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Experimental support differenciating two proposed chiral recognition models for the resolution of *N*-(3,5-Dinitrobenzoyl)-α-arylalkylamines on high-performance liquid chromatography chiral stationary phases

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Abstract

In rationalizing the odd chromatographic behavior for the separation of the enantiomers of *N*-(3,5-dinitrobenzoyl)-α-arylalkylamines on HPLC chiral stationary phases (CSPs) derived from α-(6,7-dimethyl-1-naphthyl)alkylamines, we initially suggested the occurrence of two competing, opposite sense chiral recognition processes termed the ''dipole-stacking process'' and the ''hydrogen-bonding process''. A simplified ''single mechanism'' model was later suggested with the importance of face to edge π–π interaction between aromatic rings come to recognized. The initial and subsequent chiral recognition models can be differentiated by noting the chromatographic trends for the enantioseparation of a homologous series of *N*-(3,5-dinitrobenzoyl)-α-(*p*-alkylphenyl)ethylamines on the aforementioned CSPs. Data so obtained were consistent with the second ''single mechanism'' model but not with the first ''two competing mechanism'' model. From these results, it has been concluded that the ''single mechanism'' model is more plausible than the ''two competing mechanism'' model.

Keywords: Chiral stationary phases, LC; Chiral recognition mechanism; *N*-(3,5-Dinitrobenzoyl)-α-arylalkylamines

1. Introduction

Some years ago, we developed a series of CSPs such as CSP **1** and CSP **2** (Fig. 1) derived from α-(6,7-dimethyl-1-naphthyl)alkylamines and used them to study the manner in which they distinguish between the enantiomers of several series of π-acidic analytes. For example, *N*-(3,5-dinitrobenzoyl) derivatives of α-amino esters and amides [1], α-aminophosphoric acid derivatives [2,3], various β-blockers such as propranolol and oxoprenolol [1,2], amines and amino alcohols [1,4], di- and tripeptides [5], β-lactams [6] and β-amino acid derivatives [7] have been successfully resolved on CSPs, **1** and **2**. In addition, 3,5-dinitrophenyl carbamate derivatives of racemic diols [8], 3,5-dinitrophenyl ureide derivatives of racemic cyclic amines [9] and 3,5-dinitroanilide derivatives of racemic α-arylpropionic acids (anti-inflammatory drugs) [10] have also been

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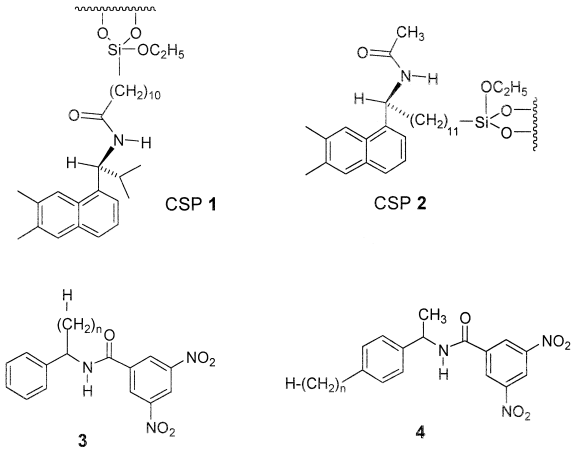

Fig. 1. The structure of CSP **1**, CSP **2**, analyte **3** and analyte **4**.

resolved on CSPs, **1** and **2**. Among others, the resolution of *N*-(3,5-dinitrobenzoyl)-α-arylalkylamines **3** (Fig. 1) on CSPs, **1** and **2** has attracted quite an attention because a curious resolution behavior was noted [1,2]. As the length of the analyte's linear alkyl substituent increases, enantioselectivity decreases on CSP **1** but increases on CSP **2**. The two CSPs are quite similar and differ principally in the orientation of the selectors with respect to the tethers linking them to the silica support. In order to rationalize the odd behavior for the resolution of a series of *N*-(3,5-dinitrobenzoyl)-α-phenylalkylamines **3** on CSPs, **1** and **2**, we initially suggested the occurrence of two competing, opposite sense chiral recognition processes such as the ''dipole-stacking process'' and the ''hydrogen bonding process'' [1,2]. Subsequently, a simplified ''single mechanism'' model was suggested to rationalize the odd resolution behavior with the importance of face to edge π–π interaction come to recognized [11].

The initial ''two competing mechanism'' model and the subsequent ''single mechanism'' model equally well rationalize the odd behavior for the resolution of a series of *N*-(3,5-dinitrobenzoyl)-α-phenylalkylamines **3** on CSPs, **1** and **2**. The face to edge π–π interaction between CSPs and analytes, which was utilized in the ''single mechanism'' model, has been widely employed later as an associative force in rationalizing chromatographic behaviors for the resolution of racemic compounds on brush-type CSPs [12–16]. In addition, face to edge π–π interactions between aromatic rings have been supported by various studies [17–20]. However, any experimental evidence to differenciate the two chiral recognition models proposed has not been provided so far. In this study, we wish to present experimental data that are consistent with the ''single mechanism'' model but inconsistent with the ''two competing mechanism'' model.

2. Experimental

Chromatography was performed with an HPLC system consisting of a Waters model 510 pump, a Rheodine model 7125 Injector with a 20 μl sample loop, a Youngin model 710 Absorbance Detector with a 254 nm UV filter and a Youngin D520B Computing Integrator. All chromatographic data were obtained by using 250 mm×4.6 mm I.D. stainless-steel columns packed with (S)-CSPs, **1** and **2**, at a flow rate of 2.00 ml/min at room temperature with a mobile phase of 20% 2-propanol in *n*-hexane. Chiral columns packed with (S)-CSPs, **1** and **2**, were prepared by the method described previously [1].

α-(*p*-Alkylphenyl)ethylamines were prepared from alkylbenzenes. Alkylbenzenes purchased from Aldrich were treated with acetyl chloride and anhydrous aluminum chloride in dichloromethane at 0°C for 2 h to afford *p*-alkylphenyl methyl ketones. These ketones were converted to the corresponding α-(*p*-alkylphenyl)ethylamines by the treatment with ammonium acetate and sodium cyanoborohydride in methanol at reflux. Finally, α-(*p*-alkylphenyl)-ethylamines were treated with 3,5-dinitrobenzoyl chloride in the presence of triethylamine in dichloromethane to afford *N*-(3,5-dinitrobenzoyl)-α-(*p*-alkylphenyl)ethyl amines **4** (Fig. 1).

3. Results and discussion

To show how the new data obtained in this study are inconsistent with the original ''two competing mechanism'' model, we briefly review the original ''two competing mechanism'' model [1]. Each enantiomer of *N*-(3,5-dinitrobenzoyl)-α-phenylalkylamines **3** was proposed to use its dinitrobenzoyl group (DNB) in an attractive face to face π–π

interaction with the face of the CSP naphthyl group *syn* to the carboxamide group while both analyte and chiral selector are in low energy, heavily populated, conformations. This face of the naphthyl group was thought to be utilized preferentially owing to the ability of either analyte enantiomer to simultaneously interact with the carboxamide group, either by hydrogen bond formation between the DNB NH and the carbonyl oxygen of the carboxamide or by antiparallel ''stacking'' of the two amide dipoles. In the case of the enantiomer incorporated into the heterochiral adsorbate (i.e. the one having nonidentical Cahn-Ingold-Prelog [21] stereochemical descriptors), the preferred interaction mode was suggested to be formation of the hydrogen bond between the DNB NH and the carbonyl oxygen of the carboxamide. In the case of the homochiral adsorbate, ''stacking'' of the two amide dipoles was presumed to occur preferentially. These interactions would aid in orienting each enantiomer with respect to the selector, different orientations being achieved. Since the two enantiomers are oriented differently with respect to the selector, their alkyl substituents at the chiral center are oriented differently and consequently intercalate between adjacent strands of CSPs, **1** and **2**, to differing extents. In 2-propanol-hexane mobile phases, such intercalation is resisted, causing a reduction in retention. The extent of this reduction depends on the length of the alkyl substituent at the chiral center. The orientation of the selector with respect to the tether determines which enantiomer has the greater intercalation difficulty.

As awareness of the importance of face to edge $\pi-\pi$ interactions developed [17], we came to question the earlier postulate as it appeared that an attractive $\pi-\pi$ interaction between the face of the α-aryl substituent and the edge of the CSP's naphthyl group could also be a factor in the chiral discrimination. By invoking face to edge $\pi-\pi$ interaction which was widely utilized later as one of the major interactions in the chiral recognition by brush-type CSPs [12–16], one need no longer to invoke ''dipole stacking''. Both analyte enantiomers might now undergo the previously mentioned face to face $\pi-\pi$ and hydrogen bonding interactions simultaneously. Only in the homochiral adsorbate would the analytes α-aryl substituent be directed so as to also permit simultaneous face to edge $\pi-\pi$ interaction. Momentarily neglecting intercalation effects, the presence or absence of this face to edge $\pi-\pi$ interaction is now thought to be the principle source of the stability difference of the diastereomeric adsorbates. As before, intercalation effects are superimposed on the fundamental source of the chiral recognition. Thus, an increase in the length of the alkyl substituent in a homologous series of type **3** analytes alters the relative retentions of a pair of enantiomers. As one proceeds through the series, enantioselectivity either progressively decreases or increases, depending on whether it is the more or the least retained enantiomer which has the greater intercalation difficulty. For CSPs, **1** and **2,** this is determined by the orientation of the selectors with respect to their tethers.

While the simplified ''single mechanism'' model was preferred in terms of its simplicity, the original ''two competing mechanism'' model was not disproved. However, the two models lead to different expectations of what one would observe if one were to chromatograph the DNB derivatives of a homologous series of α-(*p*-alkylphenyl)ethylamines, **4**, on CSPs, **1** and **2**.

The chromatographic results for the resolution of a homologous series of α-(*p*-alkylphenyl)ethylamines, **4**, on CSPs, **1** and **2**, are summarized in Table 1. The elution order shown in Table 1 was determined for *N*-(3,5-dinitrobenzoy)-α-phenylethylamine **4a** which is the only sample available as an optically active form. The elution orders for other members in a homologous series were supposed to be the same as that of *N*-(3,5-dinitrobenzoy)-α-phenylethylamine **4a** based on the technique termed TRAC (tracking of absolute configuration) [1]. The chromatographic resolution trends were illustrated in Fig. 2. As shown in Fig. 2, enantioselectivity increases on CSP **1** but decreases on CSP **2** as the length of the analyte's linear *p*-alkyl substituent increases.

In the original ''two competing mechanism'' model, neither analyte enantiomer would have been expected to intercalate its *p*-alkyl substituent between the strands of CSP **2**. Hence, the enantioselectivity noted for the members of this series on CSP **2** would have been expected to be essentially independent of the length of the *p*-alkyl substituents. On the other hand, should the more retained enantiomer directs its phenyl substituent as now suggested

Table 1
Chromatographic results for the resolution of *N*-(3,5-dinitrobenzoyl)-α-(*p*-alkylphenyl)ethylamines **4** on CSPs **1**and **2**[a]

Analyte	*n*	CSP **1**			CSP **2**		
		k'_1 [b]	α[c]	Conf.[d]	k'_1 [b]	α[c]	Conf.[d]
4a	0	52.66	1.60	S	51.00	1.69	S
4b	1	46.16	1.65	(S)	46.25	1.71	(S)
4c	3	36.01	2.04	(S)	38.50	1.79	(S)
4d	6	26.80	2.49	(S)	32.17	1.62	(S)
4e	8	22.50	2.87	(S)	29.83	1.50	(S)
4f	10	18.93	3.15	(S)	26.00	1.38	(S)
4g	12	16.41	3.38	(S)	23.42	1.25	(S)

[a] See the experimental part for the chromatographic conditions.
[b] Capacity factor of the first eluted enantiomer.
[c] Separation factor.
[d] Absolute configuration of the second eluted enantiomer. Absolute configuration in parenthesis was presumed from the TRAC technique (tracking of absolute configuration) [1].

in the ''single mechanism'' model, the *p*-alkyl substituent would be caused to intercalate between the strands of CSP **2** but not between the strands of CSP **1**. This situation is illustrated in cartoon fashion. Fig. 3 depicts the structures of the type **4** analytes, the rectangles representing the *N*-3,5-dinitrobenzoyl groups viewed edgewise. Fig. 4 depicts CSPs **1** and **2**, the rectangles representing the α-naphthyl groups viewed edgewise. Finally, Fig. 5 depicts the structures postulated for the complexes of each enantiomer on CSP **1** and on CSP **2**. Presumably, these are the structures such as those which are responsible for the observed chromatographic behavior shown in Table 1 and Fig. 2 for the resolution of *N*-(3,5-dinitrobenzoyl)-α-(*p*-alkylphenyl)ethylamines on CSPs **1** and **2**.

In the less stable heterochiral adsorbates formed from the type **4** analytes, the *p*-alkyl substituents are directed such that they intercalate between adjacent strands of CSP **1** but not between the strands of CSP **2**. In 2-propanol-hexane, intercalation is resisted, presumably for steric reasons. Hence, as the length

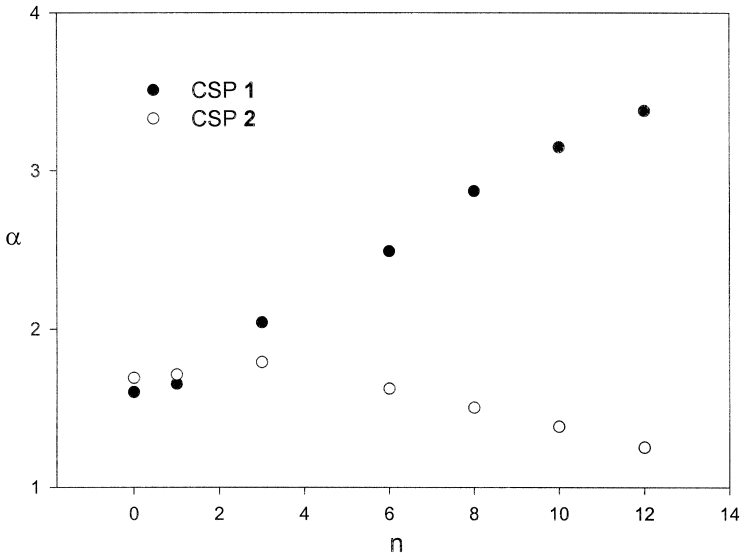

Fig. 2. The trends of the separation factors, α, for the resolution of *N*-(3,5-dinitrobenzoyl)-α-(*p*-alkylphenyl)ethylamines **4** [*p*-alkyl=$(CH_2)_n$-H] on CSPs, **1** and **2**. Chromatographic conditions are given in the experimental part.

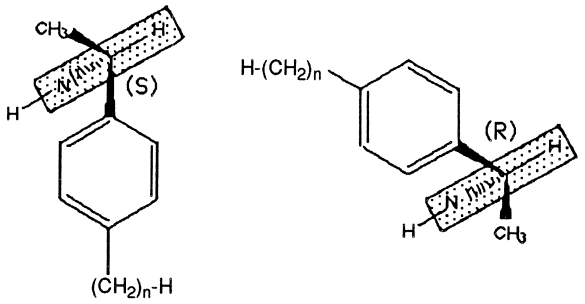

Fig. 3. The schematic presentation of type **4** analytes. The rectangles represent the 3,5-dinitrobenzoyl group viewed edgewise.

of the *p*-alkyl substituent is increased, the retention of the heterochiral enantiomer is reduced on CSP **1** relative to its antipode. Conversely, the more stable homochiral adsorbates formed from the type **4** analytes intercalate their *p*-alkyl groups between the strands of CSP **2** but not between those of CSP **1**. Thus, the level of enantioselectivity noted when this series of analytes is chromatographed is expected to diminish on CSP **2** as the *p*-alkyl groups become longer and to increase on CSP **1**. This is exactly consistent with the chromatographic resolution results shown in Table 1 and Fig. 2.

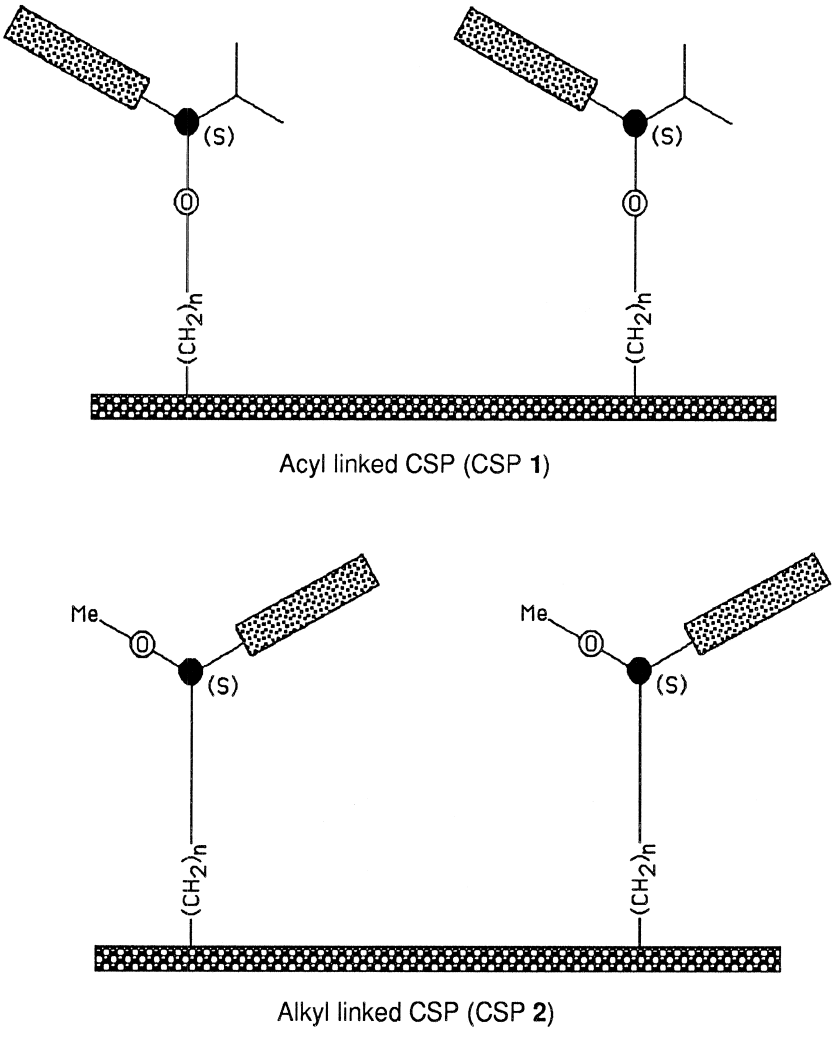

Fig. 4. The schematic presentation of CSPs, **1** and **2**. The rectangles represent the naphthyl group viewed edgewise. The solid circles represent the methine hydrogen oriented toward viewer. The circles containing ''O'' represent the carbonyl oxygen oriented toward viewer.

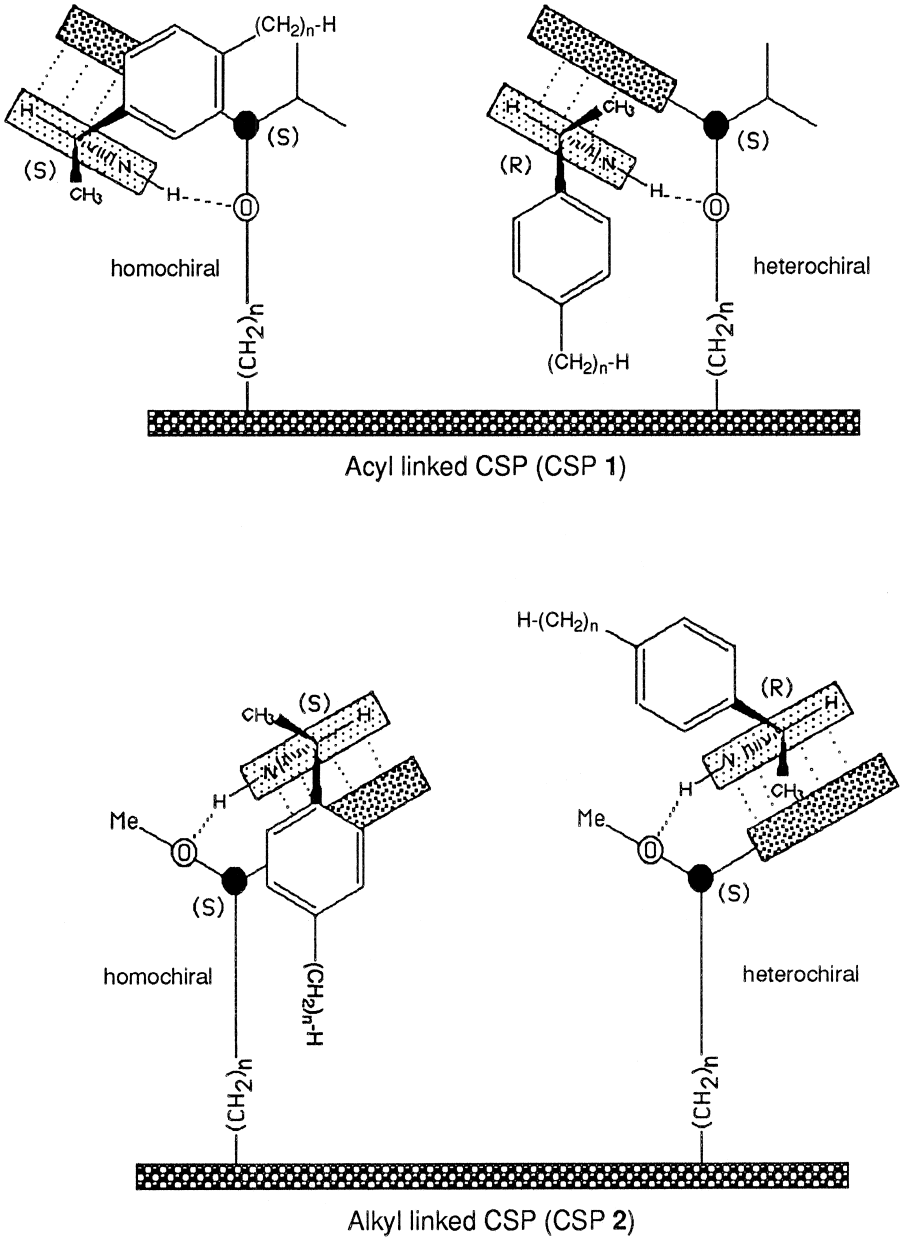

Fig. 5. The simplified ''single mechanism'' model proposed for the resolution of type **4** analyte on the acyl linked CSP (CSP **1**) and on the alkyl linked CSP (CSP **2**). In the model, more stable homochiral (S,S) complexes show the face to edge $\pi-\pi$ interaction between the naphthyl group of the CSP and the *p*-alkylphenyl group of the (S)-analyte. In this instance, the *p*-alkyl chain of the (S)-analyte intercalates between the strands of the connecting tether of CSP **2** but not between the strands of CSP **1**.

In conclusion, the data and arguments presented herein are consistent with the ''single mechanism'' model in which an attractive face to edge $\pi-\pi$ interaction between two aromatic systems is an important contributor to the presently observed chiral recognition processes. Consequently, the ''single mechanism'' model is concluded to be more plausible than the ''two competing mechanism'' model in

rationalizing the chromatographic trends for the separation of the enantiomers of *N*-(3,5-dinitrobenzoyl)-α-arylalkylamines on CSPs, **1** and **2**. However, it should be noted that the ''single mechanism'' model might also be modified as more evidences such as spectroscopic and/or crystallographic data are accumulated.

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