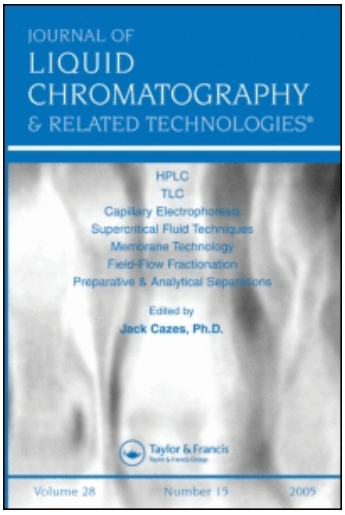

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A Mechanistic Evaluation for the Resolution of Enantiomers of α-Arylpropionic Acid Derivatives on π-Basic Chiral Stationary Phases

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A MECHANISTIC EVALUATION FOR THE RESOLUTION OF ENANTIOMERS OF α-ARYLPROPIONIC ACID DERIVATIVES ON π-BASIC CHIRAL STATIONARY PHASES

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ABSTRACT

A chiral recognition mechanism involving face to edge π-π interaction for the separation of the two enantiomers of the 3,5-dinitroanilide derivatives of nonsteroidal anti-inflammatory drugs(NSAIDs) on chiral stationary phase(CSP) **1** has been proposed. The inverse chromatographic resolution trends observed in resolving the two enantiomers of the 3,5-dinitroanilide derivatives of α-phenylalkanoic acids and α-(p-alkylphenyl)propionic acids on CSP **1** and **2** may support the postulated chiral recognition mechanism.

INTRODUCTION

Enantiomers of chiral drugs often show different metabolic behavior and pharmacological activity. Among the nonsteroidal anti-inflammatory drugs (NSAIDs), those related to α-arylpropionic acids contain many examples of this

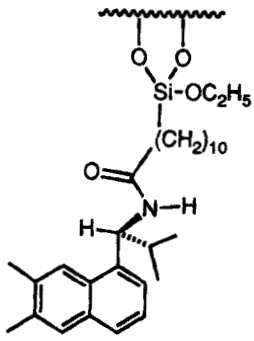
contrasting behavior. For example, (S)-(+)-ibuprofen is biologically more active than its (R)-(-)-enantiomer and the difference in activity is compensated by metabolic inversion of the (R)-(-)-enantiomer *in vivo*.[1,2] The decreased rate of metabolism and excretion of benoxaprofen in elderly patients caused by the inversion of (R)-(-)-benoxaprofen to its (S)-(+)-enantiomer leads to hepatotoxicity and, consequently, the drug has been withdrawn from the market.[3] Among the commercial NSAIDs related to α-arylpropionic acids, only naproxen is sold as a single enantiomer.

Because of the biological significance of the two enantiomers of NSAIDs, accurate and convenient means of measuring the optical purity of these substances has been sought.[4,5] In addition, recent FDA guidelines for marketing of chiral drugs require the establishment of techniques for the development and quality control of new chiral drugs.[6] Liquid chromatographic separation of enantiomers on CSPs should be the method of choice. The enantiomers of NSAIDs related to α-arylpropionic acids have been separated by liquid chromatography as their π-basic amide derivatives on a π-acidic CSP derived from (R)-N-(3,5-dinitrobenzoyl)phenylglycine[7-10] or without derivatization on a CSP based on protein or cellulose.[11-13] Recently, based on the reciprocity conception of chiral recognition, improved CSPs have been developed for the stereoselective separation of underivatized NSAIDs.[14,15]

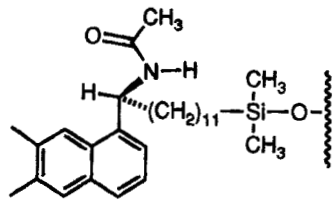
Recently, we reported that CSP **1** which has been widely used for the resolution of variety of racemates[16-18] can be used for the separation of commercial racemic NSAIDs as their 3,5-dinitroanilide derivatives **3**.[19] At that time, we proposed a chiral recognition mechanism utilizing the edge to face π-π interaction between the α-aryl group of analytes and the 6,7-dimethylnaphthyl group of CSP **1**. In this paper, we wish to provide additional experimental observations which support this chiral recognition mechanism.

EXPERIMENTAL

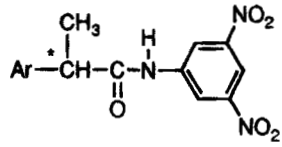
Chromatographic analysis was performed with an instrument consisting of a Waters model 510 pump, a Rheodine model 7125 injector with a 20 μl sample



CSP 1



CSP 2



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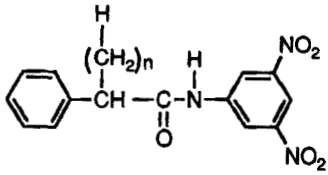

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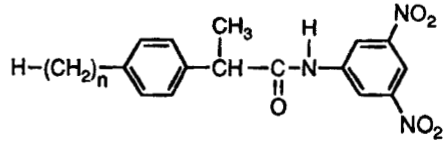

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loop, a Youngin model 710 absorbance detector with a 254 nm UV filter and a Youngin D520B computing integrator. All chromatographic data were obtained by using a 250 mm x 4.6 mm I. D. stainless-steel column packed with CSP **1** or **2**. CSP **2** used in this study was prepared according to the known procedure except for the use of dimethylchlorosilane instead of trichlorosilane in the hydrosilylation step.[16] All chromatographic separations were carried out at

a flow rate of 2.00 ml/min with a mobile phase of 10 % 2-propanol in n-hexane. Column void volume was measured by injecting 1,3,5-tri-*t*-butylbenzene.[20]

The α-phenylalkanoic acids used in this study were prepared from phenylacetic acid by the known procedures.[21] A series of α-(p-alkylphenyl)propionic acids was prepared from alkylbenzenes. Alkylbenzenes purchased from Aldrich were treated with acetyl chloride in the presence of anhydrous aluminum chloride in dichloromethane at 0 °C to afford the p-alkylphenyl methyl ketones. These methyl ketones were converted to the corresponding thiomorpholides following the Kindler-Willgerodt procedure[22] and then to p-alkylphenylacetic acids by use of acidic hydrolysis(50 % H_2SO_4 for p-alkyl = methyl, propyl : acetic acid/c-HCl (3/1, v/v) for p-alkyl = hexyl, octyl, decyl).[23] The p-phenylacetic acids prepared in this study were treated with LDA (lithium diisopropylamide, 2.3 eq.) in dry THF at -78 °C followed by methyl iodide (1.3 eq.) to afford the α-(p-alkylphenyl)propionic acids.

The α-phenylalkanoic acids and α-(p-alkylphenyl)propionic acids were converted to their 3,5-dinitroanilide derivatives **4** and **5** by treatment of the corresponding acid chlorides with 3,5-dinitroaniline and triethylamine in dry dichloromethane at room temperature as described previously.[24] All compounds prepared in this study were fully characterized by ^1H NMR and IR.

The elution orders for the two enantiomers of 3,5-dinitroanilide derivatives **4** and **5** on CSP **1** and **2** were determined by the TRAC (tracking of absolute configuration) technique[16] based on the absolute elution order of the two enantiomers of the 3,5-dinitroanilide derivative of α-phenylpropionic acid, the optically active form of which is commercially available.

RESULTS AND DISCUSSION

In our previous report, we proposed the chiral recognition model shown in Figure **1** for the resolution of the two enantiomers of N-3,5-dinitrobenzoyl derivatives **3** of NSAIDs on CSP **1** based on their elution orders and on a consideration of space-filling molecular models.[19] In this model, both the CSP and analyte are presumed to interact in their lowest energy conformations.[16,19]

To briefly review this chiral recognition model, CSP **1** and the analyte are proposed to interact through the π-π complexation between their respective 6,7-dimethylnaphthyl and 3,5-dinitroanilide groups and through the hydrogen bonding between the carbonyl oxygen of the CSP and the amide N-H hydrogen of the analyte. In this event, the face of the α-aryl substituent of the (R)-analyte is positioned at the edge of the 6,7-dimethylnaphthyl ring of the CSP, invoking the face to edge π-π interaction which has received increased attention as an associative force between aromatic rings in the recent studies.[25-27] On the contrary, the α-aryl substituent of the (S)-analyte is directed to the acyl connecting arm of the CSP and, hence, it experiences some degree of steric hindrance. Consequently, the diastereomeric (R,S)-complex shown in Figure 1 is energetically more favorable than the (S,S)-complex. This chiral recognition model is quite similar to that recently proposed for the resolution of N-(3,5-dinitrobenzoyl) derivatives of α-arylalkylamines on CSP **1**.[28]

In the chiral recognition model shown in Figure 1, the methyl substituent at the chiral center of the (R)-analyte is oriented alongside the acyl connecting arm of the CSP. Therefore, it is expected that the long alkyl substituent at the chiral center of the (R)-analyte may intercalate between the connecting arms of the CSP and make the diastereomeric (R,S)-complex increasingly more unfavorable as the alkyl chain length increases. To test this postulate, 3,5-dinitroanilide derivatives **3** of a series of α-phenylalkanoic acids were prepared and resolved on CSP **1**. Figure 2a shows the dependence of the retention of the two enantiomers on the length of the alkyl substituent at the chiral center of the analyte.

The more rapid decrease of the retention of the (R)-analyte than that of the (S)-analyte observed can be rationalized by considering the intercalation of the alkyl substituent at the chiral center of the (R)-analyte between the connecting arms of the CSP. As a result, the enantioselectivity decreases continuously as the length of the alkyl substituent at the chiral center of the analyte increases (Figure 2b). The maximum in the retention of the (R)-analyte and in the enantioselectivity at n=2 noted in Figure 2 may be a consequence of conformational factors. As the alkyl substituent at the chiral center of the analyte changes from methyl to ethyl, there is a significant change in steric bulk

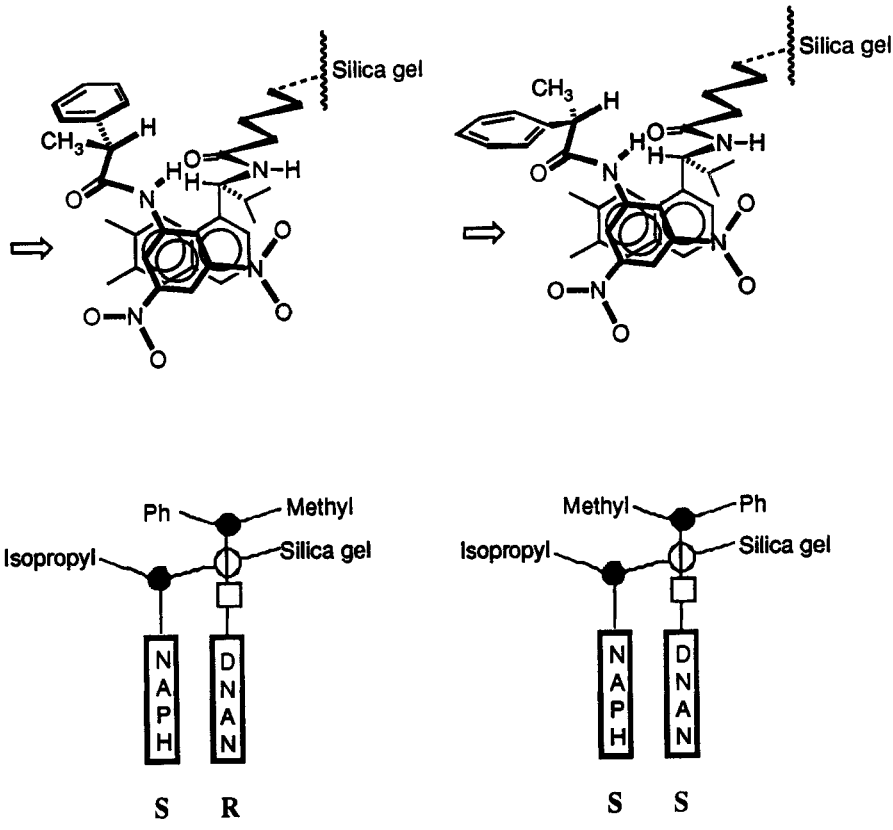

Figure 1. The proposed chiral recognition model. Above : the two diastereomeric (R,S)- and (S,S)-complexes between the 3,5-dinitroanilide derivative of racemic α-phenylpropionic acid and (S)-CSP **1**. Below : schematic representation of the above diastereomeric complexes viewed from the arrow direction. solid circle : methine hydrogen oriented toward the viewer in the CSP and away from the viewer in the analyte. empty circle : carbonyl oxygen oriented toward the viewer in the CSP. empty square : N-H hydrogen oriented away from the viewer in the analyte.

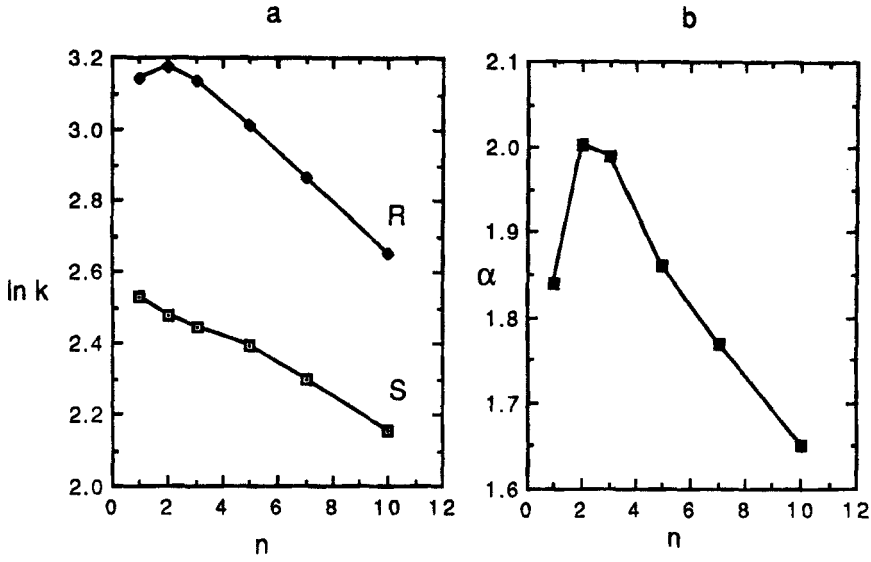

Figure 2. (a) Retention and (b) enantioselectivity trends of the two enantiomers of **4** on CSP **1**. Chromatographic conditions are given in the Experimental.

and, consequently, the conformational preferences should be altered. However, the conformational preferences may not be altered by further lengthening of this alkyl chain because the changes in the structure occur at sites remote from the stereogenic center.

From the chiral recognition model shown in Figure 1, it is also expected that the trends for resolution of N-3,5-dinitrobenzoyl derivatives **4** of a series of α-phenylalkanoic acids on CSP **2**, the connecting arm of which is oriented in the opposite way to that of CSP **1**, should be the reverse to those observed on CSP **1**. On CSP **2**, the alkyl substituent at the chiral center of the less retained (S)-enantiomer of **4** should intercalate between the connecting arms of the CSP as shown in Figure 3. Consequently, as the alkyl chain length increases, the retention time of the (S)-enantiomer should decrease more rapidly than that of the (R)-enantiomer. All of these expectations are consistent with the experimental observations as shown in Figure 4a and 4b. The discrepancy in the continuous increase of enantioselectivity shown in Figure 4b may be a result of the conformational factors discussed above.

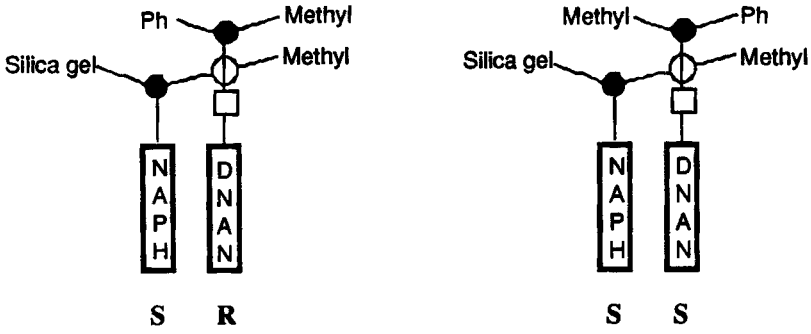

Figure 3. Schematic representation for the two diastereomeric (R,S)- and (S,S)-complexes between the 3,5-dinitroanilide derivative of racemic α-phenylpropionic acid and (S)-CSP **2**. See the caption of Figure 1 for the meaning of solid circle, empty circle and empty square symbols.

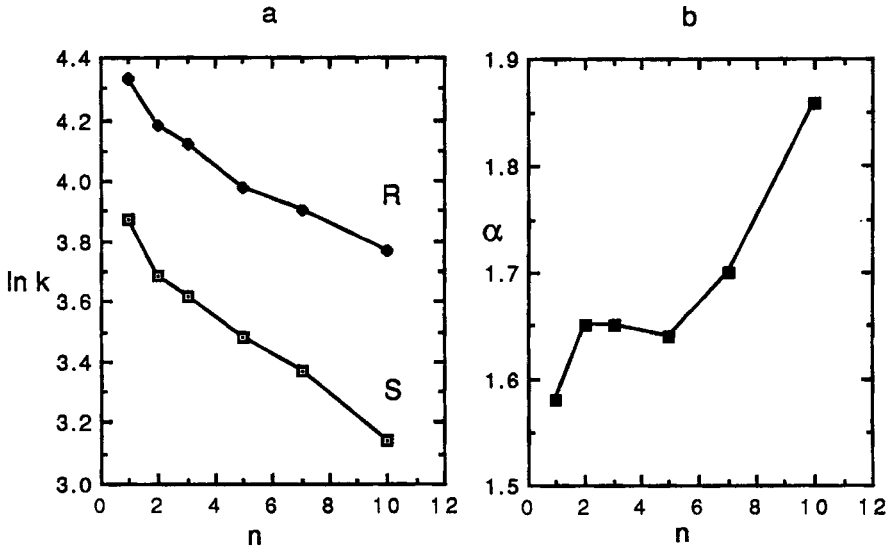

Figure 4. (a) Retention and (b) enantioselectivity trends of the two enantiomers of **4** on CSP **2**. Chromatographic conditions are given in the Experimental.

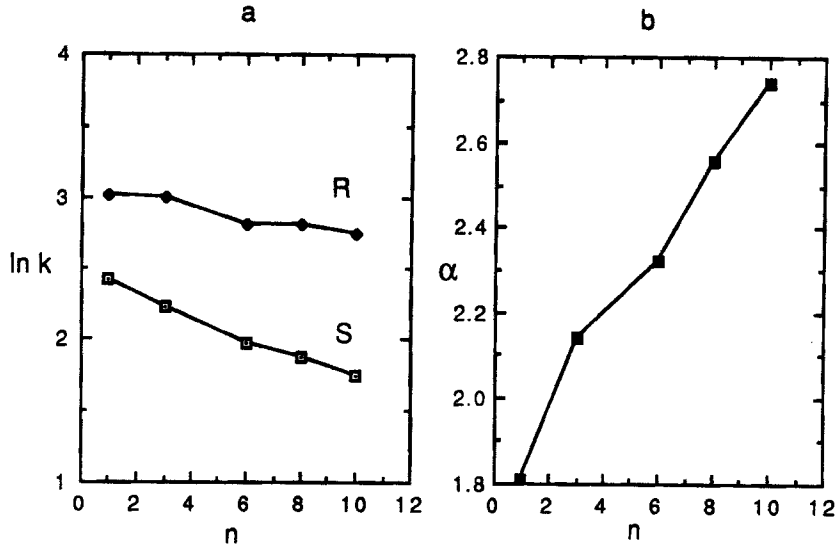

Figure 5. (a) Retention and (b) enantioselectivity trends of the two enantiomers of **5** on CSP **1**. Chromatographic conditions are given in the Experimental.

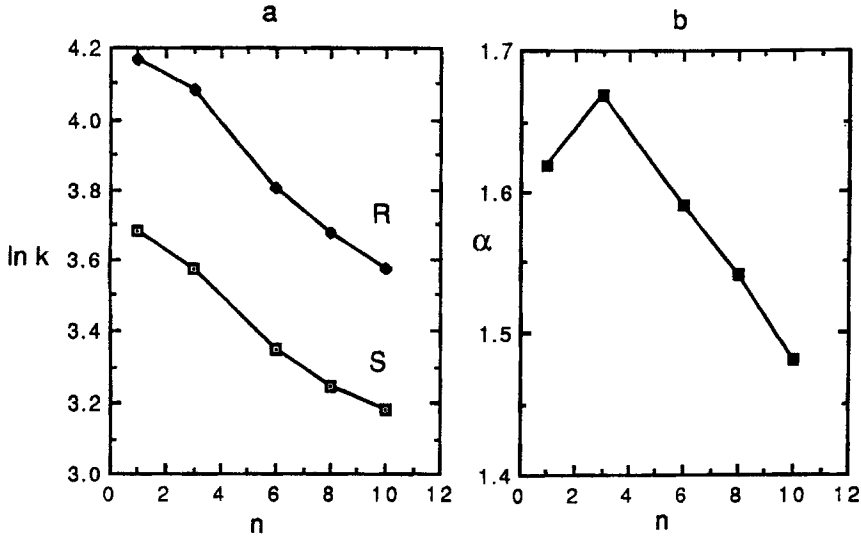

Figure 6. (a) Retention and (b) enantioselectivity trends of the two enantiomers of **5** on CSP **2**. Chromatographic conditions are given in the Experimental.

Based on the chiral recognition model shown in Figures 1 and 3, the trends for the resolution of 3,5-dinitroanilide derivatives **5** of α-(p-alkylphenyl)propionic acids are expected to be opposite to those for the resolution of 3,5-dinitroanilide derivatives **4** of α-phenylalkanoic acids. The p-alkyl substituent of the less retained (S)-enantiomer is anticipated to intercalate between the connecting arms of CSP **1**. Hence, the retention of the (S)-enantiomer should decrease more rapidly than that of the (R)-enantiomer and the enantioselectivity should increases as the p-alkyl substituent increases in length. On CSP **2**, the p-alkyl substituent of the more retained (R)-enantiomer can intercalate between the connecting arms of the CSP as expected from the model shown in Figure 3. This should lead to a decrease in the stability difference between the two diastereomeric complexes shown in Figure 3 and consequently to a decrease in enantioselectivity. Figures 5 and 6 show data obtained for trends in the resolution of 3,5-dinitroanilide derivatives **5** of α-(p-alkylphenyl)propionic acids on CSP **1** and **2**. The experimental results are fully compatible with the expectations based on the chiral recognition mechanism discussed above.

In conclusion, the trends we have noted in studies of the resolution of 3,5-dinitroanilide derivatives **4** and **5** on CSP **1** and **2** support the proposed chiral recognition model which emphasizes the importance of face to edge π-π interaction in addition to the hydrogen bonding and face to face π-π interaction between the 3,5-dinitroanilide derivatives of NSAIDs and the CSP. As shown in this and previous studies,[28] face to edge π-π interactions now seem to play an important role as an attractive force in chiral recognition by a CSP. To provide more solid evidence for the role of the face to edge π-π interaction, spectroscopic and/or crystallographic data are required. Efforts are underway in our laboratory to prove these issues.

ACKNOWLEDGEMENT

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