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Preparation of A New HPLC Chiral Stationary Phase from (S)-Naproxen and Application in Elucidating Chiral Recognition Models

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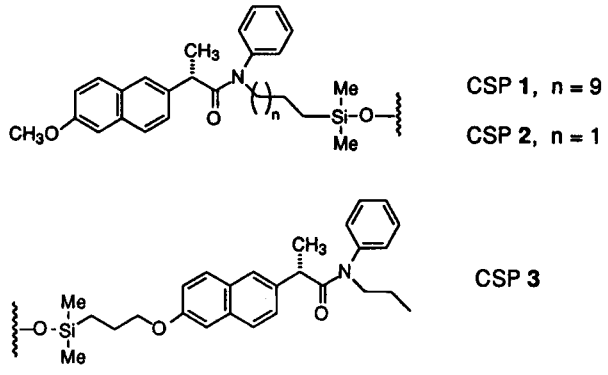
A new HPLC chiral stationary phase (CSP **3**) has been prepared by connecting N-phenyl N-propyl amide of (S)-naproxen to silica gel through the 6-methoxy-2-naphthyl group of (S)-naproxen. The new CSP has been applied in resolving a homologous series of N-(3,5-dinitrobenzoyl)-α-amino acid esters and a homologous series of N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines. The separation factors, α, for resolving a homologous series of N-(3,5-dinitrobenzoyl)-α-amino esters and a homologous series of N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines on the new CSP have been found to remain almost constant throughout the wide range of the length of the alkyl substituent of the analytes while those on the previously reported CSPs (CSP **1** and **2**) which were prepared by connecting N-phenyl N-propyl amide of (S)-naproxen to silica gel through the N-propyl group increase or decrease continuously. These results are concluded to support the chiral recognition models which utilize the intercalation of the alkyl substituent of the racemic analytes between the adjacent strands of CSP **1** or **2** to rationalize the increasing or decreasing trends of separation factors.

Introduction

Liquid chromatographic resolution of enantiomers on CSPs has been known to be one of the most convenient and accurate means in determining the enantiomeric composition of racemic compounds.[1] Consequently, various efforts have been devoted to the development of effective HPLC CSPs.[2] Among others, Pirkle-type CSPs have been known to resolve racemates through enantioselective π-π interaction between the CSP and racemic analytes.[3] For the effective π-π interaction with racemic analytes, Pirkle-type CSPs have been usually designed to contain π-acidic and/or π-basic aromatic rings.[4] In this context, (S)-naproxen, which is well known as an anti-inflammatory drug and readily available as an optically active form,[5] is an attractive chiral selector of Pirkle-type CSPs because its 6-methoxy-2-naphthyl group can be utilized as an effective π-basic interaction site.

The use of (S)-naproxen as an effective chiral selector has indeed been demonstrated by various Pirkle-type CSPs.[6] For example, CSP **1** prepared by connecting N-phenyl-N-(10-undecenyl) amide of (S)-naproxen to silica gel was successfully used in resolving various π-acidic racemates and the enantioselectivities on it were found to be greater than those on any other (S)-naproxen-derived CSPs reported.[6f] In order to elucidate the chiral recognition mechanism exerted by CSP **1**, a CSP with a short connecting tether (CSP **2**) was prepared and from the chiral resolution trends for resolving homologous series of π-acidic racemates on CSP **1** and CSP **2**, chiral recognition models utilizing the intercalation of the alkyl substituent of the analyte between the adjacent strands of bonded phase were proposed.[6h] However, the chiral recognition models proposed should be confirmed or modified by accumulating additional experimental evidences.

As an effort to provide additional experimental evidences for the chiral recognition models proposed for CSP **1** or **2**, we prepared in this study another CSP (CSP **3**) based on (S)-naproxen. CSP **3** has the same structure as that of CSP **1** or **2** except the connecting tether direction. Consequently, it is expected that the chromatographic resolution trends observed on CSP **3** should be different from those assumed to be resulted from the intercalation of the alkyl substituent of the racemic analytes between the adjacent strands of CSP **1** or **2**.



Experimental

General

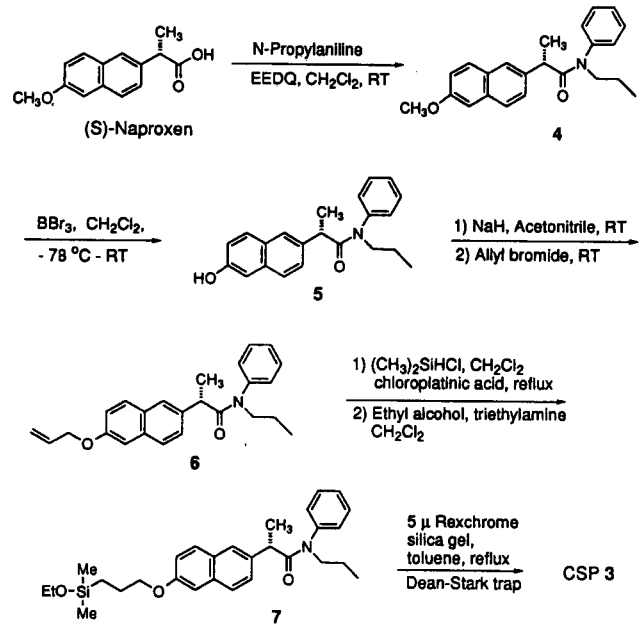
^{1}H NMR spectra were obtained with a Varian Gemini 200 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. IR spectra were measured on a Mattson Polaris FT-IR spectrometer. Melting points were taken on a Rigaku TAS 100 thermal analyzer. Elemental analysis were performed at the Organic Chemistry Research Center, Sogang University, Seoul, Korea.

Chromatography was performed with an HPLC system consisting of a Waters Model 510 pump, a Rheodyne 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 collected using 20% isopropyl alcohol in hexane as a mobile phase with a flow rate of 2.0 mL/min at 20 °C. The column void volumes were determined by injecting 1,3,5-tri-*tert*-butylbenzene, a presumed unretained solute.[7] Racemic or optically enriched analytes used in this study were available from previous studies.[6ha]

Preparation of CSP 3

CSP **3** was prepared starting from (S)-naproxen as shown in Scheme 1. All reactions were carried out under an argon atmosphere.

N-Phenyl-N-propyl-(S)-α-(6-methoxy-2-naphthyl) propionamide 4. (S)-Naproxen (5.1 g, 22.2 mmole) and EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, 6.6 g, 26.6 mmole) were dissolved in 60 ml of dichloromethane. To the stirred solution was added N-propylaniline (3.0 g, 22.2 mmole), which was prepared by the reaction between aniline and propionyl chloride followed by reduction with $LiAlH_4$, in 15 mL of dichloromethane. The whole mixture was stirred for 2 hrs at room temperature, washed with 2 N HCl solution, dried over anhydrous Na_2SO_4, and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane-dichloromethane, 1 : 30 : 1-1 : 8 : 1, v/v/v) to afford **4** as a colorless oily product (3.1 g, 40% yield). The enantiomeric purity of the product was greater than 98% ee by HPLC analysis on a commercial chiral column derived from (S)-N-(3,5-dinitrobenzoyl) leucine.[8] ^{1}H NMR ($CDCl_3$), δ 0.86 (t, 3H), 1.45 (d, 3H), 1.54-1.55 (m, 2H), 3.61-3.69 (m, 3H), 3.91 (s, 3H), 6.93-7.63 (m, 11H). IR (NaCl, CH_2Cl_2) cm^{-1} 2965, 1655, 1605, 1493.



Scheme 1.

N-Phenyl-N-propyl-(S)-α-(6-hydroxy-2-naphthyl) propionamide 5. Amide **4** (3.0 g, 8.63 mmole) was dissolved in 30 mL of dry dichloromethane. The solution was cooled to − 78 °C and then a solution of BBr_3 in 10 mL of dry dichloromethane was added over 30 min. The reaction mixture was allowed to warm to room temperature over 1 hr and then stirred for an additional 1 hr. To the reaction mixture was added water slowly with stirring until no more white fumes evolved. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane, 1 : 2, v/v) to afford a white solid material. Finally, the solid product was recrystallized from a mixed solvent of diethyl ether and hexane to afford **5** (2.88 g, 75%) as a white crystalline solid. The enantiomeric purity of **5** was greater than 98% ee by HPLC analysis on a commercial chiral column derived from (S)-N-(3,5-dinitrobenzoyl)leucine.[8] mp 128-129 °C. ^{1}H NMR ($CDCl_3$), δ 0.87 (t, 3H), 1.48 (d, 3H), 1.44-1.58 (m, 2H), 3.65-3.74 (m, 3H), 6.98-7.55 (m, 11H). IR (KBr) cm^{-1} 3262 (broad), 1628, 1412.

N-Phenyl-N-propyl-(S)-α-(6-allyloxy-2-naphthyl) propionamide 6. Compound **5** (2.88 g, 8.64 mmole) was dissolved in 40 mL of acetonitrile and then stirred with NaH (1.04 g, 25.0 mmole, 60% dispersion in mineral oil) for 30 min at room temperature. To the stirred mixture was added allyl bromide (0.9 mL, 10.4 mmole). After stirring the whole mixture for 2 hrs, solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed successively with 1 N NaOH solution and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with silica gel column chromatography (ethyl acetate-hexane, 1 : 2, v/v) to afford **6** (3.26 g, 99%) as a colorless oily material. The enantiomeric purity of **6** was greater than 98% ee by HPLC analysis on a commercial chiral column derived from (S)-N-(3,5-dinitrobenzoyl)leucine.[8] ^{1}H NMR ($CDCl_3$),

δ 0.88 (t, 3H), 1.47 (d, 3H), 1.42-1.57 (m, 2H), 3.63-3.73 (m, 3H), 4.64 (d, 2H), 5.26-5.52 (m, 2H), 6.04-6.17 (m, 1H), 6.95-7.64 (m, 11H). IR (NaCl, CH_2Cl_2) cm^{-1} 2964, 1656, 1604, 1494.

N-Phenyl-N-propyl-(S)-α-[6-(3-ethoxydimethylsilylpropyl)-2-naphthyl]propionamide 7. Compound **6** (3.26 g, 8.73 mmole) was dissolved in 150 mL of dry dichloromethane. To the solution was added 40 mL of dimethylchlorosilane and $H_2PtCl_6 \cdot 6H_2O$ (*ca.* 10 mg) dissolved in 1 mL of dry tetrahydrofuran. The whole mixture was heated to reflux for 2 hrs. Dichloromethane and excess dimethylchlorosilane were removed by simple distillation and then under reduced pressure. The residue was dissolved in 40 mL of dry dichloromethane and then 10 mL of triethylamine-absolute ethanol (1 : 1, v/v) was added slowly with stirring. The mixture was stirred at room temperature for 1 hr and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate-hexane, 1 : 20-1 : 10, v/v) to afford **7** (1.63 g, 39%) as a colorless oily material. The enantiomeric purity of **7** was greater than 98% ee by HPLC analysis on a commercial chiral column derived from (S)-N-(3,5-dinitrobenzoyl)leucine.[8] ^1H NMR ($CDCl_3$), δ 0.16 (s, 6H), 0.77 (t, 2H), 0.86 (t, 3H), 1.21 (t, 3H), 1.44 (d, 3H), 1.42-1.55 (m, 2H), 1.86-1.95 (m, 2H), 3.61-3.75 (m, 5H), 4.04 (t, 2H), 6.93-7.60 (m, 11H). IR (NaCl, $CDCl_3$) cm^{-1} 3058, 2967, 1658, 1604, 1494.

Preparation of CSP 3 and HPLC column packing. A 200-mL flask equipped with a Dean-Stark trap, a condenser and a magnetic stirring bar was charged with Regis Rexchrom silica gel (5 mm, 4.5 g) and toluene (100 mL). The mixture was heated to reflux until the complete azeotropic removal of water. To the heterogeneous solution was added silyl compound **7** (1.63 g, 3.41 mmole) dissolved in 10 mL of toluene. The whole mixture was heated to reflux for 72 hrs. The modified silica gel was filtered, washed successively with toluene, ethyl acetate, methanol, acetone, diethyl ether and hexane and then dried under high vacuum. Elemental analysis of the modified silica gel (Found: C, 6.78%; H, 0.72%; N, 0.28%) showed a loading of 0.21 mmoles of selector (based on C) or 0.20 mmoles of selector (based on N) per gram of stationary phase. The modified silica gel was slurried in methanol and packed into a 250 mm × 4.6 mm I.D. stainless-steel HPLC column using a conventional slurry packing method with an Alltech slurry packer. After washing the HPLC column thus packed with 100 ml of dichloromethane, a solution of 2 mL of hexamethyldisilazane in 50 mL of dichloromethane was eluted through the column to protect the residual silanol groups and then dichloromethane was eluted to wash out unreacted hexamethyldisilazane.

Results and Discussion

CSP **3** prepared *via* the procedure shown in Scheme 1 was applied in resolving the enantiomers of homologous series of N-(3,5-dinitrobenzoyl)-α-amino alkyl esters **8** and the resolution trends were compared to those on CSP **1** and **2**. The chromatographic resolution trends in the separation factors, α, for resolving homologous series of N-(3,5-dinitrobenzoyl)leucine alkyl esters (**8**, R=isobutyl and X= alkyl) on CSP **1** and **2** are graphically presented together

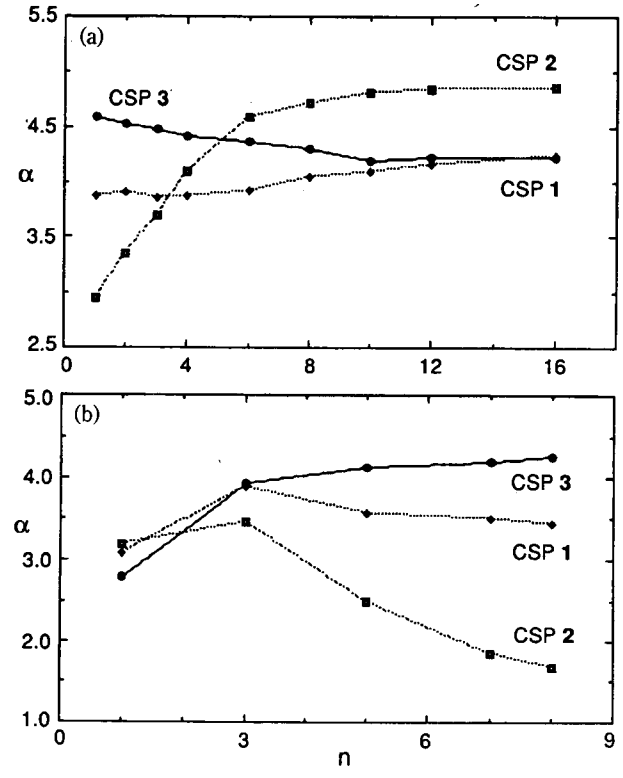
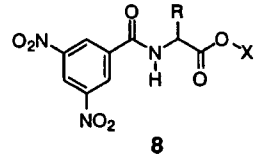


Figure 1. Trends in the separation factor, α, for resolving (a) N-(3,5-dinitrobenzoyl)leucine alkyl esters [**8**, R=isobutyl, X=$(CH_2)_n$-H] and (b) N-(3,5-dinitrobenzoyl)-α-glycine ethyl esters [**8**, R=$(CH_2)_n$-H, X=ethyl] on CSP **1**, **2**, and **3**. The length [$(CH_2)_n$-H] of the ester alkyl group or the α-alkyl substituent of the analyte is denoted by *n* on the abscissa. In every case, (R)-enantiomers are retained longer on CSP **1**, **2**, and **3**.

with those on CSP **3** in Figure 1a (the curves for CSP **1** and **2** are quoted from the previous report[6h]). Similarly, the chromatographic resolution trends in the separation factors, α, for resolving homologous series of N-(3,5-dinitrobenzoyl) alkylglycine ethyl esters (**8**, R=alkyl and X=ethyl) on CSP **1** and **2** are graphically presented together with those on CSP **3** in Figure 1b (the curves for CSP **1** and **2** are quoted from the previous report[6h]). As shown in Figure 1a, the separation factor, α, on CSP **1** and **2** generally increases as the ester alkyl chain (X of **8**) of the analyte increases in length and the increasing trends are much more significant on CSP **2** than on CSP **1**. In contrast to this, Figure 1b illustrates that the separation factor, α, on CSP **1** and **2** decreases as the α-alkyl chain (R of **8**) at the chiral center of the analyte increases, the trends being more significant on CSP **2**.

Based on the chromatographic resolution trends on CSP **1**



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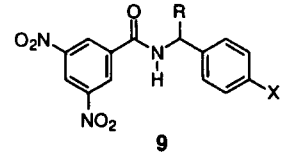

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and **2** shown in Figure 1a and b, we previously proposed a chiral recognition model in which the α-alkyl chain (R of **8**) at the chiral center of the more retained (R)-enantiomer is intercalated between the adjacent strands of bonded phase

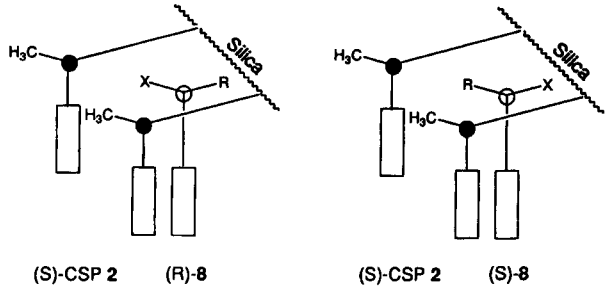

Figure 2. Schematic presentation of the proposed chiral recognition model for resolving N-(3,5-dinitrobenzoyl)-α-amino alkyl esters (**8**) on CSP **2**. The solid circle represents the methine hydrogen directed toward the viewer. The empty circle represents the methine hydrogen directed away from the viewer. The rectangle represents aromatic rings. The model illustrates that the alkyl substituent (R in the model) at the chiral center of the more retained (R)-enantiomer intercalates between the strands of bonded phase while the ester alkyl group (X in the model) of the less retained (S)-enantiomer intercalates between the strands of bonded phase.

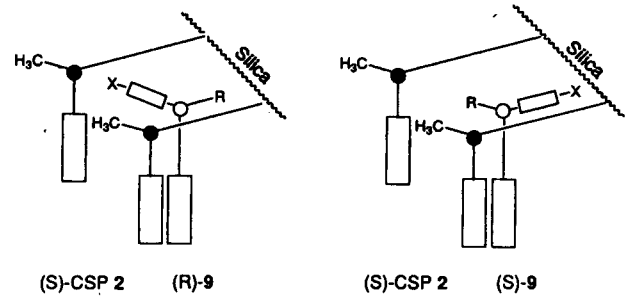

Figure 3. Schematic presentation of the proposed chiral recognition model for resolving N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines (**9**) on CSP **2**. The solid circle represents the methine hydrogen directed toward the viewer. The empty circle represents the methine hydrogen directed away from the viewer. The rectangle represents aromatic rings. The model illustrates that the α-alkyl substituent (R in the model) of the (R)-enantiomers intercalates between the adjacent strands of bonded phase while the 4-alkyl substituent (X in the model) of the phenyl group of the (S)-enantiomers intercalates between the adjacent strands of bonded phase.

whereas the ester alkyl chain (X of **8**) of the less retained (S)-enantiomer is intercalated between the adjacent strands of bonded phase.[6h] The proposed chiral recognition model which can rationalize the chiral recognition trends shown in Figure 1a and b is schematically presented in Figure 2. Even though the chiral recognition model shown in Figure 2 can successfully rationalize the chiral recognition trends shown in Figure 1, it should be modified or confirmed by additional experimental evidences.[6h]

In connection with the proposed chiral recognition model shown in Figure 2, it is speculated that the intercalation process shown in Figure 2 is not expected on CSP **3** because the connecting tether direction of CSP **3** is totally different from that of CSP **1** or **2** and consequently, the trends in the separation factors, α, on CSP **3** should be different from those on CSP **1** and **2**. This speculation indeed turns out to be true as shown Figure 1a and b. As shown in Figure 1a, the separation factors, α, for resolving homologous series of N-(3,5-dinitrobenzoyl)leucine alkyl esters (**8**, R=isobutyl and X=alkyl) on CSP **3** are almost constant throughout the wide range of the ester alkyl chain length. Similarly, the separation factors, α, for resolving homologous series of N-(3,5-dinitrobenzoyl)alkylglycine ethyl esters (**8**, R=alkyl and X=ethyl) on CSP **3** are also almost constant as shown in Figure 1b except the initial increase in the separation factors (the initial increase in the separation factors has been described to stem from conformational factors[6h]). Consequently, we can conclude that the almost invariable resolution trends shown in Figure 1 for CSP **3** might be the additional experimental evidences for the chiral recognition model shown in Figure 2.

The chiral recognition model for resolving N-(3,5-dinitrobenzoyl)-α-(4-X-phenyl)alkylamines (**9**) on CSP **1** or **2** has also been proposed based on the chromatographic trends in the separation factors for resolving homologous series of N-(3,5-dinitrobenzoyl)-α-phenylalkylamines (**9**, R=alkyl, X=H) and homologous series of N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)ethylamines (**9**, R=methyl, X=alkyl).[6g] The proposed chiral recognition model is schematically presented in Figure 3. As shown in Figure 3, the alkyl chain (R in the model) at the chiral center of the initially more retained (R)-enantiomers of **9** is intercalated between the strands of bonded phase, whereas the 4-alkyl substituent (X in the model) of the (S)-enantiomers of **9** intercalates between the strands of bonded phase. However, the intercalation process shown in Figure 3 is not expected on CSP **3** because the direction of the connecting tether is different from that of CSP **1** or **2**.

The chromatographic resolution trends for resolving homologous series of N-(3,5-dinitrobenzoyl)-α-phenylalkylamines (**9**, R=alkyl, X=H) and homologous series of N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)ethylamines (**9**, R=methyl, X=alkyl) on CSP **3** are graphically presented together with those on CSP **1** and **2** in Figure 4a and b. As shown in Figure 4a and b, the separation factors on CSP **3** remain almost constant throughout the wide range of the length of the 4-substituted alkyl chain (X of **9**) or the alkyl chain (R of **9**) at the chiral center respectively. These results are exactly consistent with our expectation based on the chiral recognition model (shown in Figure 3) proposed previously and consequently, it is concluded that the chiral recognition model shown in Figure 3 is reasonable.

In summary, we prepared in this study a new CSP (CSP **3**) by connecting N-phenyl N-propyl amide of (S)-naproxen to silica gel through the 6-methoxy-2-naphthyl group of (S)-naproxen. The connecting tether direction of CSP **3** is totally different from that of CSP **1** or **2**, which was previously prepared by connecting N-phenyl N-alkyl amide of (S)-naproxen to silica gel through the N-alkyl group. Consequently, we expected that the trends in the separation factors, α, for separating the two enantiomers of a homologous series of N-(3,5-dinitrobenzoyl)-α-amino esters (**8**) and a homologous series of N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines (**9**) on CSP **3** should be different from those on CSP **1** or **2** and these results might be recognized to support the chiral recognition models utilizing the intercalation of the alkyl substituent of the racemic analytes between the strands of CSP **1** or **2**. Indeed, the trends in the separation

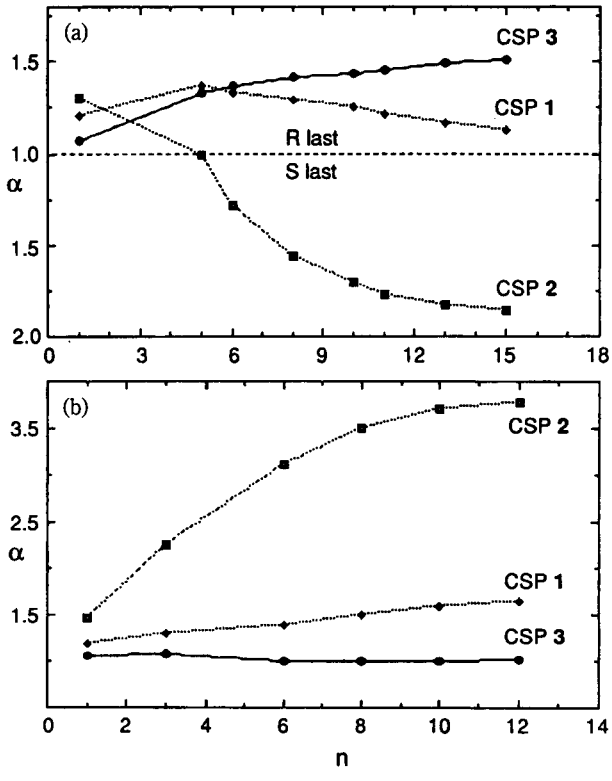

Figure 4. Trends in the separation factor, α, for resolving (a) N-(3,5-dinitrobenzoyl)-α-phenylalkylamines [**9**, R=$(CH_2)_n$-H, X=H] and (b) N-(3,5-dinitrobenzoyl)-α-4-alkylphenyl)ethylamines [**9**, R =CH_3, X=$(CH_2)_n$-H] on CSP **1**, **2**, and **3**. The length [$(CH_2)_n$-H] of the α-alkyl substituent or the 4-alkyl substituent of the analyte is denoted by n on the abscissa. For resolving N-(3,5-dinitrobenzoyl)-α-phenylalkylamines [**9**, R=$(CH_2)_n$-H, X=H], the elution orders are noted on the graph (a). For resolving N-(3,5-dinitrobenzoyl)-α-4-alkylphenyl)ethylamines [**9**, R=CH_3, X=$(CH_2)_n$-H], the (R)-enantiomers are retained longer.

factors, α, for separating the two enantiomers of a homologous series of N-(3,5-dinitrobenzoyl)-α-amino esters (**8**) and a homologous series of N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines (**9**) on CSP **3** turn out to be different from those on CSP **1** or **2**. Based on these results, we conclude that CSP **3** can successfully provide additional chromatographic evidences for the chiral recognition models proposed previously to rationalize the increasing or decreasing trends in the separation factors for resolving a homologous series of N-(3,5-dinitrobenzoyl)-α-amino esters (**8**) and a homologous series of N-(3,5-dinitrobenzoyl)-α-(4-alkylphenyl)alkylamines (**9**) on CSP **1** or **2**.

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