrobenzoyl)-α-phenylalkylamines 4 on CSP 1 and 2[a]

Analyte	R	X	CSP 1			CSP 2		
			k_1'[b]	α[c]	Configuration[d]	k_1'[b]	α[c]	Configuration[d]
4	CH_3	H	14.26	1.21	R	18.25	1.30	R
	$(CH_2)_4CH_3$	H	15.63	1.37	R	15.46	1.00	
	$(CH_2)_7CH_3$	H	14.03	1.29	R	8.04	1.56	S
	$(CH_2)_9CH_3$	H	12.90	1.25	R	6.87	1.70	S
	$(CH_2)_{14}CH_3$	H	11.20	1.13	R	5.69	1.86	S
	CH_3	CH_3	13.32	1.19	R	14.86	1.46	R
	CH_3	$(CH_2)_2CH_3$	11.58	1.30	R	8.83	2.25	R
	CH_3	$(CH_2)_5CH_3$	9.72	1.39	R	5.78	3.11	R
	CH_3	$(CH_2)_7CH_3$				5.19	3.49	R
	CH_3	$(CH_2)_9CH_3$	7.95	1.60	R	4.86	3.70	R
	CH_3	$(CH_2)_{11}CH_3$				4.57	3.78	R

[a] See Section 2 for the chromatographic conditions.
[b] Capacity factor of the first eluted enantiomers.
[c] Separation factor.
[d] Absolute configuration of the second eluted enantiomer.

Fig. 4a for resolving N-(3,5-dinitrobenzoyl)-α-amino esters. For example, the CSP interacts with the analyte through the π–π interaction between the 6-methoxy-2-naphthyl group (NAPH) of the CSP and the dinitrophenyl group (DNP) of the analyte and through the hydrogen bonding interaction between the carbonyl oxygen (A in the model) of the CSP and the N-H hydrogen (B in the model) of the analyte. In this instance, the edge of the 6-methoxy-2-naphthyl group (NAPH in the model) of the CSP confronts the face of the phenyl group at the chiral center of the (*R*)-analyte, invoking the face-to-edge π-π interaction which has been considered as an associative force between aromatic rings [19]. Therefore, the transient diastereomeric (*S*,*R*)-complex is more stable than the corresponding (*S*,*S*)-complex and consequently, the (*R*)-enantiomers retained longer on the CSP than the (*S*)-enantiomers. This is consistent with the elution orders shown in Table 2. In this event, the alkyl group (R in the model) at the chiral center of the more retained (*R*)-enantiomer is intercalated between the strands of bonded phase and directed toward the silica support while that of the less retained (*S*)-enantiomer is oriented away from the tether and the silica support. These are schematically presented in Fig. 6b. The intercalation of the alkyl group (R in the model) at the chiral center of the more retained (*R*)-enantiomer between the adjacent strands of bonded phase makes the retention of the more retained (*R*)-enantiomer decrease more rapidly than the less retained (*S*)-enantiomer as the alkyl group (R in the model) at the chiral center of the analyte increases in length and consequently, the separation factors decrease gradually. On the short tethered CSP, the intercalation of the alkyl group (R in the model) at the chiral center of the more retained (*R*)-enantiomer between the adjacent strands of bonded phase is more significantly disfavored as the alkyl substituent at the chiral center of the analyte increases in length and, finally, the retention of the more retained (*R*)-enantiomer becomes equal to that of the (*S*)-enantiomer when the alkyl substituent at the chiral center of the analyte reaches at a certain length and, after that the (*S*)-enantiomer retained longer than the (*R*)-enantiomer as the alkyl substituent at the chiral center of the analyte increases in length further, resulting in the inversion of elution order. Therefore, the inversion of elution order for the resolution of N-(3,5-dinitrobenzoyl)-α-phenylalkylamines (4, R=alkyl, X=H) on CSP 2 shown in Table 2 and Fig. 5a is precisely explained by the chiral recognition model shown in Fig. 6a.

In the chiral recognition model shown in Fig. 6a, 4-alkyl substituent (X in the model) at the phenyl group of the less retained (*S*)-enantiomer is intercalated between the adjacent strands of bonded phase and oriented to the silica support whereas that of the more retained (*R*)-enantiomer is directed away from

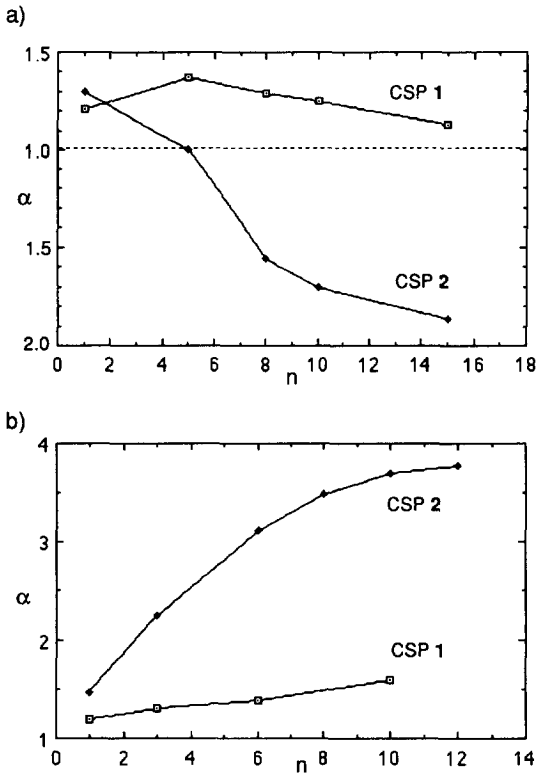

Fig. 5. Trends in the enantioselectivity, α, for resolving (a) N-(3,5-dinitrobenzoyl)-α-phenylalkylamines [4, R=$(CH_2)_n$-H and X=H] and (b) N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)ethylamines [4, R=methyl and X=$(CH_2)_n$-H] on CSP 1 and 2. The length [-$(CH_2)_n$-H] of the α-alkyl substituent or the 4-alkyl substituent of the analyte is denoted by n on the abscissa.

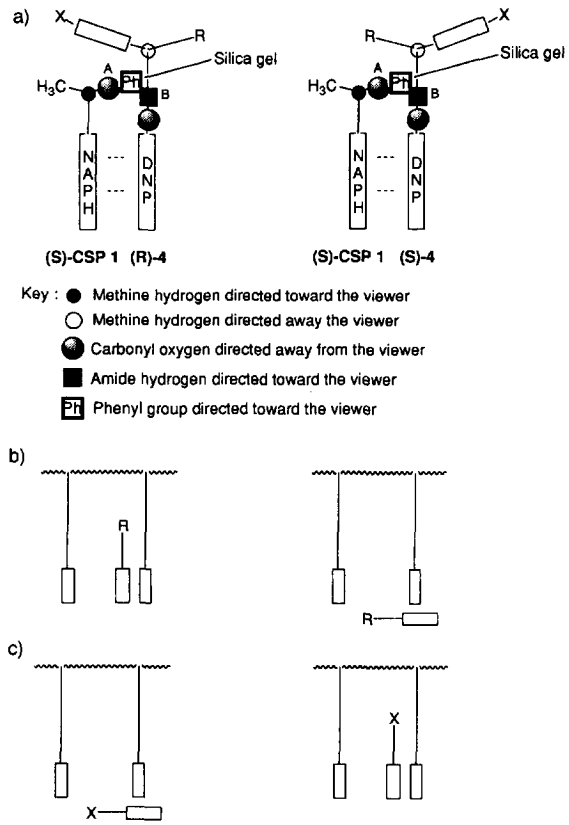

Fig. 6. (a) Proposed chiral recognition model for resolving N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines (4) on CSP 1 or 2. (b) Schematic presentation of the proposed chiral recognition model indicating the intercalation of the α-alkyl substituent of the analyte between the adjacent strands of bonded phase. (c) Schematic presentation of the proposed chiral recognition model indicating the intercalation of the 4-alkyl substituent of the phenyl group of the analyte between the adjacent strands of bonded phase.

the tether and the silica support. These are more clearly illustrated in the schematic presentation shown in Fig. 6c. In consequence, lengthening the 4-alkyl substituent (X in the model) at the phenyl group of the analyte decreases the retention of the less retained (*S*)-enantiomer more significantly than that of the (*R*)-enantiomer and, as a result, increases the separation factor α continuously. The retention of the less retained (*S*)-enantiomer decrease even more rapidly on the short tethered CSP (CSP 2) than on CSP 1 and consequently, the separation factors α should increase more rapidly on CSP 2 as the 4-alkyl substituent (X in the model) at the phenyl group of the analyte increases in length.

In summary, as an effort to elucidate the chiral recognition mechanism exerted by CSP 1 which contains a tertiary N-phenyl-N-undecylamide linkage, a short tethered CSP (CSP 2) was prepared and the enantiomers of homologous series of N-(3,5-dinitrobenzoyl)-α-amino esters 3 and N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines (4) were separated on the two CSPs which differ only in their tether length. Based on the chromatographic results for resolving N-(3,5-dinitrobenzoyl)-α-amino alkyl esters (3) and N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines (4) on CSP 1 and 2 and from the study of CPK space filling molecular models, chiral recognition models shown in Figs. 3 and 5a were proposed. For better understanding of the proposed chiral recognition models, interested readers are

advised to construct their own CPK molecular models. In the proposed models, the CSPs interact with π-acidic analytes through the π-donor–acceptor and the hydrogen bonding interaction. In this instance, the alkyl substituent of an (*R*)- or (*S*)-analyte intercalates between the neighboring strands of the bonded phase. The intercalation of the alkyl substituent of the analyte between the adjacent strands of the bonded phase is demonstrated to be enantioselective and to influence significantly the enantioselectivity especially on the short tethered CSP. As more experimental evidences are accumulated, the chiral recognition models proposed in this study might be modified.

Acknowledgments

This work was supported by grants from the Organic Chemistry Research Center sponsored by the Korea Science and Engineering Foundation and from the Basic Science Research Program, Ministry of Education, Korea (BSRI-96-3410).

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