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A RATIONAL APPROACH TO THE DESIGN OF HIGHLY-EFFECTIVE CHIRAL STATIONARY PHASES

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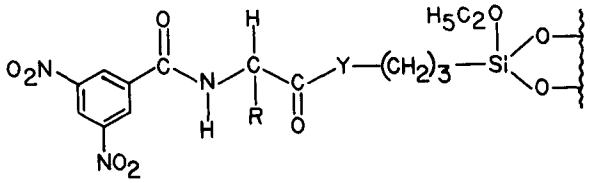
SUMMARY

Geometric considerations require that a minimum of three simultaneous interactions occur if a chiral molecule is to "recognize" the chirality of other molecules. Moreover, chiral recognition is reciprocal in that if a chiral stationary phase (CSP) derived from (+)-A can distinguish between (+)-B and (−)-B, then a CSP derived from (+)-B may distinguish (+)-A from (−)-A. These simple considerations have been instrumentally applied in the design of a series of CSPs which show great scope and power in the separation of stereoisomers and it is evident that these CSPs have the ability to separate the enantiomers of thousands of amines, amino alcohols, amino acids (and their ester and amide derivatives), alcohols, and diols, all as the 3,5-dinitrobenzoyl derivatives. Specific resolutions are presented for each of the aforementioned classes of compounds, and the relationship of analyte structure to the extent of enantiomer separation is considered. Such relationships are important to the determination of chiral recognition mechanisms. Evidence is presented for the presence of multiple competing chiral recognition mechanisms, and it is demonstrated that this mechanistic understanding can be used to design CSPs in which the balance between the competing mechanisms can be dramatically shifted.

INTRODUCTION

Chiral stationary phases (CSPs) of the type shown in 1 have unprecedented scope and generality in their ability to separate enantiomers[1–14]. These CSPs, some of which are now commercially available (Regis, J. T. Baker) are capable of separating the enantiomers of tens of thousands of compounds, many of pharmacological



1 Y = NH, $-O^{\ominus}NH_3^{\oplus}-$
R = PHENYL, i-BUTYL, β-NAPHTHYL, i-PROPYL

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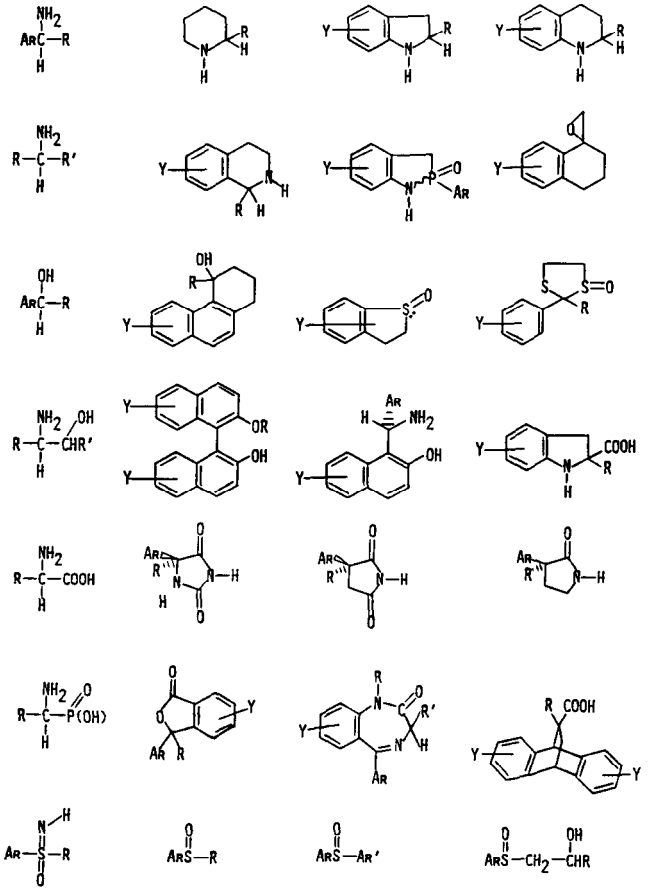


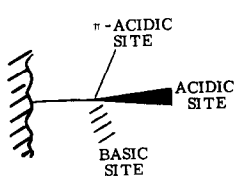
Fig. 1. A representative sampling of categories of compounds whose enantiomers may be separated on type 1 CSPs. In some instances, acylation or esterification with achiral reagents is performed prior to chromatography.

interest. Of the *ca.* forty classes of compounds thus far found to be resolvable on Type 1 CSPs, two dozen representative examples are shown in Fig. 1.

All of these CSPs function by essentially the same mechanisms but may differ quantitatively in their levels of performance for any given analyte.

In a number of cases, we have formulated chiral recognition mechanisms that account for elution orders and, qualitatively, the magnitudes of the observed separability factors. For resolution to occur, there must be at least three simultaneous interactions between the CSP and one analyte enantiomer, one or more of these interactions being stereochemically dependent. Type 1 CSPs use combinations of π–π interactions, hydrogen bonds, dipole–dipole interactions, and steric interactions to achieve chiral recognition[1–3,5,8,9,11]. To be resolvable, the analyte enantiomers must contain functionality "complementary" to that of the CSP so that the analyte is capable of undergoing the essential interactions utilized by the CSP. Hence, a successful CSP will have a "clientel" of resolvable analytes.

For example, a Type 1 CSP can be described rather generally as shown in either 2 or 3, depending upon which interactions are to be utilized. Analyte enantiomers representable as 4a and b or 5a and b are potentially resolvable, 4a and 5a being the more strongly retained at 25°C. In the case of 4a, three simultaneous bonding interactions may occur, whereas antipode 4b can have but two. Analyte enantiomers 5a and b may each undergo two bonding interactions. While undergoing these interactions, 5a suffers less steric repulsion between its "small" group and the steric interaction site of the CSP than does 5b which has its "large" group directed toward the CSPs steric interaction site. Consequently, the diastereomeric adsorbate derived from 5a is more stable than is the one derived from 5b.



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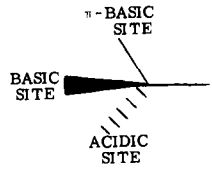
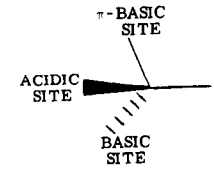
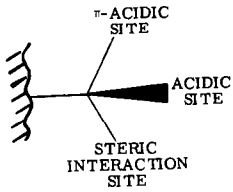


4a



4b



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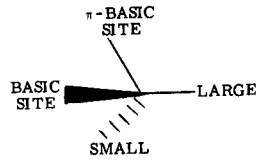
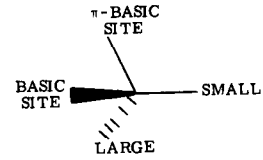


5a



5b

Chiral recognition is reciprocal in the sense that if a CSP derived from (+)-A can selectively retain (+)-B, then a CSP derived from (+)-B should selectively retain (+)-A. Rigorously, this relationship is valid only if one is dealing with a 1:1 interaction and the method of attachment to the support does not influence the mechanism of chiral recognition. Since Type 1 CSPs were designed to act in a 1:1 fashion, the reciprocal approximation is quite useful for CSP design. One quickly realizes that since there are tens of thousands of racemates potentially resolvable on Type 1 CSPs, there are then tens of thousands of chiral compounds capable of affording CSPs that will resolve Type 1-like analytes. The goal, of course, is to prepare only those reciprocal CSPs which will show significantly enhanced performance and scope.

EXPERIMENTAL

Chromatography was performed with an Altex 100A pump, Altex 210 injector, Altex model 165 detector and a Kipp & Zonen BD 41 recorder. A Rudolph Autopol III polarimeter, containing a 20-cm flow cell was often used to monitor the optical activity of the eluted enantiomers at 589 nm. The ultraviolet detector monitored

simultaneously at 254 and 280 nm. Optical rotations of the CSP precursors were measured on the same polarimeter. Melting points were obtained with a Büchi apparatus and are uncorrected. Microanalyses were performed by J. Nemeth and associates, University of Illinois. ^{1}H NMR spectra required for the characterization of the compounds described in this work were obtained on Varian EM-390 and Varian XL-200 spectrometers. Deuterated chloroform was used as the solvent and tetramethylsilane as an internal standard. Mass spectra were obtained by J. C. Cook and associates, University of Illinois, on Varian MAT CH-5 or Varian 731 mass spectrometers. IR spectra were obtained on a Nicolet FT-IR spectrometer.

The 3,5-dinitrobenzoyl derivatives used in this study were prepared from the corresponding amines or alcohols by standard methods. Many of these amines and alcohols are well-known compounds. The various homologous series were prepared by Friedel-Crafts acylation of the aromatic hydrocarbon with various commercially available acyl chlorides and reductive amination of the resultant ketones with sodium cyanoborohydride and ammonium acetate in refluxing methanol[8]. In some instances, these amines and/or ketones are commercially available.

6,7-Dimethyl-1-naphthoyl chloride

To a 100-ml round-bottom flask, equipped with a magnetic stirrer and supplied with a nitrogen atmosphere, were added 14.3 g (0.072 mole) of 6,7-dimethyl-1-naphthoic acid, prepared by a known procedure[18], about 20 g of thionyl chloride, and 2 drops of pyridine. After heating, the mixture was refluxed for 3 h with stirring, the excess thionyl chloride was removed by simple distillation. The residue was distilled under high vacuum (217–225°C at 0.15 mmHg), affording a pale yellow solid in 98% yield. To inhibit the solidification of product in the distillation condenser, steam was used as coolant: m.p. 75–77°C; ^{1}H NMR C^2HCl_3 δ 2.45 (s, 3H), 2.50 (s, 3H), 7.40 (t, 1H), 7.60 (s, 1H), 7.93 (d, 1H), 8.43 (d, 1H), 8.48 (s, 1H). Analytically calculated for $C_{13}H_{11}Cl$: C, 71.40; H, 5.07; Cl, 16.21. Found: C, 71.32; H, 5.08; Cl, 16.43.

6,7-Dimethyl-1-naphthyl 4-pentenyl ketone

To 50 ml of dry tetrahydrofuran in a 100-ml round-bottom flask, equipped with a reflux condensor and magnetic stirrer, were added, in a nitrogen atmosphere, 9 g (0.06 mole) of 4-pentenyl bromide and 1.9 g (0.078 mole) of magnesium metal turnings. This was heated to reflux with stirring, heating then being stopped. After 10 min, heat was applied to continue reflux for an additional 10 min. After cooling the Grignard reagent to room temperature, the solution was poured into a 100-ml dropping funnel, leaving the excess magnesium behind. To 50 ml of dry tetrahydrofuran in a 250-ml three-neck flask, equipped with a mechanical stirrer, reflux condensor, and a 100-ml dropping funnel (which contained the Grignard reagent), was added, in a nitrogen atmosphere, 12.18 g (0.06 mole) of 6,7-dimethyl-1-naphthoyl chloride. This was cooled to −78°C in a dry ice–acetone bath and to this stirred solution the Grignard reagent solution was added dropwise over 1.5 h. Afterwards, the solution was warmed slowly (1 h) to room temperature and, with continuous stirring, 10 ml of 1.2 *N* hydrochloric acid and 100 ml of water were added. The tetrahydrofuran was removed under vacuum and the residue was extracted with cyclohexane. The cyclohexane layer was washed with 10% sodium carbonate, with water, dried over anhydrous magnesium sulfate, and evaporated under vacuum. The residual oil was flash-

chromatographed with cyclohexane, progressing to dichloromethane, to afford 12.84 g (85%) of the ketone as a pale yellow liquid. ^{1}H NMR C^2HCl_3 δ 1.77–2.30 (m, 4H), 2.47 (broad s, 6H), 3.03 (t, 2H), 4.90–5.12 (m, 2H), 5.60–5.97 (m, 1H), 7.33 (t, 1H), 7.57 (s, 1H), 7.77 (dd, 2H), 8.33 (s, 1H); IR (Neat) cm^{-1} 3078, 2978, 2940, 2920, 2860, 1680, 1640, 1596, 1570, 1500. Analytically calculated for $C_{18}H_{20}O$: C, 85.67: H, 7.99. Found: C, 85.31; H, 7.87.

6,7-Dimethyl-1-naphthyl 10-undecenyl ketone

This ketone was obtained as pale yellow solid in 75% yield by the above method. m.p. 49–51°C ^{1}H NMR (C^2HCl_3) δ 1.34 (broad, 12H), 1.60–2.07 (m, 4H), 2.38 (s, 3H), 2.44 (s, 3H), 2.97 (t, 2H), 4.80–5.10 (m, 2H), 5.54–6.00 (m, 1H), 7.20–7.84 (m, 4H), 8.20 (5, 1H); IR (KBr) cm^{-1} 3080, 2980, 2925, 2856, 1670, 1640, 1598, 1567, 1495. Analytically calculated for $C_{24}H_{32}O$:-C, 85.66; H, 9.59. Found: C, 85.47; H, 9.67.

α-(6,7-Dimethyl-1-naphthyl)-5-hexenylamine

This amine was prepared as a viscous, pale yellow liquid by reductive amination of the corresponding ketone using a reported[8,17] procedure. Yield: 70% ^{1}H NMR (C^2HCl_3) δ 1.34–1.67 (broad, 4H), 1.67–2.20 (m, 4H), 2.44 (s, 3H), 2.50 (s, 3H), 4.67 (t, 1H), 4.80–5.07 (m, 2H), 5.50–6.00 (m, 1H), 7.14–7.67 (m, 4H), 7.84 (s, 1H). When 2 drops of ^2H_2O were added, the broad peak at 1.34–1.67 ppm was reduced to 2H. IR (Neat) cm^{-1} 3368, 3300, 3078, 3060, 3005, 2968, 2938, 2920, 2855, 1640 (w), 1600 (w). High-resolution mass spectrum, calculated for $C_{18}H_{23}N$: 253.1813. Found: 253.1831.

α-(6,7-Dimethyl-1-naphthyl)-11-dodecenylamine

This amine was prepared from the corresponding ketone as described above. Because the hydrochloride of this amine is relatively soluble in ether and insoluble in water, it is not readily purifiable by the usual extractive procedure. Without purification, the bulk of this amine was converted to the amide. However, a small amount of the amine was obtained from the extractive workup. ^{1}H NMR (C^2HCl_3) δ 1.30 (broad, 14H), 1.60–2.17 (m, 6H), 2.42 (s, 3H), 2.47 (s, 3H), 4.67 (t, 1H), 4.80–5.10 (m, 2H), 5.57–6.00 (m, 1H), 7.20–7.67 (m, 4H), 7.84 (s, 1H). When 2 drops of ^2H_2O were added, the peak at 1.60–2.17 ppm was reduced to 4H.

N-Acetyl-α-(6,7-dimethyl-1-naphthyl)-5-hexenylamine

This amide was prepared from the corresponding amine by the action of acetyl chloride and triethylamine in methylene chloride. Yield: 96%. m.p. 162–163°C. ^{1}H NMR (200 MHz) (C^2HCl_3) δ 1.43–1.56 (m, 2H), 1.96 (s, 3H), 1.95–2.16 (m, 4H), 2.42 (s, 3H), 2.46 (s, 3H), 5.03–5.04 (m, 2H), 5.67–5.88 (m, 3H), 7.33–7.40 (m, 2H), 7.61 (s, 1H), 7.67 (t, 1H), 7.91 (s, 1H). IR (KBr) cm^{-1} 3300, 2940, 2920, 2860, 1650, 1550. Analytically calculated for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.19; H, 8.43; N, 4.70.

The racemic amide was resolved on a previously described[6] chiral preparative column with 2% isopropyl alcohol in hexane as a mobile phase. High R_F enantiomer: m.p. 159.5–160.5°C; $[\alpha]_D$ +41.51 (c 0.60, CH_2Cl_2). Low R_F enantiomer: m.p. 160–161°C; $[\alpha]_D^{25}$ −41.13 (c, 0.80, CH_2Cl_2).

N-Acetyl-α-(6,7-dimethyl-1-naphthyl)-11-dodecenylamine

This amide was prepared from the corresponding amine by the action of acetyl chloride and triethylamine in methylene chloride. m.p. 124–126°C; ^{1}H NMR (C^2HCl_3) δ 1.30 (broad, 14H), 1.97 (s, 3H), 1.80–2.20 (m, 4H), 2.40 (s, 3H), 2.47 (s, 3H), 4.80–5.10 (m, 2H), 5.57–5.94 (m, 3H), 7.20–7.40 (m, 2H), 7.54–7.74 (m, 2H), 7.90 (s, 1H). IR (KBr) cm^{-1} 3290, 2920, 2855, 1650, 1560. Analytically calculated for $C_{26}H_{37}NO$: C, 82.27; H, 9.83; N, 3.69. Found: C, 82.04; H, 9.91; N, 3.63.

The racemic amide was resolved on a previously described[6] chiral preparative column. High R_F enantiomer: m.p. 132–134°C; $[\alpha]_D^{25}$ +30.86 (c 0.41, CH_2Cl_2). Low R_F enantiomer m.p. 132–133.5°C; $[\alpha]_D$ −30.13 (c 0.76, CH_2Cl_2).

N-Pivaloyl-α-(6,7-dimethyl-1-naphthyl)-11-dodecenylamine

This amine was prepared by the action of pivaloyl chloride and triethylamine in methylene chloride. m.p. 88–90°C; ^{1}H NMR (C^2HCl_3) δ 1.10–1.44 (broad, 14H), 1.17 (s, 9H), 1.77–2.34 (m, 4H), 2.40 (broad, 6H), 4.77–5.04 (m, 2H), 5.50–5.97 (m, 3H), 7.17–7.34 (m, 2H), 7.47–7.64 (m, 2H), 7.80 (s, 1H). IR (KBr) cm^{-1} 3335, 2920, 2855, 1624, 1530. Analytically calculated for $C_{29}H_{43}NO$: C, 82.60; H, 10.28; N, 3.32. Found: C, 82.78; H, 10.23; N, 3.25.

This racemic amide was resolved on a previously described[6] chiral preparative column. High R_F enantiomer: $[\alpha]_D$ + 13.35 (c 2.71, CH_2Cl_2). Low R_F enantiomer: $[\alpha]_D$ − 13.27 (c 2.11, CH_2Cl_2).

(R)-N-Acetyl-α-(6,7-dimethyl-1-naphthyl)-(6-triethoxysilylhexyl)amine

This compound was prepared by hydrosilation of the unsaturated amide by the method previously described[17]. Yield 52%; m.p. 126–129°C; ^{1}H NMR (200 MHz) (C^2HCl_3) δ 0.56–0.59 (m, 2H), 1.20 (t, 9H), 1.24 (broad s, 6H), 1.93 (s, 3H), 1.96–2.03 (m, 2H), 2.41 (s, 3H), 2.44 (s, 3H), 3.79 (q, 6H), 5.70–5.90 (m, 2H), 7.31–7.34 (m, 2H), 7.59–7.69 (m, 2H), 7.92 (s, 1H). IR (KBr) cm^{-1} 3300, 2975, 2920, 2860, 1645, 1505. High resolution mass spectrum calculated for $C_{26}H_{41}NO_4Si$: 459.2797. Found: 459.2801. $[\alpha]_D$ + 27.45 (c 0.77, CH_2Cl_2).

(R)-N-Acetyl-α-(6,7-dimethyl-1-naphthyl)-(12-triethoxysilyldodecyl)amine

This compound was prepared as a viscous liquid by the hydrosilylation method previously described[17]. Yield: 42%; ^{1}H NMR (C^2HCl_3) 0.54–0.77 (m, 2H), 1.07–1.47 (m, 27H), 1.95 (s, 3H), 1.70–2.07 (m, 2H), 2.40 (s, 3H), 2.46 (s, 3H), 3.79 (q, 6H), 7.64–7.80 (m, 2H), 7.17–7.35 (m, 2H), 7.50–7.70 (m, 2H), 7.88 (s, 1H). High resolution mass spectrum calculated for $C_{32}H_{52}NO_4Si$: 543.3744. Found: 543.3737. $[\alpha]_D$ + 18.78 (c 1.77, CH_2Cl_2).

(R)-N-Pivaloyl-α-(6,7-dimethyl-1-naphthyl)-(12-triethoxysilyldodecyl)amine

(*R*)-N-Pivaloyl-α-(6,7-dimethyl-1-naphthyl)-11-dodecenylamine (1.85 g) was dissolved in 10 ml of trichlorosilane. After adding 1.5 ml of the chloroplatinic acid solution (71.5 mg of H_2PtCl_6 in 20 ml isopropyl alcohol), the mixture was heated to reflux for about 30 min. Excess trichlorosilane was removed by simple distillation, followed by application of high vacuum. The oily material was dissolved in 30 ml CH_2Cl_2 and then 2 ml ethyl alcohol and 2 ml triethylamine were added in one portion. After stirring the mixture for 10 min, the solvent was removed, and the product

was purified by flash-chromatography on silica to give 1.88 g of colorless oil (73%). ^{1}H NMR (C^2HCl_3) δ 0.47–0.74 (m, 2H), 1.07–1.47 (m, 36H), 1.80–2.07 (m, 2H), 2.40 (s, 3H), 2.43 (s, 3H), 3.79 (q, 6H), 5.57–5.87 (m, 2H), 7.14–7.34 (m, 2H), 7.34–7.44 (m, 2H), 7.80 (s, 1H). IR (Neat) cm^{-1} 3350, 2975, 2920, 2850, 1640, 1525. High-resolution mass spectrum, calculated for $C_{35}H_{59}NO_4Si$: 585.4213. Found: 585.4158 $[\alpha]_D$ + 8.90 (c 1.69, CH_2Cl_2).

N-(4-Pentenoyl)-α-(6,7-dimethyl-1-naphthyl)isobutylamine

This amide was prepared from the corresponding amine by the action of 4-pentenoyl chloride and triethylamine in methylene chloride. Yield: 96%; m.p. 129–131°C. ^{1}H NMR (200 MHz) (C^2HCl_3) δ 0.90 (d, 3H), 1.02 (d, 3H), 2.24–2.38 (m, 4H), 2.41 (s, 3H), 2.45 (s, 3H), 4.93–5.07 (m, 2H), 5.64–5.86 (m, 3H), 7.24–7.28 (m, 2H), 7.58–7.65 (m, 2H), 7.94 (s, 1H). Analytically calculated for $C_{21}H_{27}NO$: C, 81.51; H, 8.80; N, 4.53. Found: C, 81.22; H, 9.07; N, 4.40.

This amide was chromatographically resolved on a preparative Type 1 chiral column[6]. High R_F enantiomer: m.p. 151.5–152.5°C; $[\alpha]_D$ − 58.82 (c 0.77, CH_2Cl_2). Low R_F enantiomer: m.p 152–153°C; $[\alpha]_D$ + 57.24 (c 1.45, CH_2Cl_2).

(R)-N-(5-triethoxypentyl)-α-(6,7-dimethyl-1-naphthyl)isobutylamine

This compound was prepared as a viscous oil by the previously described method[17]. Yield: 53%; ^{1}H NMR (C^2HCl_3) δ 0.60 (t, 2H), 0.90 (d, 3H), 1.04 (d, 3H), 1.20 (t, 9H), 1.34–1.80 (m, 4H), 2.10–2.34 (m, 3H), 2.44 (s, 3H), 2.51 (s, 3H), 3.87 (q, 6H), 5.50–5.87 (m, 2H), 7.17–7.34 (m, 2H), 7.50–7.67 (m, 2H), 7.94 (s, 1H). IR (Neat) cm^{-1} 3300, 3060, 2978, 2930, 2880, 1640, 1545. High-resolution mass spectrum, calculated for $C_{27}H_{43}NO_4Si$: 473.2961. Found: 473.2966. $[\alpha]_D$ −33.61 (c 1.21, CH_2Cl_2).

Chiral stationary phases 8a, 8b, 14a, 14b and 19

The preparation of the CSP 8b has been reported[17] and each of the other CSPs was similarly prepared with 5 μm Spherisorb as the support.

CSP 8a: Analytically found: C, 7.74; H, 1.05; N, 0.28; Si, 42.00. Calculated: 0.20 mmoles of amide/g (based on N); 0.21 mmoles of amide/g (based on C).

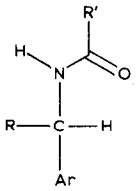
CSP 14a: Analytically found: C, 6.90; H, 0.55; N, 0.33; Si, 42.84. Calculated: 0.24 mmoles of amide/g (based on N); 0.26 mmoles of amide/g (based on C).

CSP 14b: Analytically found: C, 6.30; H, 1.18; N, 0.21; Si, 43.23. Calculated: 0.15 mmoles of amide/g (based on N); 0.19 mmoles of amide/g (based on C).

CSP 19: Analytically found: C, 6.76; H, 1.05; N, 0.21; Si, 42.67. Calculated: 0.15 mmoles of amide/g (based on N); 0.18 mmoles of amide/g (based on C).

RESULTS AND DISCUSSION

While weakly basic amines (anilines, pyridines, etc.) pass through type 1 CSPs readily, more basic amines are strongly retained. Even though we have occasionally noted resolution of underivatized basic amines, it is generally better to acylate such amines prior to chromatography. Acylation can serve the dual purpose of enhancing detectability and separability. In examining a series of acylated 1-aryl alkyl amines[8], we noted that the π-basicity of the aryl substituent, its conformational disposition, the size of the alkyl substituent and the length of the N-acyl "tail" all influenced the



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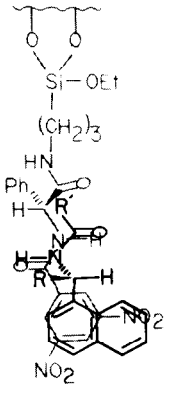
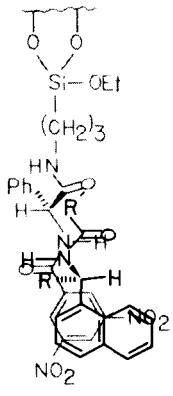
magnitude of α, the separability factor. The chiral recognition mechanism that best explains the resolution of type 6 analytes on an (*R*)-phenylglycine-derived CSP is shown in 7a and b. In nonpolar mobile phases such as hexane–2-propanol mixtures, the major attractive interactions between the analyte and the CSP are π–π bonding and antiparallel "stacking" of amide dipoles. These interactions require "face to face" approach of the analyte and the CSP. Only one face of the CSP is readily approachable, the bulky phenyl group blocking access to the other. The average conformation of Type 6 amides can be approximately described as having the methine hydrogen in the plane of the aryl substituent and eclipsed with the carbonyl oxygen. As shown in 7a for an α-naphthyl-substituted amide, this conformational preference allows only one of the enantiomers to "stack" readily. While so stacked, the acyl "tail", R′, is directed towards the silica support. Through steric interaction with the support, long tails interfere with this dipole-stacking mechanism, causing a diminution in the magnitude of α.



7a

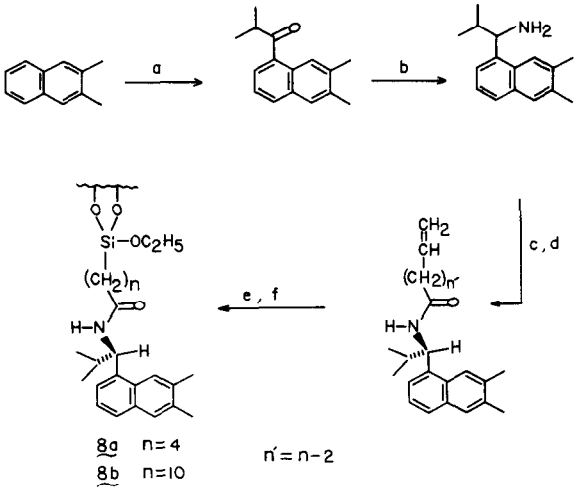
MOST RETAINED ENANTIOMER



7b

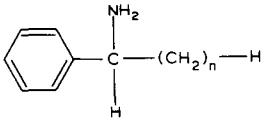
LEAST RETAINED ENANTIOMER

By application of the reciprocal concept, it was deemed likely that CSP 8 would readily separate the enantiomers of the N-3,5-dinitrobenzoyl derivatives of amines, amino alcohols, and amino acids. The development of CSP 8 occurred independently and concurrently with the important work of Oi *et al.*[15,16] who have reported that CSPs derived from α-(1-naphthyl)ethylamine indeed resolve enantiomeric 3,5-dinitroanilides and 3,5-dinitrophenylurethanes. Because CSP 8, the synthesis of which is reported elsewhere[17], contains design elements intended to enhance chiral recogni-

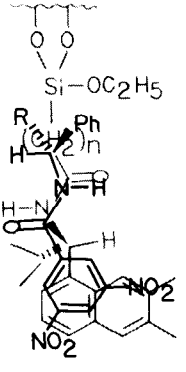


(a) $\underset{\underset{O}{\|}}{\text{i-}C_3H_7CCl}$, $AlCl_3$, CH_2Cl_2, RT, chromatographic purification, (b) NH_4OAc, $NaCNBH_3$, CH_3OH, (c) $CH_2{=}CH{-}(CH_2)_{11}\underset{\underset{O}{\|}}{C}Cl$, triethylamine, CH_2Cl_2, RT, (d) chromatographic resolution, (e) $HSi(OC_2H_5)_3$, H_2PtCl_6, and (f) silica gel, benzene, reflux.

Scheme 1.

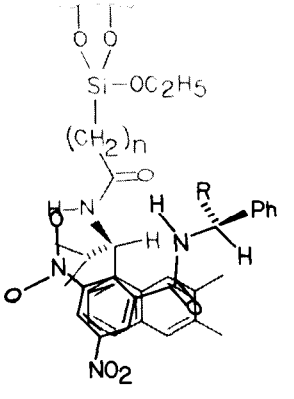


9



10

DIPOLE-STACKING PROCESS
(R)-ENANTIOMER SELECTIVELY
RETAINED



11

HYDROGEN-BONDED PROCESS
(S)-ENANTIOMER SELECTIVELY
RETAINED

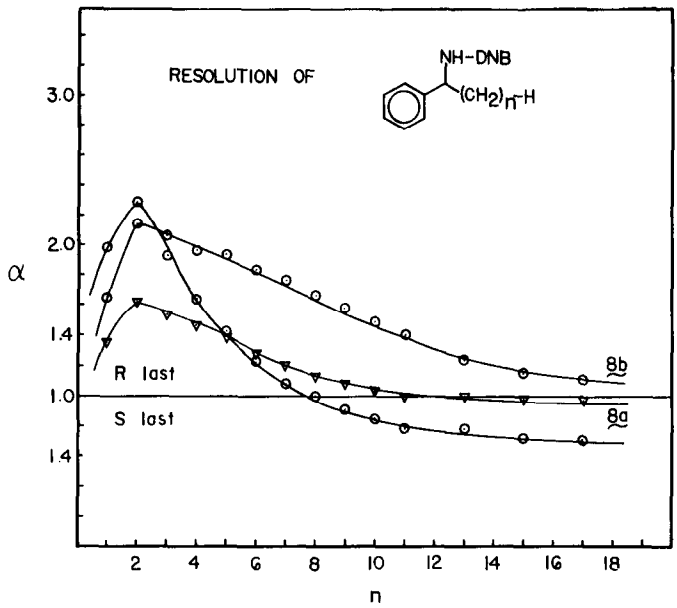
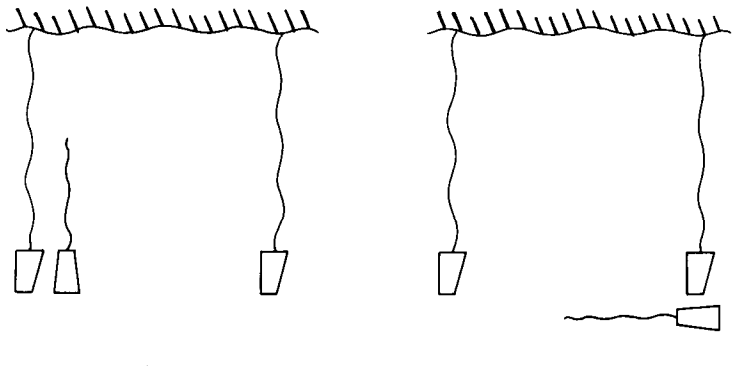


Fig. 2. Chromatographic resolution of a series of DNB derivatives on CSPs 8a and b, -⊙-, this curve was obtained using 20% 2-propanol in hexane as a mobile phase; -▽-, this curve was obtained using methanol-water (90:10) as a mobile phase.

tion, it, and its descendants, typically afford greater separability than the CSPs described by Oi *et al.*[15,16] CSP 8 was prepared as shown in Scheme 1, bonded to 5 μm Spherisorb, and slurry-packed into a 250 × 4.6 mm stainless-steel column. The precursors of the chiral silanes for 8a (n = 4) and 8b (n = 11) were resolved on a 5 × 100 cm Type 1 column[6].

A homologous series of Type 9 amines were chromatographed as the 3,5-dinitrobenzamides (DNB) on each of the type 8 CSPs with 20% 2-propanol in hexane as the mobile phase. As shown in Fig. 2, the length of the analyte's "tail" influences the magnitude of α, the degree of influence also depending upon the length of the "arm" connecting the CSP to the silica. Note particularly that long analyte "tails" invert the order in which the enantiomers are eluted from 8a, the short-armed CSP, the inversion point occurring at n = 8. Although no elution order inversion was noted for CSP 8b, the curve shape suggests that, had analytes bearing still longer tails been investigated, inversion would have been observed.

The observed inversion of elution order suggests strongly that there are two competing chiral recognition processes that work in opposite senses. This was not totally unexpected, since amide–amide interactions can, *a priori*, take three forms, dipole–dipole stacking, hydrogen bonding of the CSP to the analyte, and hydrogen bonding of the analyte to the CSP. Owing to the acidity of the DNB amide hydrogen and the reduced basicity of its carbonyl oxygen, the second hydrogen bonding process is expected to be more important than the first. The dipole-stacking mechanism is shown in 10, and the hydrogen bonding mechanism is shown in 11. The mechanism shown in 10 is basically the one shown in 7, the analyte enantiomer held most strongly by the CSP (π–π interaction, dipole-stacking) being the one with the smaller (*i.e.* alkyl



12

DIPOLE-STACKING PROCESS
(R)-ENANTIOMER RETAINED

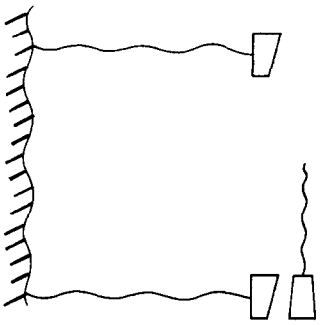
13

HYDROGEN-BONDING PROCESS
(S)-ENANTIOMER RETAINED

rather than phenyl) substituent projected toward the CSP. In hydrogen-bonded mechanism 10, π–π interaction is retained and the DNB amide hydrogen bonds to the carbonyl oxygen of the CSP. From models, it also seems probable that the CPS's N–H may hydrogen bond to one of the nitro-group oxygens although we offer no evidence that this additional interaction occurs. Chiral recognition stems from the occurrence of less steric interaction when the alkyl "tail" of the (*S*)-enantiomer is directed toward the CSP than when, for the (*R*)-enantiomer, the larger phenyl group is so directed. These steric interactions are presumed to occur both with the naphthyl's 6,7-dimethyl substituents and with the isopropyl group as well. These two mechanisms are shown schematically in 12 and 13. For the more strongly retained enantiomers, the dipole-stacking mechanism intercalates the alkyl tail between and roughly parallel to the strands of bonded phase. Study of space-filling models suggests that, in hydrogen-bonding mechanism 11, the alkyl tail of the (*S*)-enantiomer is directed more or less alongside the isopropyl group of CSP 8, longer tails projecting beyond into the mobile phase. Predictably, the use of a methanol–water mobile phase disfavors the latter process and thus delays the inversion of elution order observed on 8a. Note, from Fig. 2, that the length of alkyl tail needed to cause inversion has increased as the mobile phase is changed from hexane–2-propanol (80:20) to methanol–water (90:10).

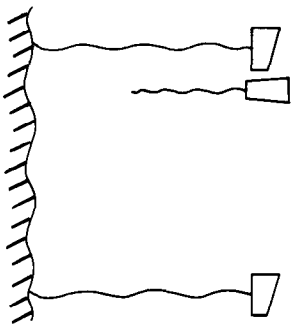
The hypothesis that CSPs 8a and b permit competing chiral recognition processes suggests that CSPs such as 14a and b (see Scheme 2) would show dramatically altered behavior. By "turning" the CSP with respect to the support, the dipole-stacking process becomes non-intercalative and is expected to remain dominant for this series of analytes regardless of the length of the alkyl tail. It is important to note that, to the extent that the (*S*)-enantiomer's alkyl tail is directed alongside the connecting arm in CSPs 14a and b, the hydrogen-bonding mechanism now becomes intercalative. Hence, long "tails" or short "arms" are expected to suppress the minor hydrogen-bonding mechanism and enhance the contribution of the already dominant dipole-stacking mechanism. This situation is depicted schematically in 15a and b.

CSPs 14a and b were prepared as shown in Scheme 2 and used to chromatograph the same homologous series of analytes. As can be seen from Fig. 3, all mem-



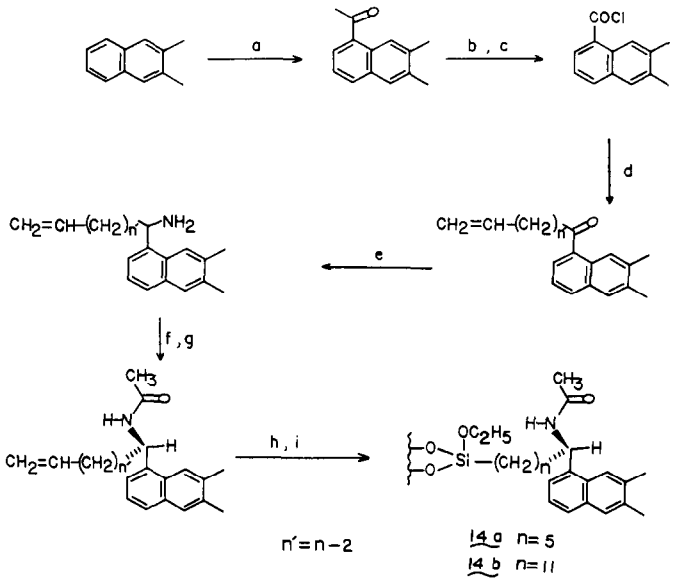
15a

DIPOLE-STACKING PROCESS
(R)-ENANTIOMER SELECTIVELY
RETAINED



15b

HYDROGEN-BONDED PROCESS
(S)-ENANTIOMER SELECTIVELY
RETAINED



(a) $CH_3\overset{O}{\overset{\|}{C}}Cl$, $AlCl_3$, CH_2Cl_2, RT, chromatographic purification, (b) KOCl, KOH, (c) $SOCl_2$, (d) $CH_2{=}CH(CH_2)_n{-}MgBr$, THF, -78 °C, (e) NH_4OAc, $NaCNBH_3$, CH_3OH, (f) $CH_3\overset{O}{\overset{\|}{C}}Cl$, triethylamine, CH_2Cl_2, RT, (g) chromatographic resolution, (h) $HSi(OC_2H_5)_3$, H_2PtCl_6, and (i) silica, benzene, reflux.

Scheme 2.

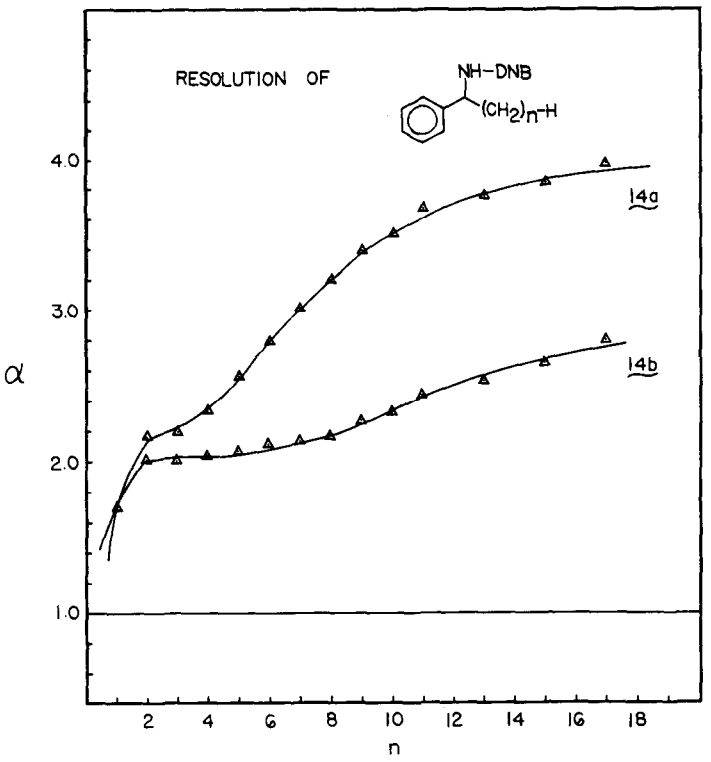
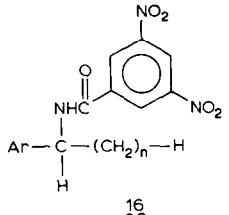


Fig. 3. Chromatographic resolution of a series of DNB derivatives on CSPs 14a and b using 20% 2-propanol in hexane as a mobile phase. The (*R*)-enantiomers are preferentially retained.

bers of the series are now eluted in the same order, α increases in magnitude as either the alkyl tail increases in length or as the length of the connecting arm is diminished.

From any of the family of curves shown in Figs. 2 and 3, one can readily determine the *relative* order of elution of all members in the series *even if an inversion of elution order should occur* (Fig. 2). Hence, if one knows the *absolute* elution order of any member in the series, one knows the absolute order of them all. We propose to term this technique "tracking of absolute configuration" (TRAC). The curves shown in Figs. 2 and 3 are quite similar to the curves similarly generated for the homologous series of analytes generally representable by 16 (see Figs. 4–6). Hence,



16

Ar = p-Anisyl, α-Naph, β-Naph, 2-Fluorenyl
n = 1-17

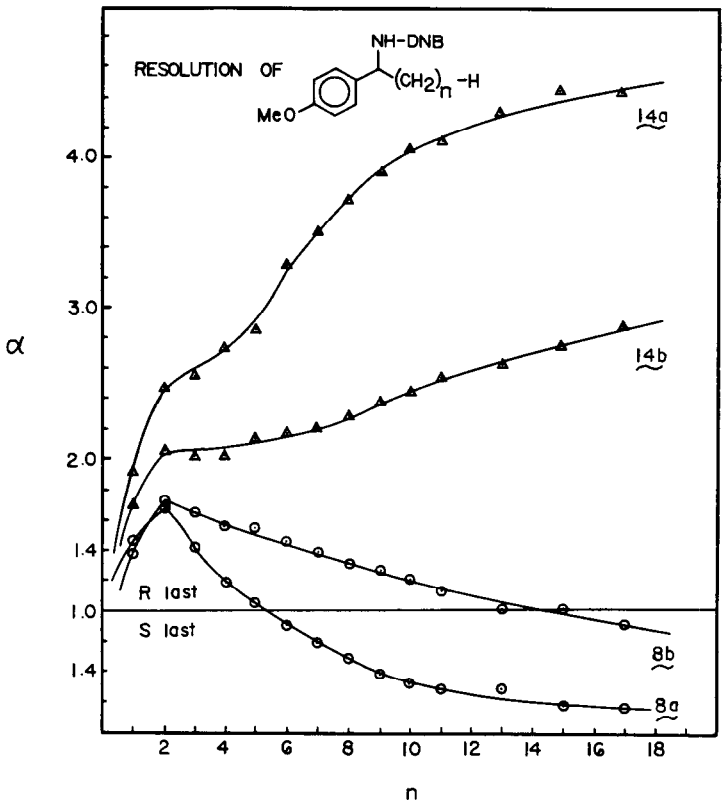
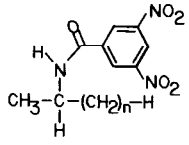


Fig. 4. Chromatographic resolution of a series of DNB derivatives on CSPs 8a and b and 14a and b using 20% 2-propanol in hexane.

the known absolute configuration of a single amine of this general class can be extended by the TRAC technique to a large number of analogs. The generation of TRAC curves on several CSPs provides additional assurance of correct assignment. Note that the TRAC curves generated on CSP 8b now show the inversion of elution order of the higher homologues that was anticipated from the 8b TRAC curve in Fig. 2. If a TRAC curve generated from racemates suggests that an inversion of elution order has occurred, one can verify this by collecting one enantiomer for reinjection on a second chiral column. From Fig. 4, one will note that the enantiomer of the $n = 7$ analyte that is eluted first from 8a is expected to be eluted last from 8b. Alternatively, to avoid collection, concentration, and reinjection, one may simply connect the two columns in series and see if their contributions to enantiomer separation are additive or subtractive.



17

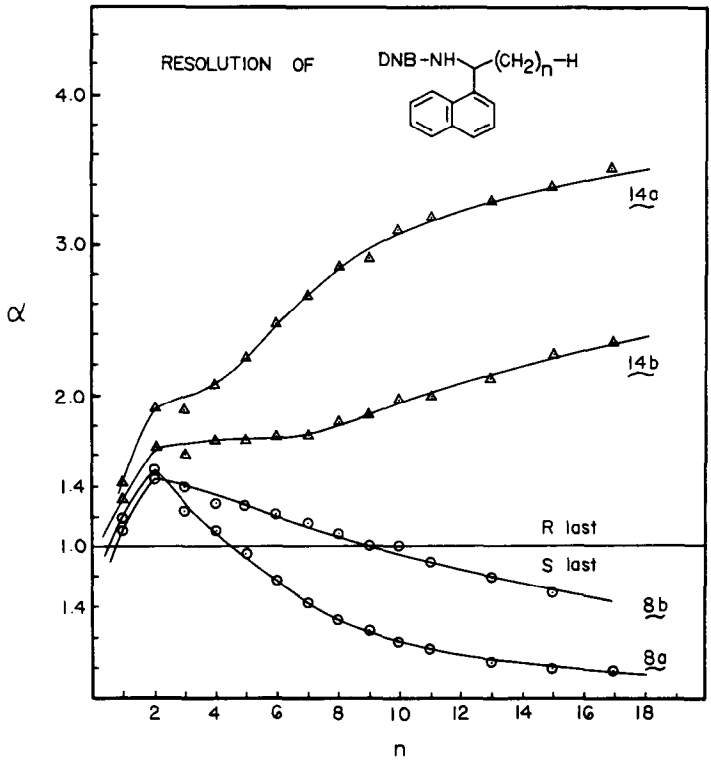
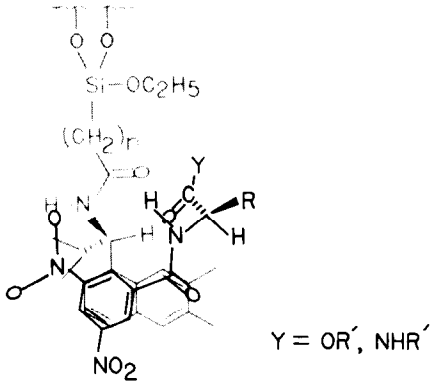


Fig. 5. Chromatographic resolution of a series of DNB derivatives on CSPs 8a and b and 14a and b using 20% 2-propanol in hexane.

Although the dipole-stacking mechanism is dominant for the DNB derivatives of 1-aryl alkyl amines, one cannot assume that this will be true for all amine DNBs. We note that the balance-point between competing mechanisms can be tipped by subtle factors not all of which are yet understood. For example, the observed elution order for a series of Type 17 analytes indicates that the hydrogen-bonded process (*e.g.* 11) is now dominant, presumably for conformational reasons. The aryl substituents in the Type 16 analytes are thought to aid in the population of conformations favorable for the dipole-stacking process. Conformationally less rigid analytes, such as the Type 17 amides, show preference for the hydrogen-bonded process as do the DNB derivatives of amino acid esters and amides. In the latter instances, the change in mechanistic balance point can be ascribed not only to reduced conformational rigidity but also to the presence of the somewhat basic carboalkoxy group. As before, π–π bonding and hydrogen bonding of the DNB N–H to the CSPs carbonyl oxygen, and hydrogen bonding of the CSPs N–H to a nitro group oxygen are invoked as attractive interactions. Chiral recognition is thought to occur partly because the steric interaction sites of the CSP can distinguish the small carboalkoxy group from the larger R-substituent and partly because the electron-deficient methine hydrogen of the CSP can interact weakly with the carbonyl oxygen of the carboalkoxy group, as shown in 18 for the selectively retained (*R*)-enantiomer. The dipole-stacking process, which preferentially retains the (*S*)-enantiomer, is a minor competitive process in



18
(R)-ENANTIOMER
RETAINED

which the alkoxyl "tail" of the ester in thought to be intercalated between and more or less parallel to the connecting arms of CSPs 8a and b. Accordingly, one expects this process to be suppressed by long alkoxy tails or by short connecting arms. Because of this, CSP 8a is expected to be superior to the "turned" CSPs, 14a and b, which less effectively suppress the minor competing chiral recognition process.

Table I provides representative data for resolution of a representative series of amino acid derivatives on CSPs 8a and b and 14a and b. One notes that, on 19a and

TABLE I

RESOLUTION OF ENANTIOMERIC 3,5-DINITROBENZAMIDES OF AMINOACID DERIVATIVES ON CHIRAL STATIONARY PHASES

The mobile phase was 20% 2-propanol in hexane. The (*R*)-enantiomers are more strongly retained on the (*R*)-CSPs.

NHDNB
|
R–C–Y
|
H

R	*Y*	*8a* α	*8b* α	*14a* α	*14b* α	*19* α
CH_3	CO_2CH_3	2.66	3.34	2.68	2.53	4.16
iso-C_3H_7	CO_2CH_3	2.93	4.30	3.38	3.01	5.96
iso-C_4H_9	CO_2CH_3	2.40	3.84	3.59	3.26	6.45
C_6H_5	CO_2CH_3	1.64	2.25	1.61	1.71	2.93
$C_6H_5CH_2$	CO_2CH_3	2.45	4.50	3.71	3.50	6.85
$C_6H_5CH_2$	$CO_2C_4H_9$	4.43	4.71	2.86	3.42	6.60
$C_6H_5CH_2$	$CO_2C_7H_{15}$	5.53	5.15	2.36	3.13	5.38
$C_6H_5CH_2$	$CO_2C_{10}H_{21}$	6.04	5.64	2.21	2.95	4.65
CH_3	$CONHC_4H_9$	1.61	1.29	1.08	1.11	1.87
iso-C_3H_7	$CONHC_4H_9$	2.05	1.98	1.27	1.33	3.64
iso-C_4H_9	$CONHC_4H_9$	1.44	1.54	1.14	1.22	3.01
$C_6H_5CH_2$	$CONHC_4H_9$	2.21	2.34	1.41	1.50	3.59

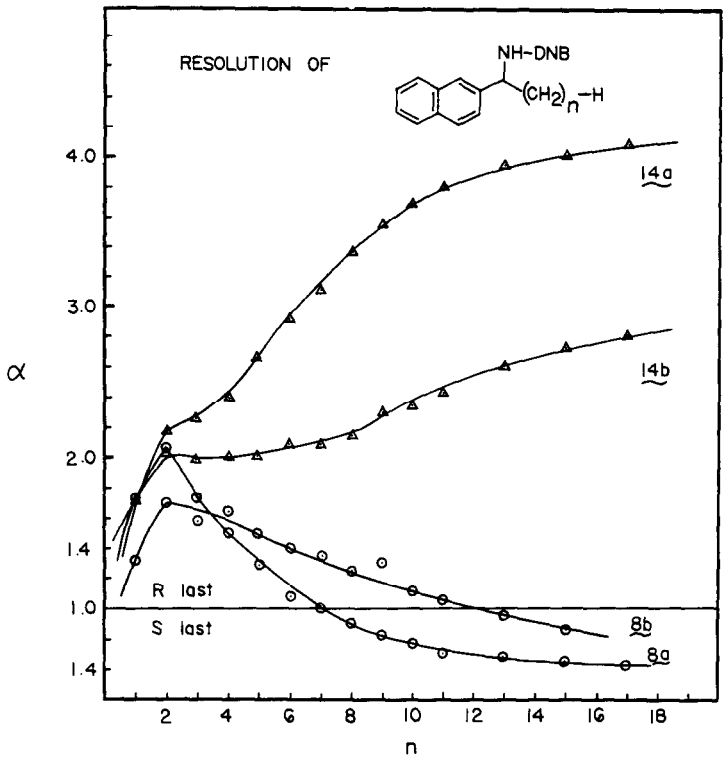
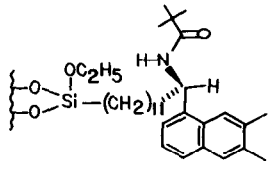


Fig. 6. Chromatographic resolution of a series of DNB derivatives on CSPs 8a and b and 14a and b using 20% 2-propanol in hexane.

b, N-3,5-dinitrobenzoyl amino acid esters (or amides) are resolved quite well and that increased alkoxy tail-length enhances the magnitude of α. For the short-tailed esters, the short-armed CSP 8a usually affords smaller α values than does 8b. This, presumably, is because short tails have little effect on the balance between the competing mechanisms. As the tail length increases, CSP 8a begins to afford larger α values than does 8b. Similar effects are noted for amides of varying tail length. For the *n*-butyl amides shown in Table I, the intermediate tail length causes similar α values on both 8a and 8b. The (*R*)-enantiomer is more strongly retained for all the compounds in the Table.

As a final demonstration of the validity of the competing mechanism hypothesis, we cite the performance of CSP 19. By using the bulkier N-pivaloyl substituent on a 'turned" CSP in lieu of the smaller N-acetyl group, we expected to suppress the



19

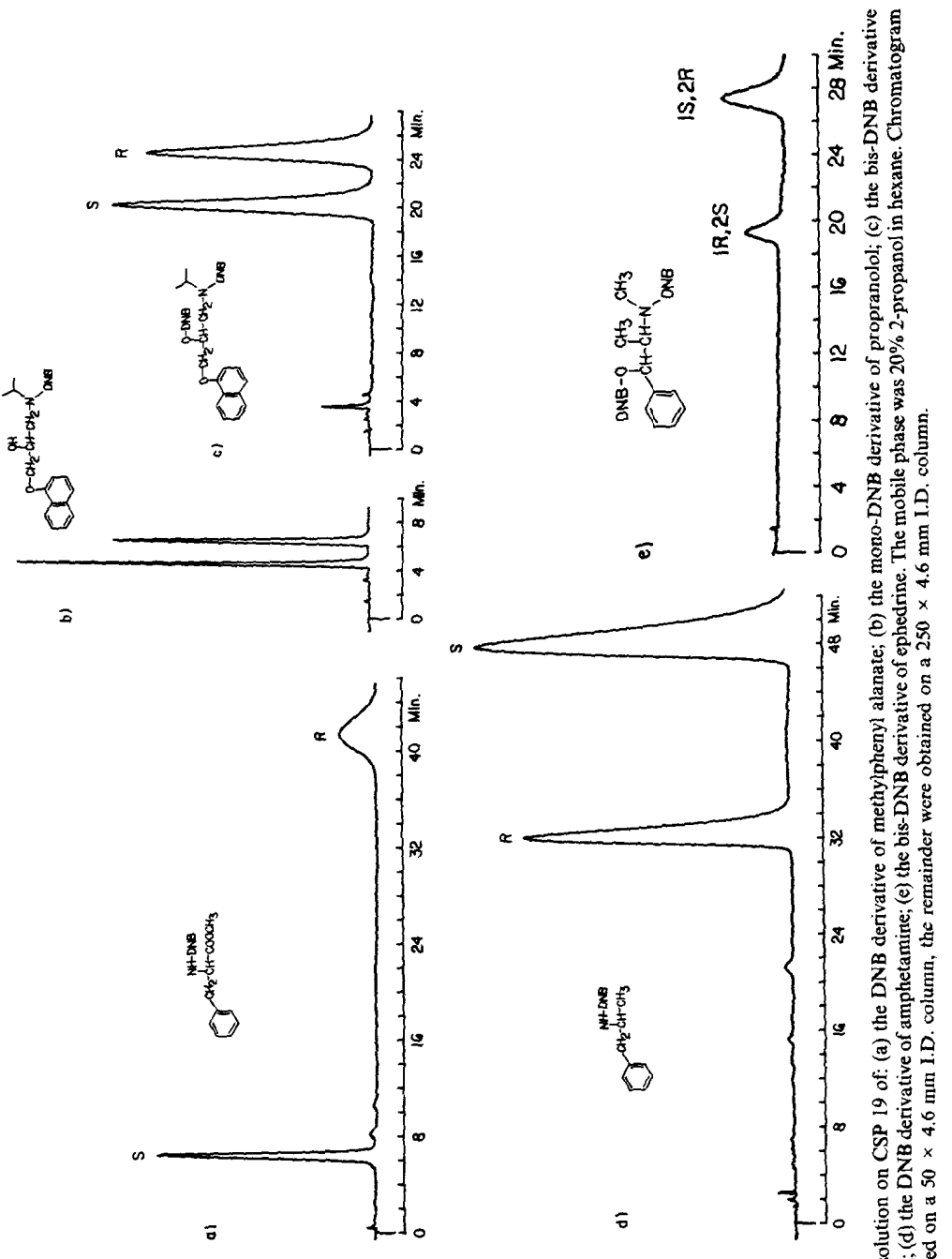
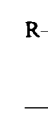


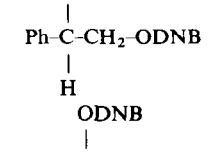
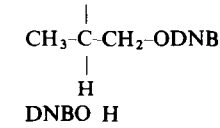
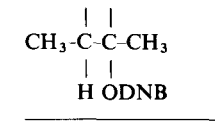
Fig. 7. The resolution on CSP 19 of: (a) the DNB derivative of methylphenyl alanate; (b) the mono-DNB derivative of propranolol; (c) the bis-DNB derivative of propranolol; (d) the DNB derivative of amphetamine; (e) the bis-DNB derivative of ephedrine. The mobile phase was 20% 2-propanol in hexane. Chromatogram (a) was obtained on a 50 × 4.6 mm I.D. column, the remainder were obtained on a 250 × 4.6 mm I.D. column.

TABLE II

RESOLUTION OF THE 3,5-DINITROBENZOYL DERIVATIVES OF SOME AMINES, AMINO ALCOHOLS AND DIOLS

The mobile phase was 20% 2-propanol in hexane.



R	*Y*	*8a*		*8b*		*14a*		*14b*		*19*	
		α	*Conf.**	α	*Conf.*	α	*Conf.*	α	*Conf.*	α	*Conf.*
CH_3	C_2H_5	1.27	*S*	1.26	*S*	1.22	*S*	1.20	*S*	1.43	*S*
CH_3	*n*-C_3H_7	1.00	–	1.17	*S*	1.21	*S*	1.15	*S*	1.44	*S*
CH_3	*n*-C_4H_9	1.18	*R*	1.16	*S*	1.28	*S*	1.16	*S*	1.47	*S*
CH_3	*n*-C_5H_{11}	1.27	*R*	1.15	*S*	1.42	*S*	1.19	*S*	1.52	*S*
CH_3	*n*-C_6H_{13}	1.45	*R*	1.11	*S*	1.53	*S*	1.22	*S*	1.57	*S*
CH_3	*iso*-C_3H_7	1.28	*S*	1.44	*S*	1.45	*S*	1.41	*S*	1.79	*S*
CH_3	*tert.*-C_4H_9	1.55	*S*	1.71	*S*	1.84	*S*	1.75	*S*	1.90	*S*
CH_3	*iso*-C_4H_9	1.12	*R*	1.15	*S*	1.27	*S*	1.19	*S*	1.56	*S*
CH_3	CH_2OH	1.21	*S*	1.00	–	1.13	*S*	1.25	*S*	1.06	*S*
C_2H_5	CH_2OH	1.16	*S*	1.16	*R*	1.00	–	1.13	*S*	1.34	*R*
C_2H_5	CH_2OCH_3	1.31	*R*	1.70	*R*	1.44	*R*	1.35	*R*	1.61	*R*
C_2H_5	$CH_2OC_2H_5$	1.43		1.58		1.39		1.32		1.42	
iso-C_3H_7	CH_2OH	1.00	–	1.42	*R*	1.19	*R*	1.00	–	1.69	*R*
iso-C_4H_9	CH_2OH	1.41	*S*	1.06	*R*	1.18	*R*	1.10	*S*	1.52	*R*
$CH_3SC_2H_4$	CH_2OH	1.00	–	1.21	*R*	1.05	*R*	1.12	*S*	1.34	*R*
C_6H_5	CH_2OH	1.86	*S*	1.06	*S*	1.51	*S*	1.78	*S*	1.29	*R*
		1.30		1.28		1.53		1.43		1.33	
		1.07		1.10		1.18		1.11		1.10	
		1.22		1.18		1.27		1.19		1.20	

* Conf. refers to the absolute configuration of the more strongly retained enantiomer. Elution orders of Entries 2–8 were assigned by the TRAC method and anchored by the known elution order of Entry 1. Although the 8a TRAC curve has, by itself, uncertain aspects, the TRAC curves on the other CSPs are clear. Relative elution orders of all CSPs were checked by the coupled-column technique.

dipole-stacking process and favor the hydrogen-bonded process. Hence, any analyte having a dominant dipole-stacking process will be resolved more poorly whereas an analyte having a dominant hydrogen-bonding mechanism will be resolved more readily. This expectation was fulfilled. The DNB derivatives of amino acid esters and

of a series of amines other than Type 9 will be resolved more readily on 19 than on any of the other CSPs reported herein. Tables I and II document a representative selection of resolutions performed on CSP 19 and compares the performance of 19 with that of 8a and b and 14a and b. Fig. 7 illustrates the resolution of DNB derivatives of the pharmacologically interesting amines, amphetamine, propranolol, and ephedrine and of the methyl ester of phenylalanine. Because CSP 19 resolves amino acid esters through the dominant alkoxyl-intercalative process depicted in 15b, longer alkoxyl tails reduce the magnitude of the observed α values. A similar trend is noted for C-terminal amide derivatives of amino acid DNBs.

Rather large separability factors are noted (Table I) for the amino acid ester DNB derivatives. Because band shapes are quite good, resolution values are rather large. Consequently, even a short column (*ca.* 1 cm) containing CSP 19 bonded to 3 μm spherical silica particles may be used for enantiomeric purity determinations with attendant gains in sensitivity and analysis speed. While CSP 19 does not yet represent the optimum for this type of CSP, it nevertheless is superior to any yet reported for the resolution of the N-3,5-dinitrobenzoyl derivatives of amino acids and of a number of pharmaceuticals. We also note that CSP 19 is quite effective for the resolution of a series of alcohols after derivatization with 3,5-dinitrobenzoyl chloride or with 3,5-dinitrophenylisocyanate, and that it also resolves a series of acids as the 3,5-dinitroanilides. This aspect of our work will be reported subsequently.

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