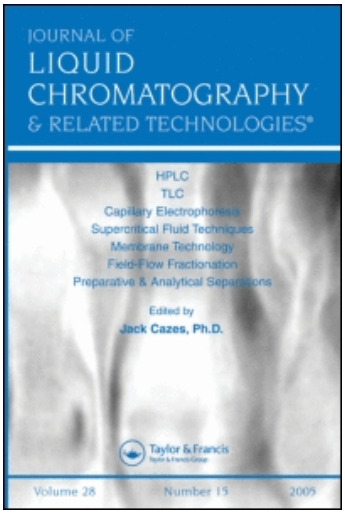

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(1S,2R)-N-(3,5-Dinitrobenzoyl) Norephedrine Bonded to Silica Gel as a Chiral Stationary Phase for the Liquid Chromatographic Separation of Enantiomers

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(1S,2R)-N-(3,5-DINITROBENZOYL) NOREPHEDRINE BONDED TO SILICA GEL AS A CHIRAL STATIONARY PHASE FOR THE LIQUID CHROMATOGRAPHIC SEPARATION OF ENANTIOMERS

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ABSTRACT

A Chiral Stationary Phase(CSP **3**) was prepared by connecting (1S,2R)-N-(3,5-dinitrobenzoyl)norephedrine to a silica support through an ester linkage. CSP **3** was found to show some differences from CSP **1**, derived from N-(3,5-dinitrobenzoyl)phenylglycine, in the resolution of N-acyl-1-aryl-1-aminoalkanes. For example, CSP **3** was found to show greater chiral recognition for conformationally rigid analytes than does CSP **1**. On the other hand, CSP **1** was found to resolve flexible analytes better than CSP **3**. To explain the chiral recognition behavior on CSP **3**, the role of the conformational flexibility of CSP **3** in chiral recognition is proposed.

INTRODUCTION

During the last decade, much progress has been witnessed in the development and the improvement of

Chiral Stationary Phases (CSPs) for the liquid chromatographic direct separation of enantiomers.[1,2,3] CSPs introduced by Pirkle and coworkers discriminate between enantiomers through the π-π interaction between the CSP and the analytes. The chiral recognition ability of these CSPs has been improved by increasing the π-π complex forming ability and/or by increasing the conformational rigidity of the CSP.[4,5]

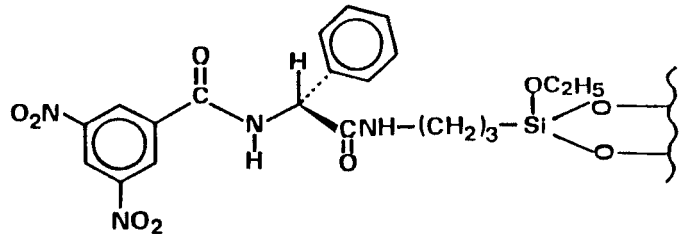
Recently, we have been interested in the preparation of a new CSP consisting of (1S,2R)-N-(3,5-dinitrobenzoyl)norephedrine covalently bound to a silica support. (1S,2R)-Norephedrine is known to be conformationally flexible because of the low energy barrier for the rotation about the bond between the carbon bearing the hydroxy group and the carbon bearing the amino group.[6] Therefore, a CSP derived from (1S,2R)-N-(3,5-dinitrobenzoyl)norephedrine is expected to retain a certain degree of conformational flexibility. However, it should be noted that the conformation of (1S,2R)-N-(3,5-dinitrobenzoyl)norephedrine supported by silica gel may be different than that of (1S,2R)-norephedrine itself.

On the other hand, Pirkle-type CSPs derived from N-(3,5-dinitrobenzoyl)-α-amino acids have been known to be conformationally quite rigid because of the intramolecular hydrogen bonding. For example, CSP 1, which has been widely applied for the resolution of various π-basic analytes, has been proposed to utilize the low energy conformation shown in the depicted structure of CSP **1**.[7,8]

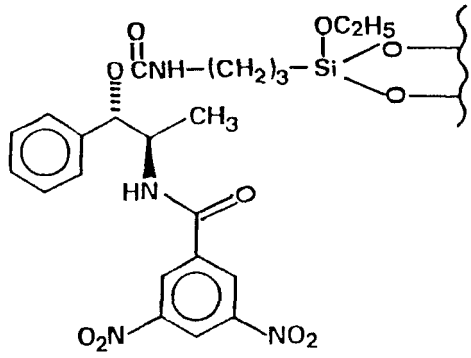
Therefore, comparison of the resolution behavior on CSP **1** and the CSP derived from (1S,2R)-N-(3,5-

dinitrobenzoyl)norephedrine may provide insights into the role of conformational rigidity or flexibility of CSPs in chiral recognition.

Based on this rationale, we previously prepared CSP **2** by connecting (1S,2R)-N-(3,5-dinitrobenzoyl)norephedrine to a silica support through an carbamate linkage and briefly reported the resolution of enantiomers on CSP **2**.[9] However, the N-H hydrogen of the carbamate group of CSP **2** is suspected to lead to nonstereoselective additional hydrogen bonding interaction with analytes and, in consequence, to retain both of two enantiomers without enantioselection between them, leading to poor resolution and long retention of analytes. Therefore, in this study, we report the preparation of CSP **3**, (1S,2R)-N-(3,5-dinitrobenzoyl)norephedrine connected to a silica support through an ester linkage, and the comparison of the resolution behavior on CSPs **1,2** and **3** in order to see the effect of the conformational rigidity or flexibility of these CSPs upon the chiral recognition.



CSP 1



CSP 2

MATERIALS AND METHODS

General

The HPLC system used in this study consists of Waters Model 510 Pump, Waters Model U6k Universal Chromatographic Injector, Waters Model 441 Absorbance Detector with 254 nm UV filter and Waters Model 740 Data Module Recorder. The chiral column packed with CSP **1** which was used in this study was generously donated by the Regis Chemical Company, Morton Grove, Illinois, U.S.A. Preparation of CSP **2** was previously reported.[9] All chromatograms were obtained using 2-propanol-hexane(10 :90, v/v) as the mobile phase with a flow rate of 2 mL/min. All analytes used in this study were prepared according to the procedure described previously.[8]

Preparation of CSP 3

CSP **3** was prepared as shown in Scheme 1.

(1S,2R)-1-[(3,5-Dinitrobenzoyl)-2-amino-1-phenyl]-propyl 9-undecenoate: To a stirred solution of 10-undecenoyl chloride(0.009 mole) and triethylamine(0.011

mole) in 40 mL of methylene chloride was added a solution of (1S,2R)-N-(3,5-dinitrobenzoyl)norephedrine slowly at room temperature. The reaction mixture was stirred at room temperature under nitrogen for 3 hrs and then washed succesively with 1 N HCl, 1N NaOH, and water. After drying over anhydrous $MgSO_4$, solvent was removed. Flash column chromatography on silica gel(mixed eluent of hexane and ethyl acetate) afforded a yellowish solid product(2.6 g, 87 %). m.p.:68-71°C; ^1H NMR(CCl_4) δ 1.28-2.30(m,18H), 4.00(q,2H), 4.80-5.80(m,4H), 7.20(s, 5H), 7.50(d,1H), 8.75(d,1H), 8.85(s,2H); IR(KBr) cm^{-1} 3380, 2900, 1720, 1650, 1550.

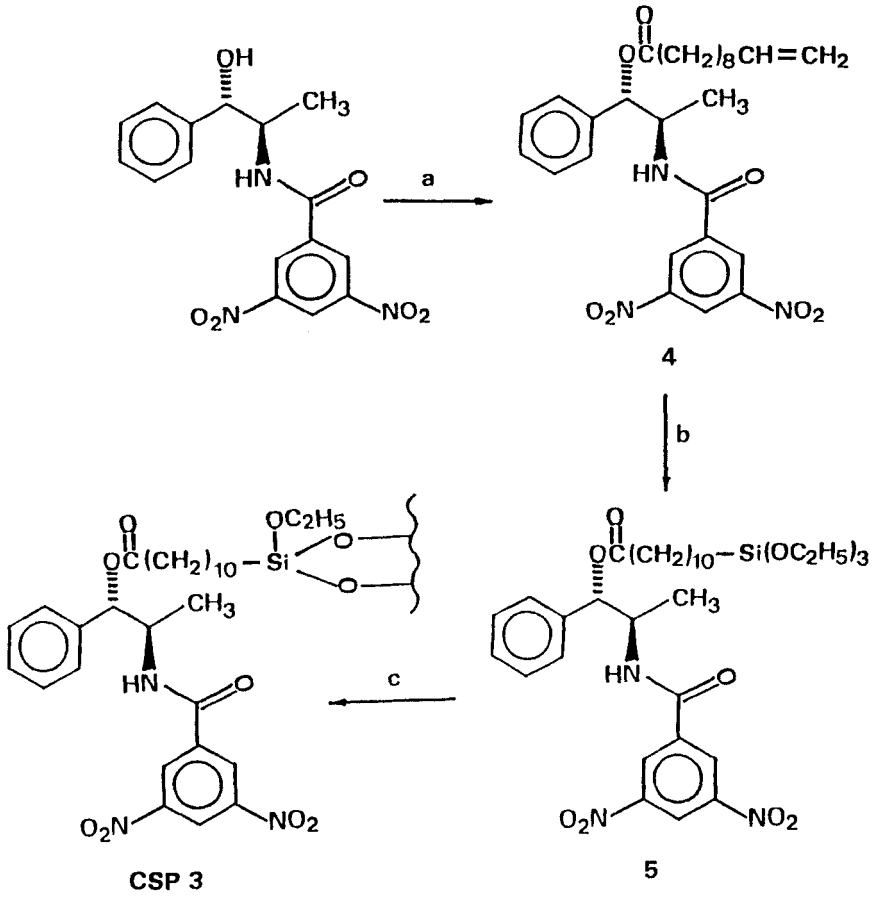
(1S,2R)-1-[N-(3,5-Dinitrobenzoyl)-2-amino-1-phenyl-]propyl 11-triethoxysilylundecanoate(5): To a stirred solution of ester **4**(0.003 mole) in 20 mL of trichlorosilane was added 1.5 mL of hexachloroplatinic acid solution(about 100 mg of $H_2PtCl_6.6H_2O$ in 20 mL of isopropyl alcohol) at one portion under nitrogen atmosphere. The resulting solution was heated to reflux for 30 min. and then the excess trichlorosilane was removed by simple distillation. To remove trichlorosilane completely, 10 mL portions of methylene chloride were added several times and continuously distilled. After complete removal of trichlorosilane, 30 mL of methylene chloride was added and stirred at room temperature. To the stirred solution was added 5 mL of 1:1 mixture of ethyl alcohol and triethylamine and the mixture was concentrated under reduced pressure. The residue was dissolved in 50 mL of diethylether and the undissolved material was removed by filtration. After removing the diethylether under reduced pressure, the resulting residue was chromatogr-

aphed on silica gel(mixed eluent of hexane and ethyl acetate) and oily product(1.2 g, 61%) was obtained. ^{1}H NMR($CDCl_3$) δ 0.70(t,2H), 1.25-2.30(m,32H), 3.85(q, 6H), 5.92(d,1H), 7.40(s,5H), 8.90(d,2H), 9.10(t,1H); IR(KBr) cm^{-1} 3380, 2900, 1730, 1550

CSP 3: In a 100 mL round bottom flask was added 4.5 g of 10 μm Sphesorb silica gel and 50 mL of benzene. From the resulting slurry water was removed azotropically. After the complete removal of water, triethoxysilyl compound **5**(1.0 g) in 20 mL of benzene was added to the slurry which was heated to reflux for 60 hrs with stirring magnetically. The modified silica gel was washed with benzene, methanol, acetone, methylene chloride and hexane and slurry packed into a 250 x 4.6 mm I.D. stainless steel column using conventional methods. Anal. Found: C,4.89; H,0.61; N,0.47. Calcd: 0.11 mmole/g(based on N), 0.14 mmole/-g(based on C)

RESULTS AND DISCUSSION

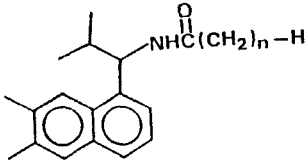
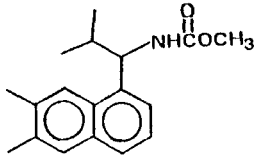
CSP **3** prepared by the simple procedure shown in Scheme **1** has a strong π-acidic site and can be used for the resolution of racemates containing π-basic functional groups. To compare the performance of CSP **3** with CSPs **1** and **2**, data for the resolutions of N-acyl-1-arylaminoalkanes on CSPs **1**, **2** and **3** are summarized in Table **1**. In this Table, the elution orders indicated were obtained by chromatographing configurationally known samples. As expected, CSP **3** always shows greater chiral recognition(α value) and, in general, shorter retention(k' value) than does CSP **2**. However, it is quite surprising to note that both CSP



SCHEME 1. a: Undecenoyl Chloride, Triethylamine, Methylene Chloride, Room Temperature. b: (1)Trichlorosilane, $H_2PtCl_6.6H_2O$, (2)Ethyl Alcohol, Triethylamine, Methylene Chloride, Room Temperature. c: 10 μm Spherisorb Silica Gel, Benzene, Dean-Stark Trap.

TABLE 1

Liquid Chromatographic Separation of Enantiomers of N-Acyl-1-aryl-1-aminoalkanes on CSPs **1**, **2** and **3**.

analyte	CSP **1**[a]		CSP **2**[a]		CSP **3**		conf.[d]
	α[b]	k_1[c]	α[b]	k_1[c]	α[b]	k_1[c]	
A	(1.14	6.8)	1.05	6.9	1.12	5.7	S
B	(1.86	8.1)	1.04	15.4	1.13	11.9	S
C	(2.20	6.2)	1.24	10.1	1.48	9.5	
D	(2.20	10.3)	1.17	22.5	1.50	14.9	
E	(2.40	4.1)	(2.70	8.8)	3.00	7.8	S
 F							
n = 2	2.08	10.5	2.57	6.5	2.87	7.6	S
n = 3	2.05	8.3	2.68	4.6	3.10	6.0	S
n = 6	1.69	5.7	2.67	2.8	3.08	4.8	S
n = 11	(1.39	1.6)	2.70	2.0	3.00	3.5	S
 G	1.73	5.9	(2.71	2.7)	2.85	2.4	S

a: The data in the parenthesis are quoted from references 8 and 9. b: Separability factor. c: Capacity factor for the first eluted enantiomer. For the chromatographic condition, see text. d: Absolute configuration of the second eluted enantiomers on CSPs **1**, **2** and **3**.

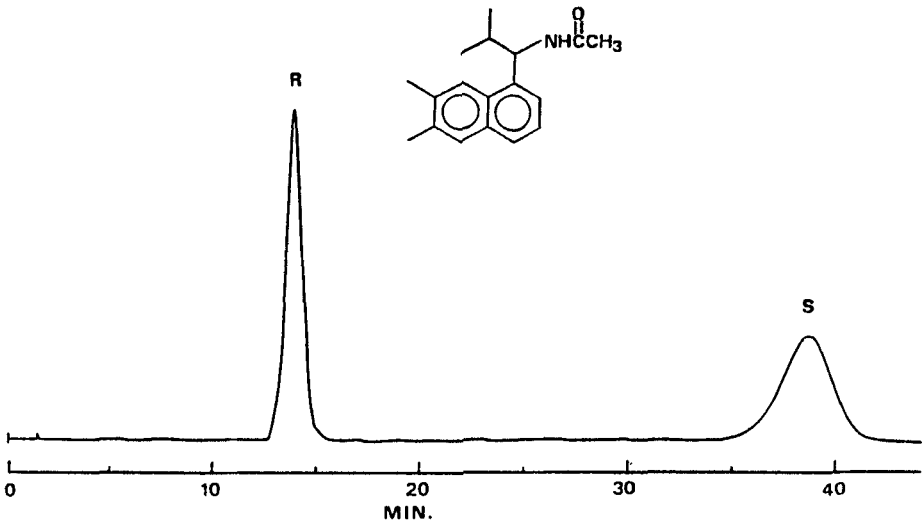


FIGURE 1. Liquid chromatographic separation of N-acetyl-1-[1-(6,7-dimethylnaphthyl)]-1-amino-2-methylpropane (E) on CSP **3**. See text for the chromatographic condition.

2 and CSP **3** show greater chiral recognition for the resolution of N-acyl and N-methoxycarbonyl-1-[1-(6,7-dimethylnaphthyl)]-1-amino-2-methylpropane(E, F and G) than does CSP **1**. A representative chromatogram obtained on CSP **3** is shown in Figure **1** and, in order to visualize the differences in the resolution behavior on CSPs **1**, **2** and **3**, part of Table **1** is presented graphically in Figure **2**. From Figure **2**, we see the most notable difference between CSP **1** and CSP **3** (or CSP **2**), which are expected to have different conformational rigidities, in the resolution of analyte E.

The chiral recognition achieved by a CSP is been known to require a minimum of three simultaneous

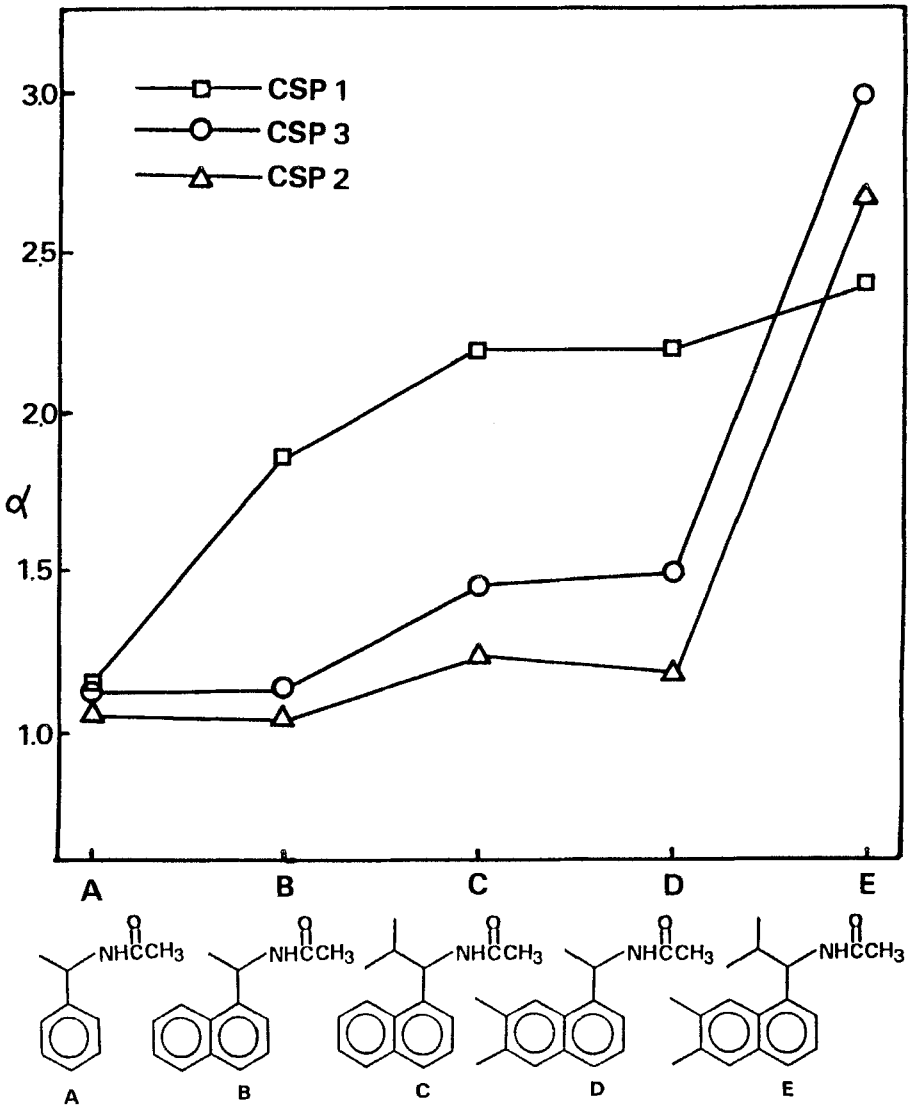


FIGURE 2. Liquid chromatographic resolutions of N-acetyl-1-aryl-1-aminoalkanes on CSPs **1**, **2** and **3**. See text for the chromatographic condition.

interactions between a CSP and at least one of the two enantiomers.[10] It is not difficult to imagine that a conformationally rigid CSP which retains three interaction sites in a distinct geometric array can best discriminate between enantiomers, one of which has three complimentary interaction sites at the proper positions. However, in most cases, the three complimentary interaction sites are not arranged properly and analyte conformation must be altered to conform to the shape of the CSP. In consequence, a rigid CSP may show better chiral recognition for conformationally flexible analytes than a flexible CSP. Similary, it is plausible to imagine that a conformationally flexible CSP can easily change its conformation to interact with conformationally rigid analytes and, in consequence, a flexible CSP may show better chiral recognition for conformationally rigid analytes than does a rigid CSP. However, the combination of a flexible CSP-flexible analytes seems to be unfavorable from the standpoint of chiral recognition.

Based on this asumption, we can understand that, in general, CSP **1**, which is more rigid or less flexible than CSP **3** (or CSP **2**) discriminates between enantiomers of N-acyl-1-arylaminoalkanes, which have a certain degree of conformational freedom, better than CSP **3** (or CSP **2**). However, in the case of the resolution of analytes E, F or G, which have appreciable conformational rigidity engendered by the peri-hydrogen and by the steric bulk of the isopropyl group on the chiral center, CSP **3** (or CSP **2**) which is expected to be conformationally more flexible or less rigid than CSP **1** is observed to show greater chiral recognition than CSP **1**. Note that the conformational rigidity of

analytes alone is not reponsible for the good chiral recognition on a conformationally flexible CSP as evidenced by the magnitude of the α value observed in the resolution of analyte C, which has the same degree of conformational rigidity as analyte E because of the same peri-hydrogen and the same steric bulk of the isopropyl group at the chiral center, on CSP **3** or CSP **2**. Therefore, in addition to the conformational rigidity of an analyte, a strong π-basic functional group seems to be needed for good chiral resolution of an analyte on a conformationally flexible π-acidic CSP such as CSP **3** or CSP **2**. Without the strongly π-basic functional group, it may be very difficult for an analyte, which has a steric bulky group controlling its conformation, to approach the CSP.

The assumption concerning the role of the conformational rigidity of CSP in the chiral recognition described above is quite similar to those mentioned by Pirkle. Pirkle, previously, proposed the role of the conformational rigidity of CSP in explaining the resolutions of 2-carboalkoxyindolines and N-aryl-α-amino esters on CSP **1**[7] and the resolutions of several racemic analytes on CSP derived from a N-(3,5-dinitrobenzoyl)-β-amino acid.[5] However, we think that our study is the first example showing that a conformationally flexible CSP can discriminate between enantiomers of conformationally rigid analytes better than a rigid CSP.

So far, we do not have any evidence that the second stereogenic center of CSP **2** or CSP **3** has an important role in chiral recognition. However, the second stereogenic center of CSP **2** or CSP **3** seems to control the orientation of the direction of the con-

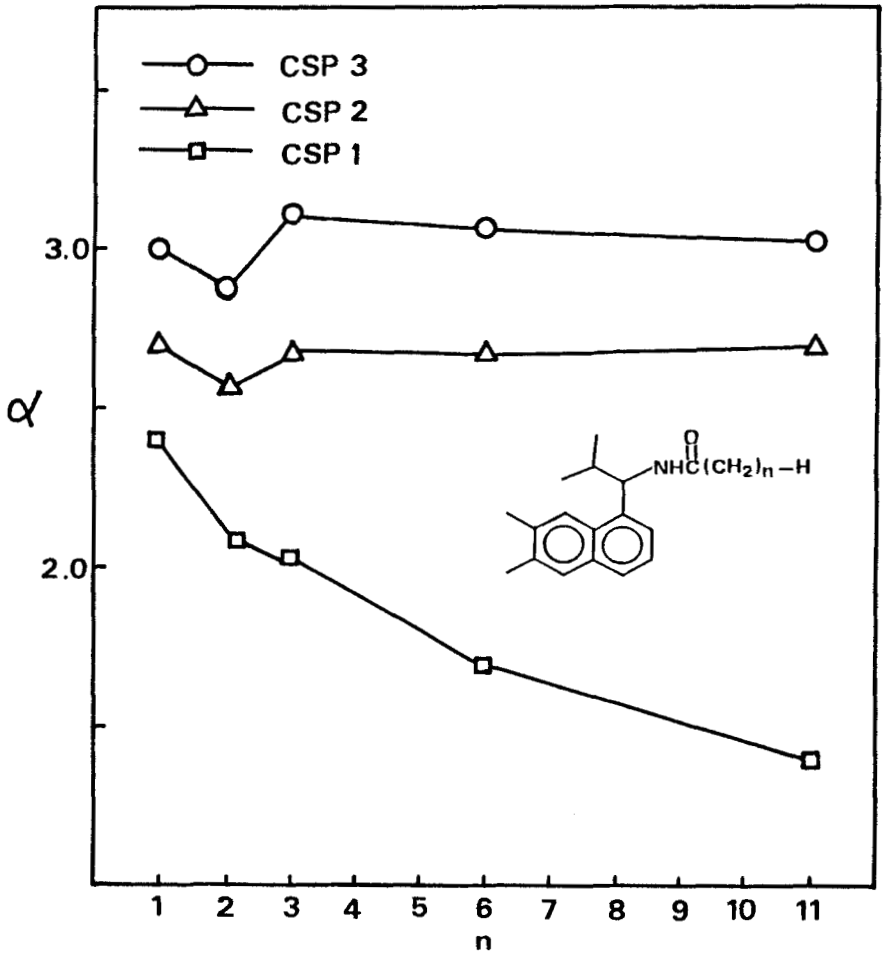


FIGURE 3. Liquid chromatographic resolutions of a series of N-acyl-1-[1-(6,7-dimethylnaphthyl)]-1-amino-2-methylpropane (F) on CSPs **1**, **2** and **3**. See text for the chromatographic condition.

necting arm of the CSP. The effect of the length of the N-acyl tail of N-acyl-1-[1-(6,7-dimethylnaphthyl)]-1-amino-2-methylpropane (compound F in Table 1) upon the chiral recognition on CSPs **1**, **2** and **3** is graphically shown in Figure **3**. As shown in Figure **3**, the length of the acyl tail does not produce any notable effect upon the separation factor on CSP **2** or CSP **3** while the separation factor observed on CSP **1** decreases continuously as the acyl tail increases in length. The continuous decrease of the α value on CSP **1** has been explained by asumming that the acyl tail intercalates between the strands of connecting arm of CSP **1**.[8] However, the direction of the connecting arm of CSP **2** or CSP **3** should be different from that of CSP **1** because of the presence of the second stereogenic center and, in consequence, the acyl tail does not intercalate between the strands of the connecting arm of CSP **2** or CSP **3**.

To explain the exact chiral recognition mechanisms exerted by CSP **2** or CSP **3** and to generalize the assumption concerning the role of the conformational flexibility of CSP **2** or CSP **3** in the resolution of conformationally rigid analytes, we need to collect more data. The efforts to elucidate the chiral recognition mechanisms for the enantiomeric separations on CSPs derived from N-(3,5-dinitrobenzoyl)norephedrine are still under progress in our laboratory.

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