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α-ARYLALKYLAMINE-DERIVED CHIRAL STATIONARY PHASES

EVALUATION OF UREA LINKAGES

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SUMMARY

Several urea-linked α-arylalkylamine-derived chiral stationary phases have been prepared and the performance of these phases has been compared to that of the corresponding amide-linked chiral stationary phases. The urea linkage is found to be a reasonable means of connecting a chiral moiety to a silica support and seems to exert some control upon the balance point between two competing chiral recognition processes, owing to the conformational rigidity and polar nature of the urea linkage.

INTRODUCTION

In an earlier paper[1], we have described the chromatographic separation of the enantiomers of α-arylalkylamines as their amide, urea and carbamate derivatives. These separations were effected on a chiral stationary phase derived from (*R*)-N-3,5-dinitrobenzoylphenylglycine[2,3]. From this work, mechanisms for the observed chiral recognition were postulated and used to aid in the design of highly effective "reciprocal" α-arylalkylamine-derived chiral stationary phases. The preparation and evaluation of several of these silica-bonded chiral stationary phases, 1a–c, has been reported[4,5]. In this paper, we describe the consequences of incorporating an urea, rather than an amide linkage into the connection arm that anchors the chiral unit to the support. Such urea linkages are not new to stationary phase design. Petrach Systems Inc. has, for some years, offered both enantiomers of N-α-phenylethyl-N'-triethoxysilylpropylurea as a reagent for treating surfaces so that they resolve enantiomers[6]. However, we are unaware of reports of the actual use of these reagents for that purpose. More recently, Ôi and co-workers[7,8] have reported an α-naphthylethylamine-derived urea-linked chiral stationary phase and used it to separate the enantiomers of N-3,5-dinitrobenzoyl amines and amino acid derivatives.

Our previous study[1] indicates that the extent of separation of the enantiomers of alkylurea derivatives of α-arylalkylamines are comparable to those of the corresponding alkyl amide or carbamate derivatives when the (*R*)-N-3,5-dinitrobenzoylphenylglycine-derived chiral stationary phase is used. Considering both the reciprocal

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aspect of chiral recognition and prior work of Ôi and co-workers[7,8], it is clear that urea-linked chiral stationary phases have the potential to work reasonably well. We have attached several selected (for good chiral recognition) α-arylalkylamines to silica gel through a urea linkage. Although we suspected that the inclusion of the polar urea moiety in the connection arm might be generally disadvantageous (leading to spurious interactions which retain the enantiomers without distinguishing between them), the urea-linked chiral stationary phases are otherwise attractive because, in some instances, they are extremely easy to prepare. Moreover, the effect that the polar urea moiety would actually exert upon the chiral recognition mechanisms was of interest.

EXPERIMENTAL

General

^{1}H NMR spectra were taken on a Varian EM-390 or on a Varian XL-200 NMR spectrometer. Tetramethylsilane was used as internal standard. IR spectra were recorded on a Perkin-Elmer 1320 or Nicolet 7199 FT-IR spectrometer. Micro-analyses were performed at the Micro-analysis Laboratory, University of Illinois at Urbana-Champaign. High-resolution mass spectra were obtained on a Varian 731 mass spectrometer. Melting points were taken on a Büchi apparatus and are not corrected. Optical rotations were observed at 589 nm at room temperature using a Rudolph Autopol III polarimeter.

The chiral stationary phases were packed into 250 × 4.6 mm I.D. stainless-steel columns as methanol slurrys by conventional methods. Chromatography was performed using an Altex 100 A pump, an Altex 210 injector, an Altex Model 165 variable-wavelength detector and a Kipp & Zonen BD 41 recorder. All solutes used in this study are available from prior studies[5,6].

Methyl N-[α(6,7-dimethyl-1-naphthyl)isobutyl]carbamate (2)

To a stirred solution of α-(6,7-dimethyl-1-naphthyl)isobutylamine (4.43 g, 0.0195 mol) and triethylamine (2.17 g, 0.0215 mol) in dry benzene (30 ml) was rapidly added a solution of methyl chlorocarbonate (2.03 g, 0.0215 mol) in dry benzene (15 ml). After stirring the reaction mixture under nitrogen for 30 min at room temperature, solvent was removed and the carbamate was purified by flash column chromatography to afford 5.06 g (91%) of 2. m.p. 159–161°C; ^{1}H NMR (C^2HCl_3) δ 0.91 (d, 3H), 1.00 (d, 3H), 2.07–2.40 (m, 1H), 2.42 (s, 3H), 2.48 (s, 3H), 3.63 (s, 3H), 5.00–5.40 (m, 2H), 7.17–7.40 (m, 2H), 7.53–7.70 (m, 2H), 7.87 (m, 1H). IR (KBr) cm^{-1} 3300, 3060, 3005, 2980, 2950, 2920, 2870, 1680, 1550. Analysis calculated for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91; found: C, 75.58; H, 7.86; N, 4.88.

Resolution of racemic carbamate 2

This compound was resolved on a previously reported preparative chiral column[9]. High-R_F enantiomer (*R*)-2: m.p. 147–149°C; $[\alpha]_D$ − 56.73 (c 0.55, CH_2Cl_2). Low R_F enantiomer (*S*)-2: m.p. 148–149.5°C; $[\alpha]_D$ + 57.57 (c 0.95, CH_2Cl_2).

(R)-α-(6,7-Dimethyl-1-naphthyl)isobutylisocyanate (3)

To a stirred solution of carbamate (*R*)-2 (1.91 g, 0.0067 mol) and triethylamine

(0.75 g, 0.0074 mol) in dry benzene (50 ml) was added dropwise a solution of trichlorosilane (1.00 g, 0.0074 mol) in dry benzene (10 ml). After adding all trichlorosilane, the stirred mixture was heated to 80°C for 20 min and allowed to cool to room temperature[10]. Triethylamine hydrochloride was removed by filtration and solvent was removed under reduced pressure to give a pale yellow liquid. After flash column chromatography, 1.69 g of the desired product was obtained as a colorless liquid in 99% yield. ^{1}H NMR (C^2HCl_3) δ 0.97 (d, 3H), 1.07 (d, 3H), 2.07–2.38 (m, 1H), 2.44 (s, 3H), 2.49 (s, 3H), 5.24 (d, 1H). 7.30–7.77 (m, 5H). IR (Neat) cm^{-1} 3060, 3010, 2970, 2928, 2260 (very strong), 1600, 1500. High-resolution mass spectrum calculated for $C_{17}H_{19}N$: 253.1466; found: 253.1466.

(R)-N-(10-Undecenyl)-N-[α-(6,7-dimethyl-1-naphthyl)isobutyl]urea (4)

Isocyanate 3 (1.83 g, 7.2 mmol) and 10-undecenylamine (1.83 g, 10.8 mmol), which was prepared by the known procedure[10], in 25 ml dry benzene were refluxed for 10 min. After removing the solvent, flash column chromatography of the reaction mixture afforded 2.81 g of urea 4 (92%). m.p. 85–87°C; ^{1}H NMR (C^2HCl_3) δ 0.90 (d, 6H), 1.00–1.47 (m, 14H), 1.80–2.20 (m, 3H), 2.40 (s, 6H), 2.40 (s, 6H), 2.80–3.13 (m, 2H), 4.60 (t, 1H), 4.77–5.07 (m, 2H), 5.13–5.30 (m, 2H), 5.50–6.00 (m, 1H), 7.20–7.33 (m, 2H), 7.47–7.67 (m, 2H), 7.87 (s, 1H). IR (KBr) cm^{-1} 3360, 3320, 3060, 2960, 2920, 2850, 1630, 1570. High-resolution mass spectrum calculated for $C_{28}H_{42}N_2O$: 422.3297; found: 422.3300. $[\alpha]_D$ − 78.23 (c 1.93, CH_2Cl_2).

(R)-N-(11-Triethoxyundecyl)-N'-[α-(6,7-dimethyl-1-naphthyl)isobutyl]urea (5a)

This compound was prepared by the hydrosilylation reaction of urea 4 with triethoxysilane and chloroplatinic acid as a catalyst, as described previously[4]. Colorless oil. Yield, 38%. ^{1}H NMR (C^2HCl_3) δ 0.50–0.70 (m, 2H), 0.95 (d, 6H), 1.08–1.40 (m, 27H), 1.90–2.33 (m, 1H), 2.40 (s, 3H), 2.43 (s, 3H), 2.87–3.16 (m, 2H), 3.78 (q, 6H), 4.38 (t, 1H), 4.98 (d, 1H), 5.20 (t, 1H), 7.20–7.38 (m, 2H), 7.53–7.67 (m, 2H), 7.87 (s, 1H). IR (neat) cm^{-1} 3360, 3320, 2960, 2925, 2855, 1630, 1570. High-resolution mass spectrum calculated for $C_{34}H_{58}N_2O_4Si$: 586.4166; found: 586.4144. $[\alpha]_D$ − 53.12 (c, 1.56, CH_2Cl_2).

(R)-N-(Triethoxypropyl)-N'-[α-(6-,7-dimethyl-1-naphthyl)isobutyl]urea (5b)

Isocyanate 3 (1.3 g, 0.005 mol) and γ-aminopropyltriethoxysilane (1.3 g, 0.006 mol) in 15 ml dry benzene were refluxed for 30 min. After cooling the mixture to room temperature and removing the solvent, pure urea 5b was obtained by flash column chromatography (2.1 g, 88%): ^{1}H NMR (C^2HCl_3) δ 0.43 (t, 2H), 0.97 (d, 6H), 1.23 (t, 9H), 1.33–1.60 (m, 2H), 1.90–2.30 (m, 1H), 2.44 (s, 3H), 2.50 (s, 3H), 2.95–3.20 (m, 2H), 3.74 (q, 6H), 4.55 (t, 1H), 4.97 (d, 1H), 5.27 (t, 1H), 7.23–7.38 (m, 2H), 7.50–7.67 (m, 2H), 7.88 (s, 1H). IR (KBr) cm^{-1} 3362, 3320, 2975, 2930, 2885, 1628, 1570. High-resolution mass spectrum calculated for $C_{26}H_{42}N_2O_4Si$: 474.2914; found: 474.2914 $[\alpha]_D$ − 67.34 (c 0.64, CH_2Cl_2).

Chiral stationary phase 6a

An amount of 4.5 g of 5-μm Spherisorb silica gel was slurried with benzene and then water was removed azeotropically using a Dean-Stark trap. After complete removal of water, 2 g (0.034 mol) of silylurea 5a was added and the gently stirred

slurry was maintained at reflux for 48 h under a nitrogen atmosphere. The resulting modified silica gel was filtered and washed with benzene, ethyl acetate, methanol, acetone, diethyl ether and pentane. Analysis: found: C, 8.30; H, 1.30; N, 0.62; Si, 4.85. Calculated: 0.22 mol of 5a/g of stationary phase (based on N); 0.23 mmol of 5a/g of stationary phase (based on C).

Chiral stationary phase 6b

Method A. This stationary phase was prepared by the procedure described for chiral stationary phase 6a. Analysis: found: C, 9.05; H, 1.24; N, 0.93; Si, 41.46. Calculated: 0.33 mmol of 5b/g of stationary phase (based on C).

Method B. Isocyanate 3 (1.55 g) solution in methylene chloride (50 ml) was recycled through a commercially available Regis "amino" HPLC column for 1 h. Flow-rate was 1 ml/min. Afterwards, methylene chloride was pumped through the column for 1 h to remove unreacted isocyanate 3.

(R)-N-(3-Triethoxysilylpropyl)-N'-(α-(1-naphthyl)ethyl)urea

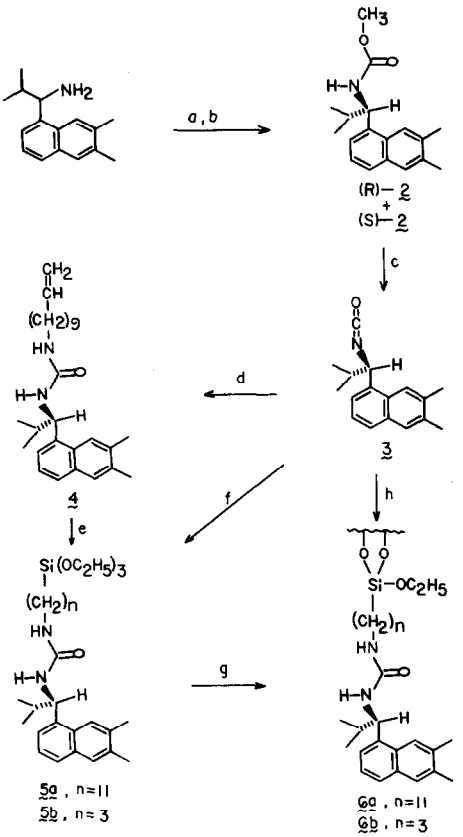
(*R*)-α-(1-naphthyl)ethylamine (5.27 g, 0.031 mol) and isocyanatopropyltriethoxysilane (7.61 g, 0.031 mol) were dissolved in 60 ml dry benzene and then heated to 80–85°C for 1 h under a nitrogen atmosphere with stirring. After cooling the reaction mixture to room temperature, solvent was removed. Flash column chromatography of the crude white solid afforded clean urea (11.87 g, 92%). m.p. 120–125°C; ^{1}H NMR (C^2HCl_3) δ 0.43–0.67 (m, 2H), 1.60 (t, 9H), 1.37–1.67 (m, 2H), 1.57 (d, 3H), 2.90–3.20 (m, 2H), 3.69 (q, 6H), 4.43–4.65 (m, 1H), 4.83 (d, 1H), 5.60 (t, 1H), 7.20–7.60 (m, 4H), 7.67–7.90 (m, 2H), 8.03–8.23 (m, 1H). IR (KBr) cm^{-1} 3320, 2975, 2925, 2880, 1620, 1580. High-resolution mass spectrum calculated, for $C_{22}H_{34}N_2O_4Si$: 418.2310; found: 418.2299. $[\alpha]_D$ − 15.00 (c 1.06, CH_2Cl_2).

Chiral stationary phase 7

This stationary phase was prepared by the procedure which was described for chiral stationary phase 6a. Analysis: found: C, 7.74; H, 0.89; N, 1.14; Si, 41.87. Calculated: 0.41 mmol/g of stationary phase (based on N); 0.36 mmol/g of stationary phase (based on C).

RESULTS AND DISCUSSION

We herein report the preparation of several urea-linked chiral stationary phases and compare their performance to that of the corresponding amide-linked phases. (See ref. 5 for data and mechanistic arguments relevant to the performance of the amide-linked chiral stationary phases.) Chiral stationary phases 6a and 6b, α-(6,7-dimethyl-1-naphthyl)isobutylamine bonded to silica gel through urea linkages but with differing length connecting arms, were prepared as shown in Scheme 1. The α-(6,7-dimethyl-1-naphthyl)isobutylamine, preparation of which has been reported previously[1], was chromatographically resolved as the methyl carbamate, 2, on a previously reported preparative chiral column. Enantiomerically pure (*R*)-2 was treated with trichlorosilane and triethylamine in benzene to afford isocyanate 3 (ref. 10). Isocyanate 3 was treated with 10-undecenylamine[11] in benzene to afford urea 4, which was hydrosilylated with triethoxysilane. Silane 5a was bonded to 5-μm Spher-



Scheme 1. (a) Methyl chlorocarbonate, triethylamine, methylene chloride; room temperature. (b) Resolution on chiral stationary phase. (c) Trichlorosilane, triethylamine, benzene. (d) 10-undecenylamine, benzene. (e) Triethoxysilane, chloroplatinic acid; 90°C. (f) α-aminopropyl triethoxysilane, benzene. (g) 5-μm silica gel, benzene; reflux. (h) aminopropylsilanized silica gel.

isorb silica to afford the "long-armed" urea-linked chiral stationary phase 6a. "Short-armed" urea-linked phase 6b was prepared by two different methods. Isocyanate 3 was treated with 3-aminopropyltriethoxysilane in benzene to give silylurea 5b, which, after bonding to 5 μm Spherisorb silica, gave chiral stationary phase 6b. Alternatively, treatment of 3-aminopropyl-silanized silica with isocyanate 3 also affords phase 6b.

In the latter method, a Regis "amino" HPLC column was modified by recycling a methylene chloride solution of 3 through the column for one hour. This "*in situ*" column turned out to be slightly inferior to the column containing chiral stationary phase 6b prepared by the first method. This may come either from retention of the solutes by residual free amino groups, a "packing" of the space between the strands of bonded-chiral phase by residual aminopropyl strands, or by interaction of the aminopropyl strands with the chiral urea strands. To compare the performance of chiral stationary phases 6a and 6b with previously reported phase 7 (ref. 7) we also prepared phase 7 by treating (*R*)-α-(1-naphthyl)ethylamine with 3-isocyanato-

TABLE I

RESOLUTION OF N-(3,5-DINITROBENZOYL)-α-ARYLALKYLAMINES ON CHIRAL STATIONARY PHASES 6a, 6b AND 7

α = Chromatographic separability factor; DNB = 3,5-dinitrobenzoyl.

Ar–C(H)–NHDNB, (CH$_2$)$_n$–H		*Chiral stationary phase*								
		6a			*6b*			*7*		
Ar	*n*	α	*k'**	*Configuration****	α	*k'**	*Configuration****	α	*k'***	*Configuration****
Phenyl	1	1.37	20.3	*R*	1.84	7.5	*R*	2.29	10.1	*R*
	2	1.79	23.6		2.02	7.9		2.25	10.3	
	3	1.81	24.6		1.62	8.4		1.98	9.9	
	4	1.80	24.0		1.34	7.4		1.64	9.7	
	5	1.79	23.0		1.06	7.2		1.45	9.1	
	6	1.73	22.2		1.14	6.1		1.29	8.7	
	7	1.68	20.5		1.38	4.9		1.17	8.1	
	8	1.62	19.5		1.53	4.1		1.10	7.5	
	9	1.57	18.6		1.71	3.9		1.03	7.7	
	10	1.50	17.9		1.83	3.6		1.00	7.6	
	11	1.44	17.3		1.94	3.5		1.02	7.6	
	13	1.24	16.0		2.00	2.7		1.05	6.7	
	15	1.17	15.5		2.05	2.9		1.07	6.5	
	17	1.15	14.7		2.11	3.1		1.10	6.6	
1-Naphthyl	1	1.15	18.4	*R*	1.07	8.3	*R*	3.37	14.6	*R*
	2	1.14	25.4		1.33	8.9		3.39	14.9	
	3	1.14	25.8		1.06	8.9		2.69	14.6	
	4	1.15	25.0		1.09	7.3		2.22	14.8	
	5	1.14	25.2		1.29	5.5		1.95	12.0	
	6	1.11	22.2		1.70	4.6		1.86	10.7	
	7	1.07	22.0		1.94	3.8		1.57	11.4	
	8	1.02	21.0		2.00	3.0		1.49	10.4	
	9	1.00	19.4		2.35	2.9		1.44	9.8	
	10	1.05	18.4		2.41	2.7		1.39	9.6	
	11	1.10	17.2		2.60	2.7		1.34	9.9	
	13	1.21	15.1		2.77	2.4		1.31	9.4	
	15	1.30	13.2		2.67	2.5		1.29	9.3	
	17	1.38	11.7		2.80	2.4		1.27	9.2	

* Capacity factor for the first eluted enantiomer. Mobile phase is isopropanol–*n*-hexane (20:80).
** Capacity factor for the first eluted enantiomer. Mobile phase is isopropanol–*n*-hexane (10:90).
*** Absolute configuration of the second eluted enantiomer.

propyltriethoxysilane in benzene and bonding the resulting chiral silane to 5-μm Spherisorb silica.

In Table I, representative data for the resolution of series of α-arylalkylamines, always as their 3,5-dinitrobenzoyl derivatives, on chiral stationary phases 6a, 6b and 7 are summarized. The general trends of α values on phases 6a, 6b and 7 are quite similar to those on chiral stationary phases 1a, 1b and 1c, as shown in Fig. 1. Interestingly, one infers from Fig. 1 that the influence of the length of the solute's alkyl

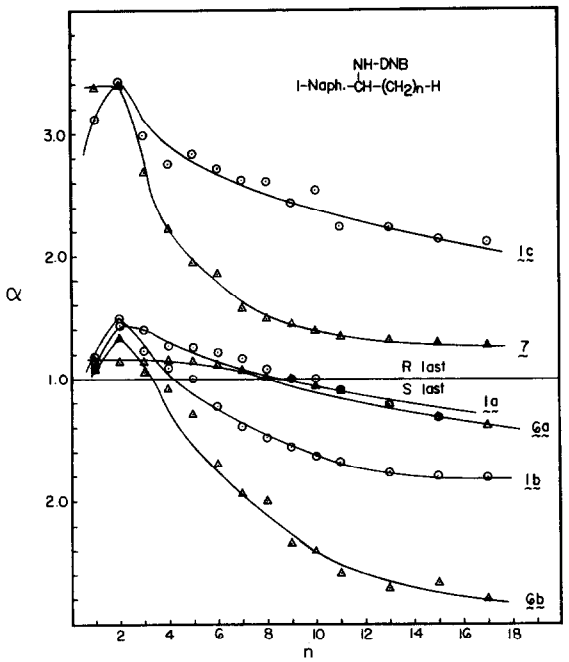
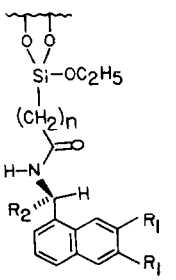


Fig. 1. Resolution of N-(3,5-dinitrobenzoyl)-α-(1-naphthyl)alkylamines on the amide and urea-linked chiral stationary phases.

"tail" on the magnitude of α is much more dramatic on the urea-linked chiral stationary phases (especially on the "short-armed" urea-linked phases) than on the corresponding amide-linked phases. In consequence, the reported inversion of elution order comes earlier (*i.e.* a shorter chain of methylene units suffices to cause inversion). It must also be noted that the magnitudes of the observed α values are usually less for the urea-linked chiral stationary phases than for the corresponding amide-linked phases.

Previously, we proposed the occurrence of two competing chiral recognition processes having opposite senses of enantioselectivity during the resolution of 3,5-



1 a $R_1 = CH_3$, R_2 = isopropyl, $n = 10$
b $R_1 = CH_3$, R_2 = isopropyl, $n = 4$
c $R_1 = H$, $R_2 = CH_3$, $n = 10$

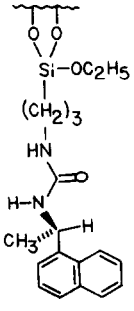


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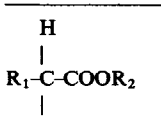
TABLE II

RESOLUTION OF N-(3,5-DINITROBENZOYL) AMINO ACID ESTERS ON CHIRAL STATIONARY PHASES 6a, 6b AND 7



		Chiral stationary phase								
		6a			*6b*			*7*		
R_1	R_2	α	k'*	*Configuration***	α	k'*	*Configuration***	α	k'**	*Configuration***
CH_3	CH_3	3.62	10.0	*R*	3.40	6.4	*R*	2.20	9.0	*R*
Isopropyl	CH_3	4.99	8.2	*R*	3.35	3.9	*R*	2.72	4.9	*R*
Isobutyl	CH_3	5.17	9.3	*R*	2.82	4.1	*R*	2.12	5.6	*R*
Phenyl	CH_3	2.67	10.0	*R*	1.97	7.3	*R*	1.10	13.6	*R*
	n-Butyl	3.07	6.1	*R*	3.62	2.8	*R*	1.50	5.4	*R*
	n-Pentyl	3.15	5.6	*R*	3.82	2.4	*R*	1.50	5.4	*R*
	n-Heptyl	3.29	4.8	*R*	4.31	2.0	*R*	1.67	4.0	*R*
	n-Decyl	3.47	4.0	*R*	4.58	1.7	*R*	1.66	3.6	*R*
Benzyl	CH_3	5.54	9.3	*R*	3.01	5.9	*R*	1.39	13.0	*R*
	n-Butyl	5.78	6.0	*R*	5.91	2.1	*R*	1.92	4.8	*R*
	n-Heptyl	6.15	4.9	*R*	7.60	1.5	*R*	2.33	3.2	*R*
	n-Decyl	6.45	3.8	*R*	8.44	1.3	*R*	2.41	2.9	*R*

*,**,*** Footnotes as in Table I.

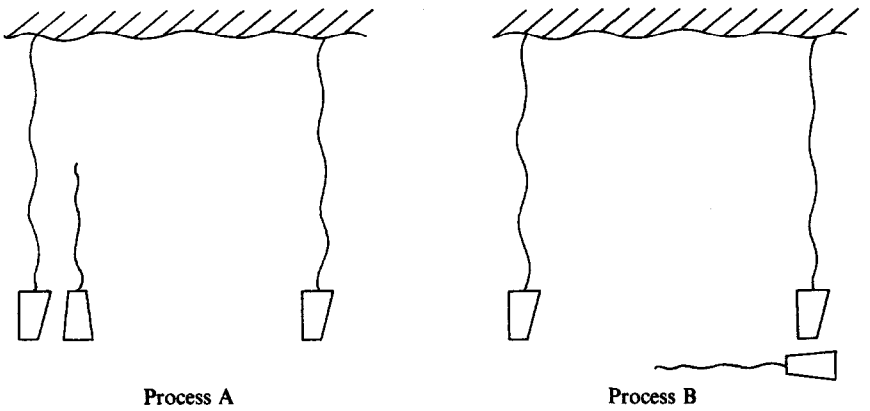


Fig. 2. Schematic representation of the two competing chiral recognition processes.

dinitrobenzamide enantiomers on the amide-linked chiral stationary phases[5]. The extent to which each of the competing chiral recognition processes contributes controls the observed sense and degree of chiral recognition. Analogous competing processes are shown schematically in Fig. 2 for urea-linked chiral stationary phases. In process A, the alkyl tail of the solute is approximately parallel to the connecting arm of the chiral stationary phase and essentially directed toward the solid support. In process B, the tail of the solute is directed more or less into the bulk mobile phase. Consequently, steric interaction between the analytes alkyl tail and the connecting

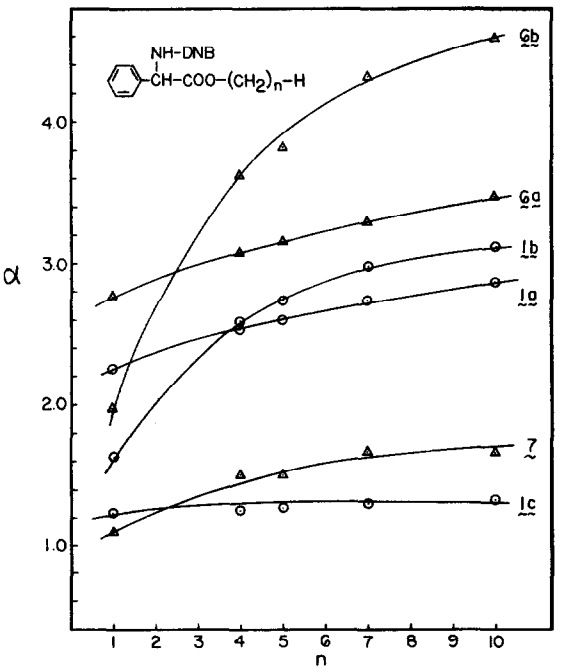
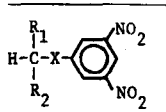


Fig. 3. Resolution of α-(3,5-dinitrobenzoyl)phenylglycine esters on the amide and urea-linked chiral stationary phases.

TABLE III

RESOLUTION OF VARIOUS ENANTIOMERS ON CHIRAL STATIONARY PHASES 6a, 6b AND 7



		Chiral stationary phase								
		6a			*6b*			*7*		
R_1	R_2	α	*k'**	*Configuration****	α	*k'**	*Configuration****	α	*k'***	*Configuration****
	X = –NH–C(=O)–									
CH_3	CONH-*n*-butyl	1.07	3.1	*R*	1.36	2.0	*R*	1.71	2.4	*R*
Isopropyl	CONH-*n*-butyl	1.93	1.3	*R*	2.18	1.0	*R*	2.53	1.0	*R*
Isobutyl	CONH-*n*-butyl	1.57	1.9	*R*	1.41	1.1	*R*	1.74	1.0	*R*
Benzyl	CONH-*n*-butyl	2.71	1.5	*R*	2.42	1.2	*R*	1.50	2.0	*R*
Phenyl	CONH-methyl	1.24	5.5	*S*	2.15	6.1	*S*	2.25	6.9	*S*
	CONH-*n*-butyl	1.00	3.5		1.00	2.4		1.35	3.2	*S*
	CONH-*n*-hexyl	1.00	3.0		1.39	1.3	*R*	1.14	2.4	*S*
	CONH-*n*-octyl	1.00	2.7		1.70	0.9	*R*	1.00	2.0	
	CONH-*n*-decyl	1.00	2.4		1.67	0.9	*R*	1.00	1.9	

CH_3	CH_2CH_3	1.34	11.7	*S*	1.18	6.3	*S*	1.10	6.9	*S*
	$(CH_2)_2CH_3$	1.30	11.6	*S*	1.00	4.8		1.00	6.4	
	$(CH_2)_3CH_3$	1.33	11.1	*S*	1.21	4.4	*R*	1.19	4.8	*R*
	$(CH_2)_4CH_3$	1.35	10.5	*S*	1.40	3.4	*R*	1.30	3.9	*R*
	$(CH_2)_5CH_3$	1.30	9.9	*S*	1.66	2.8	*R*	1.39	3.2	*R*
CH_3	CH_2OH	1.15	10.8	*S*	1.35	9.0	*S*	1.03	12.8	*S*
CH_2CH_3	CH_2OH	1.12	7.1	*R*	1.31	5.8	*S*	1.00	8.3	
	CH_2OCH_3	1.55	8.7	*R*	1.14	6.2	*R*	1.61	7.7	*R*
Isopropyl	CH_2OH	1.43	4.9	*R*	1.14	3.9	*S*	1.05	5.5	*R*
Isobutyl	CH_2OH	1.23	4.9	*R*	1.57	2.4	*S*	1.26	3.5	*S*
$CH_3SCH_2CH_2$	CH_2OH	1.26	11.1	*R*	1.18	9.5	*S*	1.10	11.9	*S*
Phenyl	CH_2OH	1.06	16.9	*R*	1.88	9.7	*S*	1.62	10.8	*S*
Phenyl	$PO(OC_2H_5)_2$	1.38	6.8		2.69	3.3		1.37	10.1	
4-$CH_3C_6H_4$	$PO(OC_2H_5)_2$	1.47	5.7		3.18	2.3		1.05	7.5	
4-ClC_6H_4	$PO(OC_2H_5)_2$	1.30	8.8		3.69	2.5		1.00	9.1	
$X=-\overset{O}{\overset{\|}{C}}NH-$										
Phenyl	CH_2CH_3	1.40	9.3		1.41	4.4		2.32	11.1	
Phenoxy	CH_3	1.30	6.8		1.40	4.2		1.39	12.0	
2-Phenoxyethyl	CH_3	1.30	4.8		1.10	3.1		1.40	8.4	

*,**,*** Footnotes as in Table I.

arm (or solid support) of the chiral stationary phase can lessen the contribution of process A. This effect increases with longer alkyl tails or shorter connecting arms. As the contribution of process A lessens, process B, by default, becomes relatively more significant. Since process A selectively retains the (*R*)-enantiomers of 3,5-dinitrobenzoyl derivatives of α-arylalkylamines whereas process B selectively retains the (*S*)-enantiomers, the shapes of the curves in Fig. 1 are explained. One might additionally ask why the urea linkage causes earlier "inversion of elution order" than does the amide linkage. One expects the urea functionality to be conformationally "stiffer" than an amide, an effect which should be important to steric interactions, and to be more effectively solvated by the isopropanol in the mobile phase. The greater size of the solvated urea linkage than the solvated amide linkage would be expected to accentuate steric repulsion. Both effects would tend to suppress process A relative to process B.

A similar situation was observed in the resolution of N-(3,5-dinitrobenzoyl)-α-amino acid esters. In the resolution of these compounds, chiral recognition process B is dominant because of the additional hydrogen bonding site (*i.e.* the ester carbonyl oxygen)[5]. Increasing the length of the ester alkoxy tail also lessens the contribution of process A and, by default, makes the contribution of process B relatively more important. Therefore, as the ester's alkoxy tails become longer, the magnitudes of the observed α values increase as shown in Fig. 3. The corresponding chromatographic data are summarized in Table II.

For the reasons mentioned above, urea-linked chiral stationary phases show somewhat larger α values for the resolution of N-3,5-dinitrobenzoylamino acid esters than do the corresponding amide-linked chiral stationary phases. Moreover, the influence of the length of alkyl (or alkoxy) "tails" on the magnitude of the analyte α values is much more significant on the "short-armed" urea-linked phases.

In Table III are summarized data obtained on the urea-linked chiral stationary phases for the resolution of other types of analytes such as N-3,5-dinitrobenzoyl derivatives of α-amino acid amides, amino alcohols, secondary alkylamines and aminophosphonates and 3,5-dinitroanilide derivatives of chiral carboxylic acids. In each case, enantiomer separation is relatively easy.

In summary, we have provided further evidence that the urea linkage is a reasonable means of connecting a chiral moiety to a silica support. Through direct comparison with previously reported amide-linked chiral stationary phases, we think that the rigid, polar urea linkages exert some control upon the balance-point between the two competing chiral recognition processes, and that this mechanistic insight may provide further guidance in the rational design of chiral stationary phases.

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