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AN IMPROVED CHIRAL STATIONARY PHASE FOR THE FACILE SEPARATION OF ENANTIOMERS

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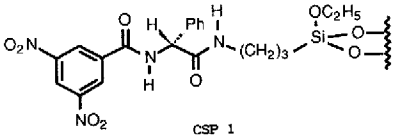
SUMMARY

A chiral stationary phase (CSP) derived from *cis*-3-(1,1-dimethylethyl)-4-phenyl-2-azetidinone is quite effective for the chromatographic separation of the enantiomers of a variety of compounds. This CSP (CSP 2) is conceptually related to the N-(3,5-dinitrobenzoyl) amino acid derived phases (*e.g.* CSP 1), but has two stereogenic centers. For many enantiomers, CSP 2 exhibits superior performance to that of the widely used analogue, phenylglycine-derived CSP 1.

INTRODUCTION

Considerable progress has been made recently in the development of totally synthetic chiral stationary phases (CSPs) for the direct chromatographic separation of enantiomers[1–3]. An innate advantage of totally synthetic CSPs is the ability to prepare either optical antipodes of the CSP as well as the racemic analogues[4]. Earlier papers from this laboratory describe the preparation[5] of synthetic CSP 1, derived from the 3,5-dinitrobenzamide of (*R*)-phenylglycine, and evaluate the ability of this CSP to separate the enantiomers of a variety of compounds[6–8].



CSP 1

We have previously used the magnitude of the chromatographic separation factor of enantiomers on a given CSP to gauge how well a CSP derived from one of those enantiomers might work in a reciprocal fashion[5]. Several classes of reciprocal CSPs have resulted from such studies conducted on CSP 1. More recently, several of these reciprocal CSPs have been employed for the chromatographic resolution of the enantiomers of a variety of N-3,5-dinitrobenzoyl derivatives of the β-amino acid esters derived from alcoholysis of β-lactams[9,10]. The enantiomers of several β-amino acid derivatives having two stereogenic centers are impressively separated by some

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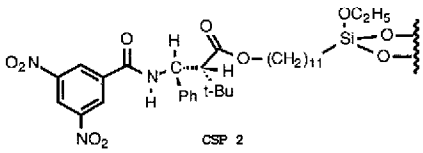
of the reciprocal CSPs, thus indicating that an effective CSP could, in turn, be derived from these β-amino acid derivatives.

To our knowledge, CSPs derived from β-amino acids have not been reported. In fact, the additional conformational freedom engendered by the increased distance between the two functional groups will normally diminish the chiral recognition properties of most β-amino acids. However, the presence of an additional stereogenic center and bulky substituents which lead to appreciable conformational rigidity can enhance chiral recognition properties. We note that adding stereogenic centers to either an analyte or a CSP does not automatically enhance its chiral recognition properties. CSPs derived from biomaterials having multiple stereogenic centers are well known although the mechanistic origin of their enantioselectivity is little understood. Several α-amino acid containing synthetic CSPs having two or more stereogenic centers have been reported[11], some being commercially available[12], but discussions of their mechanisms of operation are rare. In this paper, we describe the preparation of β-amino acid-derived CSP 2, and provide data concerning its efficacy.

Because of its similarity to the extensively studied CSP 1, a mechanistic hypothesis concerning CSP 2's anticipated enantioselectivity was formulated on a first approximation basis even before CSP 2 was prepared. This hypothesis, consistent with the data herein presented, confers a considerable practical advantage to the user for it permits accurate estimation of which enantiomers may be separable on CSP 2 and what their order of elution will be.



CSP 2

EXPERIMENTAL

Apparatus

Chromatography was performed with a Beckman A-100 pump, 210 injector, and Model 165 variable-wavelength detector. A Rudolph Autopol III with a 20-cm flow cell was used to monitor the sign of $[\alpha]_D$.

cis-3-(1,1-Dimethylethyl)-4-phenyl-2-azetidinone (±)-(4)

To a −70°C solution of 10.8 g (0.11 mol) of diisopropylamine in 100 ml of anhydrous tetrahydrofuran, under a nitrogen atmosphere, was added 0.11 mol of *n*-butyllithium in hexane (1.4–1.6 *M*) maintained at −70°C. This solution was stirred for 15 min followed by the addition of 14.4 g (0.10 mol) of ethyl-3,3-dimethyl butanoate in 50 ml of anhydrous tetrahydrofuran. The addition was at a rate such that the temperature did not exceed −60°C. The solution was stirred for an additional 45 min followed by addition of 20.83 g (0.12 mol) of N-(trimethylsilyl)benzaldimine[13] (3) in 50 ml of anhydrous tetrahydrofuran, again at a rate such that the temperature did not exceed −60°C. The mixture was stirred at −70°C for 1 h, the cold bath was removed, the mixture was allowed to warm to room temperature and then was stirred for 18 h. The resulting solution was diluted with 500 ml of diethyl

ether and washed sequentially with 100 ml of dilute 2 *M* hydrochloric acid and two 200-ml portions of water. The combined aqueous washes were extracted with two 200-ml portions of diethyl ether. The combined organic layers were dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by recrystallization from ethyl acetate–hexane to give 14.54 g (72% yield) of colorless lactam of somewhat higher melting point (m.p. = 164–166°C) than that reported[11] (151–152°C) but the NMR data are in accord with that reported: ^{1}H NMR (C^2HCl_3) δ 0.84 (s, 9H), 3.43 (dd, 1H, J = 3.6, 2.1 Hz), 4.95 (d, 1H, J = 5.7 Hz), 6.17 (br s, 1H), 7.26–7.43 (m, 5H); IR (KBr) 3233, 1748, 700 cm^{-1}.

(R,R-S,S)-10-Undecenyl 3-amino-3-phenyl-2-(1,1-dimethylethyl)propanoate (5)

To 1.40 g (7.35 mmol) of azeotropically dried (benzene) *p*-toluenesulfonic acid in 50 ml of benzene was added 1.00 g (4.9 mmol) of racemic *cis*-3-(1,1-dimethylethyl)-4-phenyl-2-azetidinone and 0.83 g (5.4 mmol) of 10-undecen-1-ol. The solution was heated to refluxe (81°C) for 75 min, diluted to 150 ml with benzene, washed twice with 100-ml portions of 5% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residual yellow oil (1.76 g) was carried on to the next step: ^{1}H NMR (C^2HCl_3) δ 1.17 (s, 9H), 1.02–1.41 (m, 14H), 1.49 (br s, 2H), 2.02–2.09 (m, 2H), 2..57 (d, 1H, J = 10.2 Hz), 3.50–3.70 (m, 2H), 4.25 (d, 1H, 10.2 Hz), 4.90–5.05 (m, 2H), 5.71–5.92 (m, 1H), 7.14–7.31 (m, 5H); IR (neat) 3372, 3308, 1726, 1640 cm^{-1}; high-resolution mass spectrum, calculated for $C_{24}H_{39}NO_2$:373.2980. Found: 373.2978.

(R,R-S,S)-10-Undecenyl N-3,5-dinitrobenzoyl-3-amino-3-phenyl-2-(1,1-dimethylethyl)propanoate (6)

To 1.76 g of yellow oily 5 in 50 ml of tetrahydrohydrofuran cooled to 0°C was added 1.30 g (5.60 mmol) of 3,5-dinitrobenzoyl chloride in portions. The resulting solution was maintained at 0°C and 0.43 g (7.35 mmol) of propylene oxide in 10 ml of tetrahydrofuran was added dropwise over a period of 5 min. The solution was stirred at room temperature for 1 h and the tetrahydrofuran was evaporated under reduced pressure. The resulting oil was diluted with 100 ml of methylene chloride and washed twice with 100 ml portions of 2 *M* aqueous sodium hydroxide. The organic layer was dried (using sodium sulfate) and concentrated under reduced pressure to give 2.60 g of racemic 6 as a yellow oil.

Resolution of racemic 6

Simultaneous purification and separation of the enantiomers of 6 was accomplished by preparative medium pressure chromatography on a 30 × 2 in. I.D. column containing the (*R*)-(+)-N-(2-naphthyl)alanine-derived CSP bonded to 60-μm irregular silica. The mobile phase was 1% 2-propanol in hexane, and the flow-rate was 30 ml/min. Two chromatographic fractions were collected. The first (1.07 g, 1.88 mmol) was (2*S*,3*S*)-6 of 90% enantiomeric purity, by HPLC assay, after recrystallization from ethyl acetate–hexane. The (2*R*,3*R*) enantiomer was eluted second (0.85 g, 1.50 mmol) and, again after recrystallization, was >99% enantiomerically pure, by HPLC assay. Total yield based on β-lactam was 69%: m.p. = 106.5–107°C; ^{1}H NMR δ 1.17 (s, 9H), 1.22–1.4 (m, 14 H), 2.01–2.08 (m, 2H), 3.00 (d, 1H, J = 10.2 Hz), 3.68–3.8 (m, 2H), 4.92–5.03 (m, 2H), 5.65–5.72 (m, 1H), 5.77–5.83 (m, 1H), 6.72 (b

d,1H, 9.3 Hz), 7.10–7.14 (t, 1H), 7.18–7.39 (m, 5H), 8.88 (d, 2H, 1.8 Hz), 9.15 (dd, 1H, 1.8 Hz); IR (melt) 3314, 1728, 1638 cm^{-1}. Calculated for $C_{31}H_{41}O_7N_3$: C, 65.58; H, 7.28; N, 7.40. Found: C, 65.46; H, 7.25; N, 7.42.

(2R,3R)-11-Triethoxysilylundecanyl N-3,5-dinitrobenzoyl-3-amino-3-phenyl-2-(1,1-dimethylethyl)propanoate (7)

To 1.72 g (3.03 mmol) of (*R,R*)-6 in 20.0 ml of trichlorosilane under a nitrogen atmosphere was added 0.1 g (0.24 mmol) hexachloroplatinic acid in 0.5 ml of 2-propanol. The resulting solution was heated to reflux (35°C) for 5 h. The excess trichlorosilane was removed by distillation at atmospheric pressure, 10 ml of methylene chloride was added as a chase and then removed by distillation. The resulting mixture was quenched with 10 ml of 1:1 (mol/mol) ethanol–triethylamine and concentrated under reduced pressure. The residue was dissolved in 100 ml of diethyl ether and the triethylamine hydrochloride precipitate was removed by filtration. The diethyl ether was evaporated under reduced pressure and the resulting residue was chromatographed rapidly upon silica [hexane–ethyl acetate (8:1)] to afford the hydrosilylated product (1.26 g, 1.72 mmol) as an oil in 57% yield: ^1H NMR δ 0.59–0.67 (m, 6H), 1.08–1.45 (m, 36H), 3.05 (d, 1H, J = 10.6 Hz), 3.58–4.05 (m, 6H), 4.08–4.19 (m, 2H), 5.64–5.73 (m, 1H), 7.16–7.40 (m, 5H), 8.89–8.90 (m, 2H), 9.09–9.11 (m, 1H).

Chiral stationary phase 2

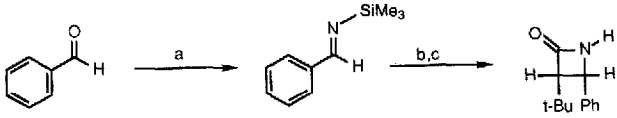
Water was azeotropically removed from a slurry of 5.0 g of 5 μm Spherisorb® in 100 ml of benzene. After drying was complete, 2.56 mmol of (*R,R*)-7- dissolved in 50 ml of methylene chloride was added. The solvents were evaporated under reduced pressure and the resulting slurry was mechanically rocked under reduced pressure at 115°C for 12 h. The modified silica was washed with three 100-ml portions of methanol and then slurry packed into a 250 × 4.6 mm I.D. column by conventional methods. Found: C, 9.11; H, 1.26; N, 0.79. Calculated: 0.23 mmol/g (based on C); 0.19 mmol/g (based on N).

Analytes

The various analytes used in this study to evaluate CSP 2 were available from prior studies.

RESULTS AND DISCUSSION

Following the procedure of Hart *et al.*[11], hexamethyldisilazane was treated with *n*-butyl lithium to generate lithium bis(trimethylsilyl)amide *in situ*. Addition of



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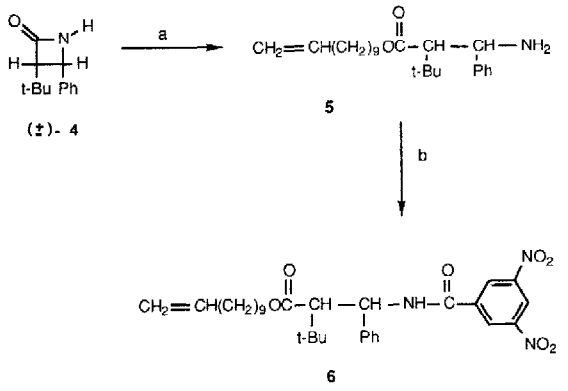
Scheme 1. Steps: (a) lithium bis(trimethylsilyl)amide; (b) ethyl-3,3-dimethyl butanoate, lithium diisopropylamide; (c) hydrochloric acid. Me = Methyl; Ph = phenyl; t-Bu = *tert.*-butyl.



Scheme 2. Steps: (a) 10-undecen-1-ol, *p*-toluenesulfonic acid, benzene; (b) 3,5-dinitrobenzoyl chloride, propylene oxide.

benzaldehyde to this anion affords imine 3. Addition of imine 3 to the enolate of ethyl-3,3-dimethyl butanoate in tetrahydrofuran, formed *in situ* with diisopropylamide, gives the β-lactam 4 (Scheme 1). An interesting and important feature of this condensation is that *cis*-stereochemistry is obtained exclusively. Hart *et al.*[11] have noted that the observed *cis*-stereoselectivity can be explained by a transition state

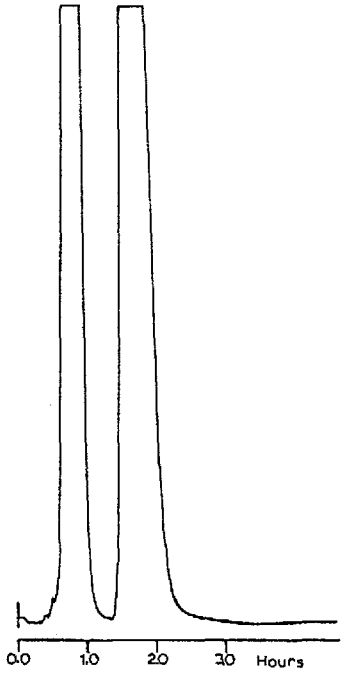
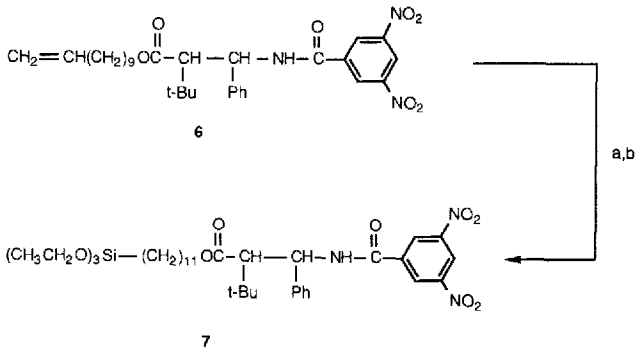


Fig. 1. Resolution of 1.92 g racemic 6 on a 30 × 2 in. I.D. column of (*R*)-(+)-N-(2-naphthyl)alanine derived CSP. Mobile phase was 1% 2-propanol in hexane; flow-rate was 30 ml/min.



Scheme 3. Steps: (a) trichlorosilane, hexachloroplatinic acid; (b) triethylamine, ethanol.

model similar to that frequently used to rationalize the sterochemical course of aldol condensations.

Acid catalyzed alcoholysis of the β-lactam 2 with 10-undecen-1-ol gives β-amino ester 5, no change in stereochemistry being involved in this reaction. The N-3,5-dinitrobenzoyl derivative (6) of amine ester 5 is easily prepared by introduction of 3,5-dinitrobenzoyl chloride and propylene oxide to a tetrahydrofuran solution of 5 (Scheme 2).

Racemic 6 was resolved by medium pressure chromatography using a preparative *R*-(+)-N-(2-naphthyl)alanine (siloxyundecyl ester) column as shown in Fig. 1.

The most strongly retained (*R,R*)-enantiomer was hydrosilylated with trichlorosilane–hexachloroplatinic acid catalyst to afford the trichlorosiloxy derivative which was directly converted to triethoxysilane 7 with triethylamine–ethanol (1:1) and purified by rapid chromatography on silica. The purified silane was bonded

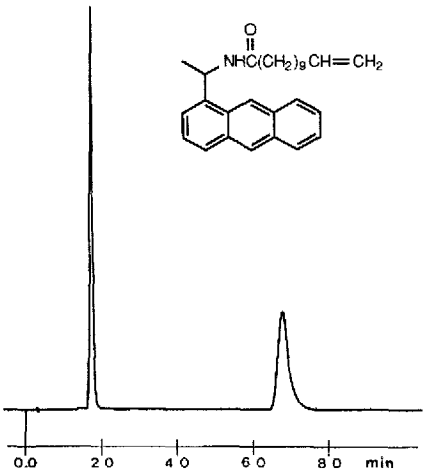
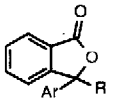


Fig. 2. Resolution of an acylated α-(1-anthryl)ethylamine on CSP 2. Mobile phase was 20% 2-propanol in hexane; flow-rate was 1 ml/min.

TABLE I

RESOLUTION OF PHTHALIDE ENANTIOMERS ON CSPs 1 AND 2



Ar	*R*	*CSP 1*			*CSP 2*		
		α^*	$k_1'^{**}$	$[\alpha]_D^{***}$	α^*	$k_1'^{\S}$	$[\alpha]_D^{***}$
1-Naphthyl	H	1.09	1.95	(+)*R*	1.39	4.50	(−)*S*
	CH_3	1.57	4.00		2.27	7.43	(−)
	CF_3	1.15	1.43		1.33	2.00	(−)
2-Naphthyl	H	1.04	8.50[§§]	(−)*R*	1.09	5.80	(+)*S*
	CH_3	≈1.00	4.00	(−)*R*	1.12	4.80	(+)*S*
6,7-$(CH_3)_2$-1-Naphthyl	CH_3	2.03	4.71		2.73	14.80	(−)
	iso-C_3H_7	2.89	2.57		3.00	8.40	(−)
	Cyclohexyl	3.72	2.57		3.21	10.90	(−)
6,7-$(CH_3)_2$-2-Naphthyl	*iso*-C_3H_7	1.00	2.43		1.15	2.44	
3,7-$(CH_3)_2$-1-Naphthyl	CH_3	2.17	3.29		2.56	10.80	(−)
	Phenyl	3.05	2.71		2.56	5.73	(−)
4,7-$(CH_3)_2$-1-Naphthyl	H	1.15	6.57		1.32	7.93	
	CH_3	2.06	4.61	(+)*R*	2.50	11.40	(−)*S*
	n-C_4H_9	2.39	2.57	(+)	2.27	7.38	(−)
	n-C_8H_{17}	2.55	2.07	(+)	2.19	7.20	(−)
	$C{\equiv}C\text{-}(CH_2)_5CH_3$	2.42	2.71	(+)	1.88	7.33	(−)
Phenyl	C_2H_5	1.00	1.87		1.00	2.33	
p-Anisyl	CH_3	1.00	3.50		1.08	4.93	
10-Methoxy-9-anthryl	H	1.05	8.14		1.00	1.33	
9-Anthryl	H	1.05	7.71		1.00	1.27	

* Chromatographic separation factor.

** Capacity factor for the first eluted enantiomer using 10% 2-propanol in hexane as the mobile phase; flow-rate 2 ml/min.

*** Sign of $[\alpha]_D$ and configuration of the most strongly retained enantiomer as determined by a polarimetric HPLC detector.

§ Capacity factor for the first eluted enantiomer using 20% 2-propanol in hexane as the mobile phase; flow-rate 2 ml/min.

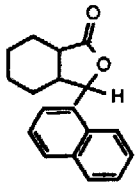
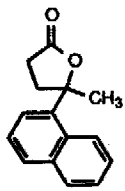
§§ Capacity factor for the first eluted enantiomer using 5% 2-propanol in hexane as the mobile phase; flow-rate 2 ml/min.

to 5-μm Spherisorb silica to give CSP 2 and slurry packed into a 250 × 4.6 mm I.D. column using methanol (Scheme 3).

Our studies indicate that, in many cases, CSP 2 provides performance superior to that of CSP 1 for the resolution of enantiomers. The magnitude of α, the chromatographic separation factor for analyte enantiomers, is often observed to be much larger on CSP 2 than on CSP 1. In some instances, the differences between CSPs 1 and 2 are profound. For example, the enantiomers of the 1-anthryl derivative shown in Fig. 2 do not separate on CSP 1 but separate very easily (α = 4.61) on CSP 2.

TABLE II

RESOLUTION OF PHTHALIDE ANALOGUES ON CSPs 1 AND 2

Compound	*CSP 1*			*CSP 2*		
	α^*	$k_1'^{**}$	$[\alpha]_D^{***}$	α^*	$k_1'^{**}$	$[\alpha]_D^{***}$
	≈1.00	3.88	(+)	≈1.00	3.88	(−)
	1.12	2.63	(−)	1.39	4.50	(+)

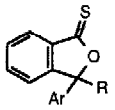
* Chromatographic separation factor.

** Capacity factor for the first eluted enantiomer using 5% 2-propanol in hexane as the mobile phase; flow-rate 2 ml/min.

*** Capacity factor for the first eluted enantiomer using 10% 2-propanol in hexane as the mobile phase; flow-rate 2 ml/min.

TABLE III

RESOLUTION OF 1-THIONOPHTHALIDE ENANTIOMERS ON CSPs 1 AND 2



Ar	*R*	*CSP 1*			*CSP 2*		
		α^*	$k_1'^{**}$	$[\alpha]_D^{***}$	α^*	$k_1'^{\S}$	$[\alpha]_D^{***}$
1-Naphthyl	H	1.21	2.38	(−)	1.86	2.40	(+)
	CH_3	1.21	2.38	(+)	2.42	2.07	(−)
2-Naphthyl	H	1.06	3.25	(−)	1.26	2.07	(+)*S*
	CH_3	1.01	1.50	(−)	1.17	1.60	(+)

* Chromatographic separation factor.

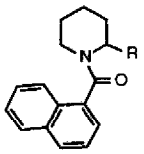
** Capacity factor for the first eluted enantiomer using 5% 2-propanol in hexane as the mobile phase, flow-rate 2 ml/min.

*** Sign of $[\alpha]_D$ and configuration of the most strongly retained enantiomer as determined by a polarimetric HPLC detector.

§ Capacity factor for the first eluted enantiomer using 20% 2-propanol in hexane as the mobile phase, flow-rate 2 ml/min.

TABLE IV

SEPARATION OF THE ENANTIOMERS OF THE N-(1-NAPHTHOYL) DERIVATIVES OF SOME SUBSTITUTED PIPERIDINES



R	*CSP 1*			*CSP 2*		
	α^*	$k_1'^{**}$	$[\alpha]_D^{***}$	α^*	$k_1'^{**}$	$[\alpha]_D^{***}$
CH_3	1.15	4.7	(+)*S*	1.15	12.10	(−)
CH_2CH_3	1.19	4.0	(+)	1.10	11.70	(−)
$CH_2CH_2CH_3$	1.25	11.7[§]	(+)	1.30	9.70	(−)
$CH_2(CH_2)_3CH_3$	1.25	10.0[§]	(+)	1.29	8.14	(−)
Phenyl	1.19	7.6	(+)	1.09	14.70	(−)
$CH_2CH(cis\text{-Hexyl})_2$	1.23	7.6	(+)	1.86	5.14	(−)

* Chromatographic separation factor.

** Capacity factor for the first eluted enantiomer using 10% 2-propanol in hexane as the mobile phase, flow-rate 2 ml/min.

*** Sign of $[\alpha]_D$ of the most strongly retained enantiomer as determined by a polarimetric HPLC detector.

§ 5% 2-propanol in hexane as the mobile phase, flow-rate 2 ml/min.

Tables I and II provide chromatographic data for the separation of the enantiomers of a variety of phthalides and phthalide analogues on CSPs 1 and 2. Examination of the chromatographic data in Tables I–III reveals that CSP 2 affords better selectivity than does CSP 1 for twelve of twenty phthalides, one of two phthalide analogues, and all of the 1-thiono-phthalides*.

Examination of optical rotation data in Tables I–III reveals that (*R*)-CSP 1 and (*R,R*)-CSP 2 afford opposite elution orders for enantiomers. Because of the Cahn–Prelog–Ingold priority sequence, (*R,R*)-CSP 2 is stereochemically analogous to (*S*)-CSP 1 and should in fact *not* give the same elution orders as (*R*)-CSP 1.

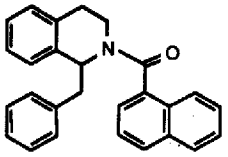
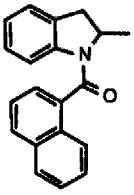
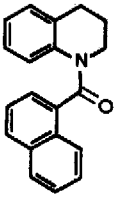
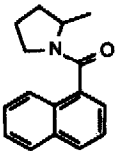
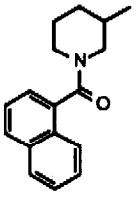
Data in Tables IV and V for the resolution of racemic α-naphthamides of cyclic and heterocyclic amines show that CSP 2 is usually capable of providing greater selectivity than does CSP 1*. Similar conclusions are drawn from the data in Table VI for the resolution of a homologous series of O-acyl phenyl carbinols.

At the suggestion of a reviewer, data allowing a comparison of the efficiency of CSP 2 with that of CSP 1 are presented. The original column containing CSP 2 was used to generate this data, the column having been subjected to heavy usage for eighteen months. A Regis covalent phenylglycine column of comparable age and usage was used to generate the CSP 1 data. Hence, these data are conservative and greater efficiences might be noted for new columns. Mobile phases were selected so that k_1 was approximately the same on each CSP.

* Some of these data are taken from recent reports[7,14] so that they might be compared with data obtained using CSP 2.

TABLE V

SEPARATION OF THE ENANTIOMERS OF N-(1-NAPHTHOYL) DERIVATIVES OF SOME HETEROCYCLIC AMINES

Compound	*CSP 1*			*CSP 2*		
	α^*	$k_1'^{**}$	$[\alpha]_D^{***}$	α^*	$k_1'^{**}$	$[\alpha]_D^{***}$
	1.42	7.5	(−)*S*	2.24	13.30	(−)
	1.03	≈8[§]		1.09	9.9	(+)
	1.31	4.9	(−)	2.17	6.43	(+)
	1.11	8.6	(+)	1.14	12.86	(−)
	1.00			1.05	12.14	(−)

* Chromatographic separation factor.

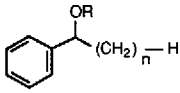
** Capacity factor for the first eluted enantiomer using 10% 2-propanol in hexane as the mobile phase; flow-rate 2 ml/min.

*** Sign of $1\alpha]_D$ of the most strongly retained enantiomer as determined by a polarimetric HPLC detector.

[§] 1% 2-propanol in hexane was used as the mobile phase; flow-rate 2 ml/min.

TABLE VI

SEPARATION OF THE ENANTIOMERS OF A HOMOLOGOUS SERIES OF O-ACYL PHENYL ALKYL CARBINOLS



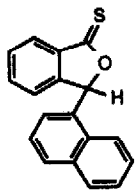
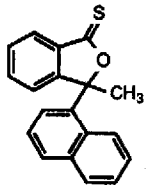
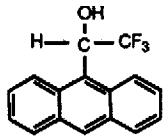
n	*R*	*CSP 1*		*CSP 2*	
		α*	k_1'**	α*	k_1'**
4	Acetyl	1.19	0.93	1.75	0.14
7		1.31	0.73	1.73	0.78
9		1.30	0.83	2.20	0.71
10		1.30	0.75	1.73	0.64
11		1.30	0.75	1.90	0.71

* Chromatographic separability factor using 0.5% 2-propanol in hexane as the mobile phase; flow-rate 2 ml/min.

** Capacity factor for the first eluted enantiomer.

TABLE VII

COMPARISON OF HETP AND RESOLUTION OF CSPs 1 AND 2

CSP	*Compound*	α*	k_1'**	R_S***	$HETP_1$§	$(b'/a')_1$§§	$HETP_2$§	$(b'/a')_2$§§
1		1.18	2.18§§§	2.15	4.45	2.42	4.55	2.49
2		1.84	2.06†	6.06	7.41	2.85	8.88	2.74
1		1.27	1.55†	2.91	3.82	2.36	4.35	2.40
2		2.42	1.67†	7.60	8.17	2.88	11.10	2.65
1		1.32	0.82†	2.47	4.44	4.08	4.33	2.85
2		1.33	0.94††	2.47	5.57	3.90	5.63	3.57

* Chromatographic separation factor.

** Capacity factor, the subscripts (1 and 2) refer to the first and second eluted enantiomers respectively.

*** Resolution, flow-rate 1 ml/min.

§ Height equivalent to a theoretical plate ($\times 10^{-2}$mm) flow-rate 1 ml/min.

§§ Peak asymmetry values from $As^2 = (b'/a')^2$, where a' and b' are the leading and tailing half of a peak measured at 10% of the total height.

§§§ 25% 2-propanol in hexane.

† 20% 2-propanol in hexane.

†† 10% 2-propanol in hexane.

One notes that the height equivalent to a theoretical plate (HETP) values obtained for CSP 2 are somewhat greater than those observed for CSP 1 as are the asymmetries. However, the resolution factors for CSP 2 can be significantly greater than for CSP 1, owing to the larger separation factors. The data in Table VII are averages of five consecutive runs. Since these data stem from but a single column of each type, there is no assurance that they adequately represent the norm for each type of CSP, were a series of columns of each type evaluated. Nevertheless, the data do afford some idea of the performance to be expected.

The chiral recognition mechanisms employed by CSP 2 are thought to be fundamentally the same as those employed by CSP 1 but modified by the following consideration. CSP 2 is thought to be conformationally more rigid than CSP 1 and the C-terminal carbonyl oxygen is differently oriented relative to the remainder of the chiral moiety. Earlier work[10] suggests that the second stereogenic center does not give rise to a second chiral recognition component, but simply controls the orientation of the carboalkoxy carbonyl oxygen, a major interaction site. The additional rigidity may either aid or detract from the degree of chiral recognition afforded, depending upon the ability of the analyte enantiomers to "conform," to the shape of the CSP. More detailed discussion of the chiral recognition processes await the completion of intermolecular nuclear Overhauser NMR studies similar to those recently reported for a different system.

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