Journal of Chromatography, 322 (1985) 309–320
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 17,526

PREPARATION AND USE OF HYDANTOIN-BASED CHIRAL STATIONARY PHASES*

WILLIAM H. PIRKLE* and MYUNG HO HYUN
Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, IL 61801 (U.S.A.)
(Received January 2nd, 1985)

SUMMARY

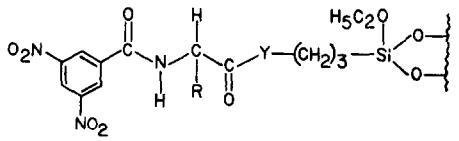
Starting from α-naphthyl 4-pentenyl ketone, hydantoin-based chiral stationary phase 6a has been prepared. Chiral stationary phase 6a has proven to be quite effective for the separation of the enantiomers of hundreds of 3,5-dinitrobenzamides derived from amino acids, amino esters, amino amides, amino phosphonates, amino alcohols and amines. A chiral recognition model involving three simultaneous stereochemically-dependent interactions is advanced to account for the observed elution orders of the enantiomers. On the basis of the chiral recognition model, a rational improvement was made in the design of the hydantoin chiral stationary phase. For example, enhancing the π-basicity of the naphthyl system [chiral stationary phase 6b, derived from (*R*)-5-(6,7-dimethyl-1-naphthyl)-5-(5-triethoxysilyl)hydantoin] has led to significantly improved performance relative to phase 6a, which lacks the 6,7-dimethyl groups. Ring-alkylated chiral stationary phase 6c has also been prepared and evaluated relative to phase 6a.

INTRODUCTION

As a means of determining enantiomeric purity, direct separation of enantiomers by modern chromatographic methods has no equal for accuracy and sensitivity. However, such separations require the intervention of some chiral agent such as a chiral stationary phase or a chiral mobile phase. We have been involved in a systematic study of chiral stationary phases and the chiral recognition mechanisms by which they operate. A series of N-(3,5-dinitrobenzoyl)-α-amino acid-derived chiral stationary phases, 1, some now commercially available, have proven to be effective for determination of enantiomer purity, absolute configuration, and preparative-scale separation of a wide variety of enantiomers[1–4]. Moreover, these phases can serve as guides for the development of other highly effective chiral stationary phases. Chiral recognition is a reciprocal process, and, in principle, any enantiomer from one of the thousands of racemates which are resolvable on type 1 chiral stationary phases can, in turn, be used to prepare a reciprocal chiral stationary phase capable of separating the enantiomers of N-(3,5-dinitrobenzoyl)-α-amino acids and related compounds. In

* Part of this study has been presented at the *185th ACS National Meeting, Seattle, WA, U.S.A., March 20–25, 1983.*

0021-9673/85/$03.30



1a: R = Phenyl, Y = $-O^-N^+H_3-$
1b: R = Phenyl, Y = –NH–
1c: R = Isobutyl, Y = –NH–

the interest of performance and scope, only those enantiomers which themselves show efficient chiral recognition (when chromatographed on type 1 chiral stationary phases) are selected for incorporation into reciprocal chiral stationary phases. The soundness of this rationale has been demonstrated by the preparation of highly effective and widely applicable α-arylalkylamine based chiral stationary phases[5,6]. In this paper we describe the preparation and evaluation of chiral stationary phases derived from 5-arylhydantoins. Such hydantoins are attractive candidates for incorporation into reciprocal chiral stationary phases owing both to their high separability on type 1 phases[2,3] and to their relatively easy preparation. Our initial selection of 5-α-naphthyl-5-(4-pentenyl) hydantoin, 3a, was based on the observation that hydantoins bearing both naphthyl and long alkyl substituents at the 5-position are readily resolvable on type 1 chiral stationary phases[2,3]. A terminal double bond is included in the alkyl substituent so that, after hydrosilylation, the chiral silane may be bonded to the silica support. This mode of attachment was hoped to have little effect on the chiral recognition process.

EXPERIMENTAL

General

Melting points were taken on a Büchi apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM-390 spectrometer. IR spectra are recorded on a Perkin-Elmer 1320 or Nicolet 7199 FT-IR spectrometer. Micro-analyses were performed by the Micro-analytical Laboratory, University of Illinois, Urbana-Champaign. High-resolution mass spectra were obtained on a Varian 731 mass spectrometer. 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 column as methanol slurrys. Chromatography was performed using an Altex 100A pump, and Altex 210 injector, an Altex model 165 variable-wavelength UV detector and a Kipp & Zonen BD 41 recorder. Preparative resolution of the hydantoins used in this study[4] as well as the preparation of solutes[6] has been previously reported.

1-Naphthyl 4-pentenyl ketone (2a)

This ketone was prepared by the procedure used for the preparation of ketone 2b, reported elsewhere[5]. Yield 87%, a pale yellow liquid. ^1H NMR (C^2HCl_3) δ 1.70–2.30 (m, 4H), 3.03 (t, 2H), 4.90–5.15 (m, 2H), 5.60–6.03 (m, 1H), 7.30–8.60 (m, 7H); IR (neat) cm^{-1} 3080, 2950, 1720, 1690, 1515. High-resolution mass spectrum calculated for $C_{16}H_{15}O$: 224.1193; found: 224.1197.

5-(1-Naphthyl)-5-(4-pentenyl)hydantoin (3a)

To 50 ml of ethanol in a 200 ml hydrogenation pressure bottle with a magnetic stirring bar was added 3.5 g (0.016 mol) of ketone 2a. To this was added a solution of potassium cyanide (3.05 g, 0.047 mol) and ammonium carbonate (9 g, 0.094 mol) in water (50 ml) and an additional 50 ml of ethanol. The pressure bottle was sealed, heated to 65–70°C for 10 days while being stirred magnetically. After being cooled to room temperature, the reaction mixture was evaporated to about one-third volume, 30 ml of water was added and the solution was twice extracted with ethyl acetate (80 ml). The organic layer was washed with 100 ml of water and dried over anhydrous magnesium sulfate. The residue was purified by flash chromatography to give 3.22 g (70%) of white solid as a final product. Starting material 2a was also recovered (1.10 g, 29%). m.p. 185–186°C; ^{1}H NMR ($C^2H_2Cl_2$) δ 1.30–1.70 (m, 2H), 1.90–2.15 (m, 2H), 2.25–2.60 (m, 2H), 4.80–5.10 (m, 2H), 5.50–5.90 (m, 1H), 6.78 (s, 1H), 7.30–8.20 (m, 7H), 8.90 (s, 1H). When two drops of ^2H_2O were added, the peaks at 6.78 and 8.90 ppm disappeared. IR (KBr) cm^{-1} 3400, 3250, 3070, 1730. Analysis calculated for $C_{18}H_{18}N_2O_2$: C, 73.47; H, 6.12; N, 9.52; found: C, 73.51; H, 6.21; N, 9.60.

5-(6,7-Dimethyl-1-naphthyl)-5-(4-pentenyl)hydantoin (3b)

Hydantoin 3b was prepared from ketone 2b by the procedure used to prepare hydantoin 3a. Reaction time was 12 days. The yield of product was 49%; 49% of the starting material was also recovered. m.p. 205–207°C; ^{1}H NMR ($C^2H_3O^2H$) δ 1.40–1.70 (m, 2H), 2.03–2.27 (m, 2H), 2.46 (s, 3H), 2.50 (s, 3H), 2.37–2.57 (m, 2H), 4.90–5.10 (m, 2H), 5.57–6.03 (m, 1H), 7.03–7.40 (t, 1H), 7.57–7.77 (m, 3H), 8.03 (s, 1H); IR (KBr) cm^{-1} 3450, 3290, 1770, 1720, 1640, 1500. Analysis calculated for $C_{20}H_{22}N_2O_2$: C 74.50; H, 6.88; N, 8.69; found: C, 74.13; H, 6.80; N, 8.79.

Resolution of racemic hydantoins 3a and 3b

Hydantoins 3a and 3b were resolved on a preparative column containing chiral stationary phase 1a as reported previously[4]. High-R_F enantiomer (*R*)-3a: see ref. 5; low-R_F enantiomer (*S*)-3a: m.p. 198–199°C, $[\alpha]_D$ + 6.2 (c 0.81, ethyl acetate). High-R_F enantiomer (*R*)-3b: m.p.. 245–247°C, $[\alpha]_D$ + 70.0 (c 0.09, ethyl acetate); Low-R_F enantiomer (*S*)-3b: m.p. 246–247°C, $[\alpha]_D$ − 69.7 (c 0.35, ethyl acetate).

Racemic 1-methyl-5-(1-naphthyl)-5-(4-pentenyl)hydantoin (racemic 4a)

Racemic hydantoin 3a (1.47 g, 0.005 mol) was dissolved in 50 ml of dry tetrahydrofuran and cooled to 0°C under a nitrogen atmosphere. To the cool solution was added dropwise 8.5 ml of *n*-BuLi solution (2.2 *M* in hexane) and the deep brown solution was stirred at 0°C for 30 min. To the stirred solution was added dropwise 1.12 g (0.0175 mol) of methyl iodide in 10 ml dry tetrahydrofuran. This reaction was monitored by thin-layer chromatography [silica, methylene chloride–ethyl acetate (10:1)]. After stirring the reaction mixture at 0°C for 3.5 h, almost all starting material was gone. The reaction was quenched with saturated ammonium chloride solution and tetrahydrofuran was removed under reduced pressure. The aqueous solution was twice extracted with methylene chloride, the organic layers were combined, washed with water, and then dried over anhydrous magnesium sulfate. Finally, the desired 1-methylated hydantoin was isolated by flash column chromatography, affording

1.40 g (91%) of white solid. m.p. 179–182°C; ^{1}H NMR (C^2HCl_3) δ 1.40–1.73 (m, 2H), 2.03–2.50 (m, 4H), 2.62 (s, 3H), 5.00–5.20 (m, 2H), 5.57–6.00 (m, 1H), 7.37–7.90 (m, 7H), 8.60 (broad s, 1H); IR (KBr) cm^{-1} 3460, 1773, 1718. Analysis calculated for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09; found: C, 73.83; H, 6.52; N, 9.14. In the above reaction, 1,3-dimethyl-5-(1-naphthyl)-5-(4-pentenyl)hydantoin was obtained in 6% yield. m.p. 139–141°C; ^{1}H NMR (C^2HCl_3) δ 1.13–1.47 (m, 2H), 2.00–2.30 (m, 2H), 2.31–2.50 (m, 2H), 2.60 (s, 3H), 3.20 (s, 3H), 4.90–5.13 (m, 2H), 5.50–6.00 (m, 1H), 7.30–7.87 (m, 7H); IR (KBr) cm^{-1} 2940, 1768, 1713. Analysis calculated for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.88; N, 8.68; found: C, 74.63; H, 6.97; N, 8.88.

(S)-1-Methyl-5-(1-naphthyl)-5-(4-pentenyl)hydantoin [(S)-4a]

Enantiomerically pure hydantoin (*S*)-3a was methylated by the procedure described above. m.p. 203–205°C; $[\alpha]_D$ + 26.7 (c 0.92, CH_2Cl_2).

Racemic 1-ethyl-5-(1-naphthyl)-5-(4-pentenyl)hydantoin (racemic 4b)

This compound was prepared by the procedure described for the 1-methylated hydantoin, 4a, except that the reaction was carried out under reflux for 1 h. Yield was 50%. m.p. 208–210°C; ^{1}H NMR (C^2HCl_3) δ 0.78 (t, 3H), 1.43–1.70 (m, 2H), 2.02–2.30 (m, 2H), 2.33–2.57 (m, 2H), 3.05 (q, 2H), 4.97–5.20 (m, 2H), 5.50–6.03 (m, 1H), 7.37–7.93 (m, 7H), 8.50 (broad s, 1H); IR (KBr) cm^{-1} 1760, 1720. High-resolution mass spectrum calculated for $C_{20}H_{22}H_2O_2$: 322.1681; found 322.1680.

(R)-5-(1-Naphthyl)-5-(5-triethoxysilylpentyl)hydantoin (5a)

Hydrosilylation of (*R*)-3a was carried out by using triethoxysilane and a catalytic amount of chloroplatinic acid as described previously[6]. Pale yellow viscous oil (53.5%). ^{1}H NMR (C^2HCl_3) δ 0.60 (t, 2H), 1.20 (t, 9H), 1.20–1.50 (m, 6H), 2.30–2.60 (m, 2H), 3.80 (q, 6H), 7.04 (s, 1H), 7.20–8.20 (m, 7H), 9.20 (s, 1H); IR (Neat) cm^{-1} 3230, 3060, 2975, 2930, 2895, 1772, 1720, 1512. High-resolution mass spectrum calculated for $C_{24}H_{34}N_2O_5Si$: 458.2245; found: 458.2241.

(R)-5-(6,7-Dimethyl-1-naphthyl)-5-(5-triethoxysilyl)hydantoin (5b)

White solid (50%). m.p. 201–203°C; ^{1}H NMR (C^2HCl_3) δ 0.47–0.70 (m, 2H), 1.20 (t, 9H), 1.25–1.50 (m, 4H), 2.30–2.57 (broad, 8H), 3.75 (q, 6H), 6.80 (s, 1H), 7.10–7.80 (m, 5H), 8.80 (s, 1H); IR (KBr) cm^{-1} 3280, 3218, 2975, 2928, 1770, 1722, 1500. High-resolution mass spectrum calculated for $C_{26}H_{38}N_2O_5Si$: 486.2550; found: 486.2559. $[\alpha]_D$ + 36.8 (c 0.62, CH_2Cl_2).

(S)-1-Methyl-5-(1-naphthyl)-5-(5-triethoxysilyl)hydantoin (5c)

White solid (55.4%). m.p. 71–74°C; ^{1}H NMR (C^2HCl_3) δ 0.67 (t, 2H), 1.27 (t, 9H), 1.33–1.57 (m, 4H), 2.30–2.60 (m, 2H), 2.52 (s, 3H), 3.80 (q, 6H), 7.37–7.93 (m, 7H), 8.50 (s, 1H); IR (KBr) cm^{-1} 3450, 3200, 2976, 2930, 1774, 1730, 1720. High-resolution mass spectrum calculated for $C_{25}H_{36}N_2O_5Si$: 472.2393; found: 472.2397. $[\alpha]_D$ + 16.7 (c 0.52, CH_2Cl_2).

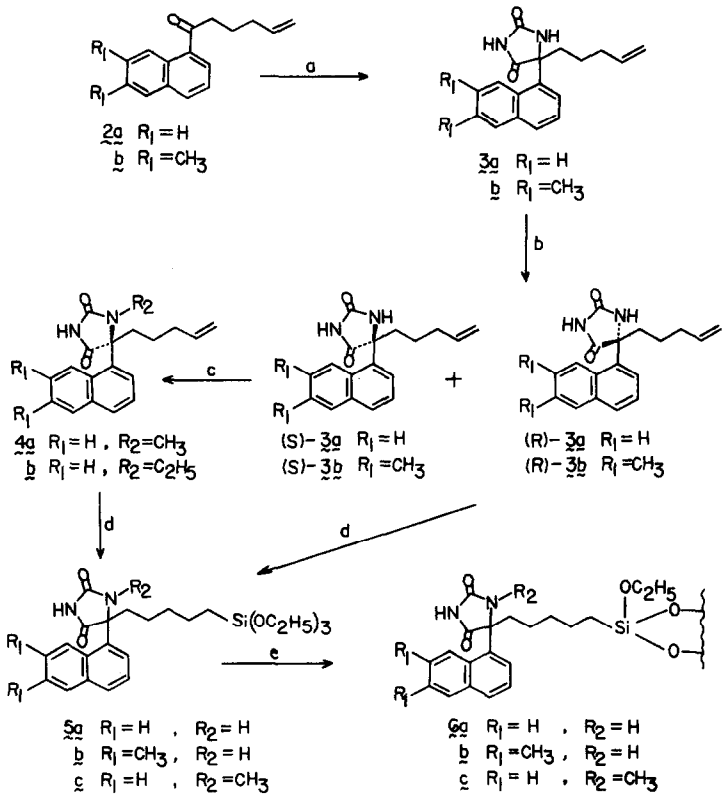
Chiral stationary phases 6a, 6b and 6c

An amount of 5 g of Spherisorb silica gel (5 μm) was slurried with 50 ml of

toluene in a 250-ml three-neck flask equipped with a Dean-Stark trap, magnetic stirrer, and a nitrogen atmosphere, and heated to reflux to remove water azotropically. After removing all water, 6 mmol of hydrosilylated hydantoin was added and the gently stirred slurry was maintained at reflux for 35 h under a nitrogen atmosphere. The modified silica gel was isolated by filtration and washed with toluene, ethyl acetate, methanol, acetone, diethyl ether and pentane. Phase 6a: analysis found: C, 11.29; H, 1.27; N, 1.38; Si, 39.56; calculated: 0.49 mmol/g of chiral stationary phase (based on N); 0.47 mmol/g of chiral stationary phase (based on C). Phase 6b: analysis found: C, 9.04; H, 1.06; N, 0.94; Si, 40.61; calculated: 0.34 mmol/g of chiral stationary phase (based on N); 0.34 mmol/g of chiral stationary phase (based on C). Phase 6c: analysis found: C, 8.83; H, 0.92; N, 1.00; Si, 40.35; calculated: 0.36 mmol/g of chiral stationary phase (based on N); 0.35 mmol/g of chiral stationary phase (based on C).

RESULTS AND DISCUSSION

Reciprocal hydantoin-based chiral stationary phase 6a, bonded to 5-μm Spherisorb silica gel, was prepared starting from ketone 2a (Scheme 1). Heating a 65%



Scheme 1. (a) Potassium cyanide ammonium carbonate 65% ethanol, 65°C. (b) Resolution upon phase 1a. (c) *n*-BuLi, methyl iodide (or ethyl iodide), tetrahydrofuran, 0°C (reflux for ethyl iodide). (d) Triethoxysilane, chloroplatinic acid, 110–130°C. (e) 5-μm Silica gel, toluene, reflux.

ethanolic solution of ketone 2a, potassium cyanide, and ammonium carbonate to 65–70°C in a sealed but stirred pressure bottle for 10 days gives hydantoin 3a in 70% yield. Hydantoin 3a was chromatographically resolved on a preparative 1a column[4] and the (*R*)-3a (the absolute configuration was determined from the elution order from 1a) was treated with excess triethoxysilane and a catalytic amount of chloroplatinic acid at 110–130°C to afford hydrosilylated hydantoin (*R*)-5a. Finally, chiral silane (*R*)-5a was bonded to 5 μm Spherisorb silica gel by heating the two in toluene at reflux for 35 h. The resulting chiral stationary phase 6a was slurry packed into a 250 × 4.6 mm I.D. stainless-steel column using conventional methods.

Hydantoin-based chiral stationary phase 6a is quite effective for the resolution of 3,5-dinitrobenzamides derived from α-amino acids, α-amino acid esters, α-amino acid amides, amino alcohols, α-amino phosphonates and α-arylalkylamines. Data pertinent to a number of these resolutions are summarized in Table I. Elution orders were established by chromatographing samples derived from configurationally known compounds.

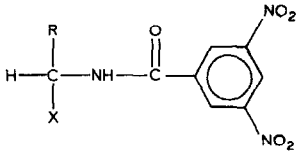
With the exception of the α-arylalkylamines, the X substituents of the solutes in Table I contain electronegative functionality near the chiral center. To summarize the data reported for resolutions of these compounds, an increase in the length of the alkyl portion of the electronegative X substituent diminishes the efficiency of the chiral recognition process as reflected by the diminuation of the separability factor, α. However, for the α-arylalkylamines where X is a simple alkyl group, its length has little effect on the magnitude of α. Elution orders are consistent. In every case where configurationally known samples are available, the (*S*)-enantiomers elute last except in the case of the N-3,5-dinitrobenzoyl-α-arylalkylamines. Here, the apparently "inverted" elution orders actually stem from the "inversion" of the substituent priority sequence about the chiral center. There is no clear trend in the magnitude of the α values as the size or length of the R substituent is altered.

A chiral recognition model capable of explaining most of the experimental observations is shown in Fig. 1. Chiral recognition requires at least three simultaneous interactions between the chiral stationary phase and a solute enantiomer, at least one of these interactions being stereochemically dependent[7]. More than three interactions can be used, of course. In Fig. 1, the analyte enantiomer is shown in its most stable solution conformation. Note that the carbonyl oxygen of the 3,5-dinitrobenzoyl group is essentially eclipsed with the aminyl hydrogen. The preferential occurrence of this type of conformation has been corroborated by NMR studies[8] and by X-ray crystallography[9] for similar amides. In Fig. 1, the analyte is positioned with respect to the chiral stationary phase so that the essential simultaneous interactions may be visualized. The first of these is suggested to be π–π interaction between the α-naphthyl group of the chiral stationary phase and the 3,5-dinitrobenzoyl group of the analyte. Secondly, electrostatic interaction (either hydrogen bonding or dipole alignment) is postulated to occur between the 4-carbonyl of the hydantoin and the amide functionality of the analyte. One can also visualize electrostatic interaction between the hydantoin NH at the 1-position and the dinitrobenzoyl carbonyl oxygen. Clearly, this interaction would be quite dependent on the dihedral angle between the hydantoin ring and its α-naphthyl substituent. Finally, the formation of a hydrogen bond between the hydantoin imide hydrogen and the electronegative X group of the analyte is suggested. The stereochemical dependence of this interaction is easily visu-

TABLE I

RESOLUTION OF ENANTIOMERIC 3,5-DINITROBENZAMIDES ON HYDANTOIN-BASED CHIRAL STATIONARY PHASES

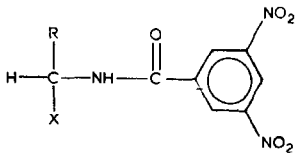
α = Chromatographic separation factor.



		Chiral stationary phase								
		6a			*6b*			*6c*		
		α	k'*	*Configuration***	α	k'*	*Configuration***	α	k'*	*Configuration***
R	*X*									
Isopropyl	COOH	1.37	2.7(1)	*S*	1.42	6.8(1)	*S*	1.27	1.2(2)	*S*
Isobutyl	COOH	1.37	4.6(1)	*S*	1.39	10.8(1)	*S*	1.28	2.4(1)	*S*
n-Butyl	COOH	1.42	5.8(1)	*S*	1.51	16.3(1)	*S*	1.29	2.4(1)	*S*
sec.-Butyl	COOH	1.55	4.1(1)	*S*	1.52	10.0(1)	*S*	1.32	1.7(1)	*S*
Phenyl	COOH	1.44	7.2(1)	*S*	1.46	14.4(1)	*S*	1.29	2.8(1)	*S*
Methyl	$COOCH_3$	1.38	12.7(2)	*S*	2.35	9.8(3)	*S*	1.07	14.7(2)	*R*
	$COOCH_2CH_3$	1.29	8.2(2)	*S*	2.16	6.0(3)	*S*	1.00	9.1	
	COO-Isopropyl	1.27	5.4(2)	*S*	2.06	3.8(3)	*S*	1.00	6.0	
Isopropyl	$COOCH_3$	1.29	3.2(2)	*S*	1.90	5.5(3)	*S*	1.12	9.7(2)	*R*
Isobutyl	$COOCH_3$	1.40	2.3(2)	*S*	2.04	3.4(3)	*S*	1.16	5.9(2)	*R*
Phenyl	$COOCH_3$	1.39	5.2(2)	*S*	1.94	7.1(3)	*S*	1.00	4.3	
	COO-*n*-Butyl	1.21	3.5(2)	*S*	1.59	4.1(3)	*S*	1.13	6.2(2)	*S*
	COO-*n*-Pentyl	1.17	3.4(2)	*S*	1.50	3.7(3)	*S*	1.16	5.4(2)	*S*
	COO-*n*-Heptyl	1.13	3.2(2)	*S*	1.39	3.3(3)	*S*	1.20	4.6(2)	*S*
	COO-*n*-Decyl	1.11	2.9(2)	*S*	1.33	3.0(3)	*S*	1.23	4.0(2)	*S*
Benzyl	$COOCH_3$	1.34	8.7(1)	*S*	1.98	7.7(3)	*S*	1.13	9.6(2)	*R*
	$COOCH_2CH_3$	1.31	8.0(2)	*S*	2.07	7.1(3)	*S*	1.12	9.8(2)	*R*
	COO-*n*-Butyl	1.14	4.6(2)	*S*	1.51	4.0(3)	*S*	1.00	4.6	
	COO-*n*-Heptyl	1.00			1.28	3.2(3)	*S*	1.00	3.5	
	COO-*n*-Decyl	1.00			1.24	2.9(3)	*S*	1.00	3.0	
Isopropyl	CONH-*n*-Butyl	1.38	4.6(2)	*S*	1.66	2.6(3)	*S*	1.21	2.8(2)	*S*
Isobutyl	CONH-*n*-Butyl	1.23	4.0(2)	*S*	1.70	2.2(3)	*S*	1.27	2.1(2)	*S*
Phenyl	CONH-*n*-CH_3	1.62	5.0(2)	*S*	2.39	10.1(3)	*S*	1.18	10.4(2)	*S*
	CONH-*n*-Butyl	1.49	5.6(2)	*S*	2.00	4.0(3)	*S*	1.28	4.3(2)	*S*
	CONH-*n*-Hexyl	1.44	4.4(2)	*S*	1.78	3.1(3)	*S*	1.30	3.4(2)	*S*
	CONH-*n*-Octyl	1.42	3.8(2)	*S*	1.70	2.6(3)	*S*	1.31	2.7(2)	*S*
	CONH-*n*-Decyl	1.42	3.4(2)	*S*	1.63	2.5(3)	*S*	1.29	2.6(2)	*S*

(Continued on p. 316)

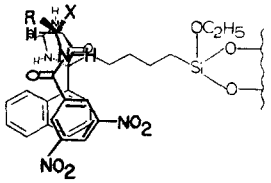
TABLE I *(continued)*



		Chiral stationary phase								
		6a			*6b*			*6c*		
		α	*k'**	*Configuration***	α	*k'**	*Configuration***	α	*k'**	*Configuration***
R	***X***									
$CH_3SCH_2CH_2$	CONH-*n*-Butyl	1.62	9.9(2)	*S*	2.31	4.9(3)	*S*	1.16	6.0(2)	*S*
Benzyl	CONH-*n*-Butyl	1.19	6.9(2)	*S*	1.56	4.3(3)	*S*	1.29	4.1(2)	*S*
Methyl	CH_2OH	1.59	16.9(2)	*S*	1.91	9.8(3)	*S*	1.26	15.7(2)	*S*
Ethyl	CH_2OH	1.86	10.1(2)	*S*	2.11	5.8(3)	*S*	1.20	10.0(2)	*S*
	CH_2PCH_3	1.38	8.4(2)	*S*	1.49	5.8(3)	*S*	1.08	8.8(2)	*S*
	$CH_2PCH_2CH_3$	1.15	6.0(2)		1.21	4.8(3)		1.10	5.6(2)	
Isopropyl	CH_2OH	1.84	7.3(2)	*S*	2.00	4.1(3)	*S*	1.25	7.3(2)	*S*
Isobutyl	CH_2OH	1.59	4.8(2)	*S*	1.70	3.3(3)	*S*	1.16	4.8(2)	*S*
Phenyl	CH_2OH	2.08	11.5(2)	*S*	2.53	7.1(3)	*S*	1.17	11.4(2)	*S*
$CH_3SCH_2CH_2$	CH_2OH	1.70	17.9(2)	*S*	1.80	10.6(3)	*S*	1.20	16.6(2)	*S*
 HO NHDNB (*trans*)		1.25	18.1(2)	*S*	1.39	11.0(3)		1.19	18.5(2)	
Phenyl	O	1.40	10.0(2)		1.68	7.1(3)		1.53	6.2(2)	
4-Methylphenyl	‖	1.24	8.4(2)		1.45	5.9(3)		1.49	4.8(2)	
4-Methoxyphenyl	$P(OC_2H_5)_2$	1.38	15.6(2)		1.64	10.4(3)		1.52	8.7(2)	
4-Cl-Phenyl		1.00	10.1(2)		1.08	7.9(3)		1.35	5.5(2)	
Phenyl	CH_3	1.25	7.1(2)	*R*	1.23	5.9(3)	*R*	1.00	13.4(2)	
	CH_2CH_3	1.19	6.5(2)		1.15	4.0(3)		1.00	14.3(2)	
	$(CH_2)_2CH_3$	1.17	5.7(2)		1.13	3.3(3)		1.05	10.9(2)	
	$(CH_2)_3CH_3$	1.13	5.2(2)		1.06	3.1(3)		1.08	9.0(2)	
	$(CH_2)_4CH_3$	1.12	4.7(2)		1.08	2.7(3)		1.11	8.3(2)	
	$(CH_2)_5CH_3$	1.14	4.5(2)		1.08	2.6(3)		1.13	7.6(2)	
	$(CH_2)_6CH_3$	1.14	4.1(2)		1.09	2.4(3)		1.15	6.9(2)	
	$(CH_2)_7CH_3$	1.15	3.9(2)		1.08	2.4(3)		1.16	6.4(2)	
	$(CH_2)_8CH_3$	1.15	3.9(2)		1.07	2.3(3)		1.17	6.3(2)	

	$(CH_2)_9CH_3$	1.14	3.7(2)		1.12	2.1(3)		1.18	6.0(2)	
	$(CH_2)_{10}CH_3$	1.15	3.7(2)		1.11	2.1(3)		1.18	6.0(2)	
	$(CH_2)_{12}CH_3$	1.14	3.4(2)		1.09	2.0(3)		1.19	5.4(2)	
	$(CH_2)_{14}CH_3$	1.15	3.2(2)		1.08	2.0(3)		1.19	5.1(2)	
	$(CH_2)_{16}CH_3$	1.14	3.1(2)		1.09	1.9(3)		1.20	5.0(2)	
4-Methoxyphenyl	CH_3	1.25	8.3(2)	*R*	1.29	7.1(3)	*R*	1.00	10.4(2)	*R*
1-Naphthyl	CH3	1.21	9.6(2)	*R*	1.23	6.3(3)	*R*	1.08	13.7(2)	*R*
2-Naphthyl	CH_3	1.22	10.7(2)	*R*	1.25	7.1(3)	*R*	1.05	17.1(2)	*R*
Benzyl	CH_3	1.08	6.6(2)	*R*	1.00	3.4(3)		1.13	4.1(2)	*S*

* Capacity ratio for the first eluted enantiomer. The mobile phase noted in the parentheses is:
(1) 20% methanol–water (0.3% $KHCO_3$) (20:80);
(2) 2-propanol–hexane (10:90);
(3) 2-propanol–hexane (20:80).
** Absolute configuration of the second eluted enantiomer.



X = COO^-, COOR, CONHR, CH_2OH, CH_2OH, CH_2OR, $PO(OC_2H_5)_2$, alkyl.
R = Aryl, alkyl.

Fig. 1. Chiral recognition model for enantiomeric 3,5-dinitrobenzamides on the hydantoin-based chiral stationary phase. The most stable diastereomeric adsorbate is shown.

alized. While maintaining the other bonding interactions, imagine the consequences of interchanging the R group and the methine hydrogen of the depicted analyte enantiomer. This would result in the larger R group being eclipsed with the dinitrobenzoyl carbonyl, clearly a higher energy situation. Hence, the depicted analyte enantiomer is the more strongly retained. Analytes lacking an electronegative X substituent may use steric interactions as an alternative to the aforementioned hydrogen-bond interaction. For example, when X is an alkyl group, it may sterically interact with the imide functionality of the chiral stationary phase. Again the stereochemically dependent nature of the third interaction is easily visualized. Imagine in Fig. 1 that the R and X groups are interchanged. Depending upon whether X or R undergoes the least steric repulsion (or, in the case of an electronegative X group, the most attraction) toward the chiral stationary phase, the diastereomeric adsorbate presenting that group toward the imide hydrogen will be most stable and the enantiomer incorporated into that adsorbate will be most strongly retained. For the series of α-arylalkylamine derivatives, aromatic R groups are apparently "larger" than linear alkyl groups, regardless of the length of the alkyl group.

The preceding model rationalizes the observed elution orders and affords a qualitative view of the relationship between structure and the magnitude of α, the separability factor for the enantiomers. An increase in the length of the X substituent is believed to increase steric repulsion with the imide region of the chiral stationary phase, thus weakening bonding interactions (when X is electronegative) or lessening the perceived size difference between X and R. Thus, α diminishes as the length of the X group is increased. However, the point of diminishing returns is soon reached; long X groups are not significantly more deleterious than are X groups of intermediate length. This observation is significant; for, if the X group were directed toward the silica support, long X groups would have noticeable impact.

On the basis of the chiral recognition model proposed, rational improvements in the design of the hydantoin-based chiral stationary phase may be made. For example, enhancing the strength of one of the three simultaneous interactions should enhance chiral recognition. One possible improvement would be to increase the π-basicity of the naphthyl system of the chiral stationary phase by adding methyl substituents[10]. Accordingly, phase 6b was prepared (Scheme 1) and found to generally afford enhanced chiral recognition as evidenced by the larger enantiomeric separability factors (Table I).

Another interesting feature of the chiral recognition model shown in Fig. 1 is that the amide hydrogen at the 1-position of the hydantoin ring does not appear to be involved in chiral recognition. Indeed, this amide hydrogen was suspected of reducing chiral recognition by participating in interactions which retain both enantiomers without discrimination, thus leading to longer retention and diminuation of α.

The resolution of 1-methyl and 1-ethyl hydantoins, racemic 4a, b shows (Table II) that the hydantoin amide hydrogen is not essential to chiral recognition. Indeed, the α values are slightly larger than that of the unalkylated parent. However, alkylation of the imide nitrogen does interfere with chiral recognition, for the imide hydrogen does interact with the carboxyl group of chiral stationary phase 1b[11].

TABLE II

RESOLUTION OF 1-SUBSTITUTED HYDANTOINS ON CHIRAL STATIONARY PHASE 1b

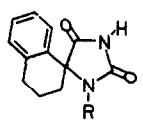
α = Chromatographic separability factor. k'_1 = Capacity factor for the first eluted enantiomer. The mobile phase was 2-propanol–hexane (20:80).

Hydantoin	α	k'_1**
3a	1.39	11.6
Racemic 4a	1.51	9.9
Racemic 4b	1.47	8.8

To investigate the effect of alkylation of the amide nitrogen, chiral stationary phase 6c was prepared from enantiomerically pure (*S*)-hydantoin 3a, as shown in Scheme 1. (*S*)-Hydantoin 3a was selectively methylated at the 1-position, hydrosilylated, and attached to silica gel to afford phase 6c. Data relevant to the resolution of racemates on chiral stationary phase 6c is contained in Table I and may be compared to similar data for the other two chiral stationary phases*. One seldom observes the expected superiority of phase 6c relative to phase 6a. Moreover, elution orders and trends of α values are dissimilar in several cases. Clearly, the methylation has lead to unexpected results. A significant difference between phases 6a and 6c requires comment. The enantiomers of esters of the dinitrobenzoyl derivatives of alanine and phenylalanine elute in opposite order from the two columns and, as the length of the alkyl portion of alkoxyl group increases, α diminishes. However, for esters and amides of N-(3,5-dinitrobenzoyl)phenylglycine, the columns show the same order of elution and an increase in the length of the alkoxy (or amide) alkyl group enhances α on chiral stationary phase 6c but diminishes α on phase 6a. This behavior suggests strongly that hydantoin phase 6c has available to it two chiral recognition mechanisms which work in opposite stereochemical senses. A similar situation has been noted recently for a series of reciprocal chiral amide stationary phases[5]. Because amide analytes may interact with amide stationary phases in several different ways (dipole stacking, several modes of hydrogen bonding), one should not be surprised

* To avoid confusion concerning elution orders (chiral stationary phases 6a and 6c have opposite absolute configuration), the elution orders reported in Table I for phase 6c are inverted with respect to what was actually observed. The discussion also considers phase 6c to have the *same* configuration as 6a.

if systematic studies of such systems reveal the operation of multiple chiral recognition mechanisms. In such systems, seemingly subtle structural changes, by altering the balance point between competing chiral recognition mechanisms, can manifest themselves in a pronounced manner. By alkylating the 1-nitrogen, one replaces the small hydrogen with a larger substituent, a change which may have non-trivial conformational consequences. This substitution might be expected to alter the average dihedral angle between the planes of the hydantoin and naphthalene rings, a change which could allow a second and competing chiral recognition process to make a significant contribution to the overall chromatographic behavior. It seems likely that a chiral stationary phase derived from a conformationally rigid hydantoin, perhaps 7, could be helpful in elaboration of this point.



7

The hydantoin chiral stationary phases may be used in the reversed-phase mode as well. Table I contains data relevant to the resolution of N-(3,5-dinitrobenzoyl)-amino acids using aqueous methanol buffered with bicarbonate. Elution orders are identical on all three chiral stationary phases and correspond to those observed (on phases 6a and 6b) for the corresponding esters. Although chiral stationary phase 6c is again inferior to phase 6a, phase 6b does not show its usual superiority to phase 6a. The chiral recognition mechanism presented in Fig. 1 accounts for the observed reversed-phase elution orders as well.

ACKNOWLEDGEMENT

This work was partially supported by grants from the National Science Foundation and the Eli Lilly Company.

REFERENCES

1 W. H. Pirkle, D. W. House and J. M. Finn, *J. Chromatogr.*, 192 (1980) 143.
2 W. H. Pirkle, J. M. Finn, J. L. Schreiner and B. C. Hamper, *J. Amer. Chem. Soc.*, 103 (1981) 3964.
3 W. H. Pirkle, J. M. Finn, B. C. Hamper, J. L. Schreiner and J. R. Pribish, in E. L. Eliel and S. Otsuka (Editors), *Asymmetric Reactions and Processes in Chemistry*, ACS Symposium Series, No. 185, American Chemical Society, Washington, DC, 1982, pp. 245–260.
4 W. H. Pirkle and J. M. Finn, *J. Org. Chem.*, 47 (1982) 4037.
5 W. H. Pirkle, M. H. Hyun and B. Bank, *J. Chromatogr.*, 316 (1984) 585.
6 W. H. Pirkle and M. H. Hyun, *J. Org. Chem.*, 49 (1984) 3043.
7 C. E. Dalgliesh, *J. Chem. Soc.*, 137 (1952) 3940.
8 G. Helmchen, H. Völter and W. Schüle, *Tetrahedron Lett.*, (1977) 1417.
9 A. M. Mathieson, *Tetrahedron Lett.*, (1965) 4137.
10 R. Foster, *Organic Charge-Transfer Complexes*, Academic Press, London, 1969.
11 J. L. Schreiner, *Ph.D. Dissertation*, University of Illinois, Urbana, IL, 1981.