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Diphenylethanediamine derivatives as chiral selectors V.[1] Efficient normal-phase high-performance liquid chromatographic enantioseparation of underivatized chiral arylalcohols on four differently linked 3,5-dinitrobenzoyldiphenylethanediamine-derived chiral stationary phases

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Abstract

Four brush-type chiral stationary phases (CSPs) have been prepared, via immobilization of (*R,R*)-3,5-dinitrobenzoyl-1,2-diphenylethane-1,2-diamine (DNB-DPEDA) with structurally different anchoring groups. These phases separate at normal-phase HPLC conditions the enantiomers of numerous *underivatized* chiral aromatic alcohols, including ArCH(OH)R, $ArCH_2CH(OH)R$, $Ar(CH)_2CH(OH)R$, simple tertiary arylalkylcarbinols and *trans*-2-arylcyclohexanols. In mobile phases of low polarity separations are characterized by considerate levels of enantioselectivity ($\alpha = 1.1-2.7$), excellent band shapes and short elution times. The hydroxyl group of the analytes is shown to be essential for stereodiscrimination, while π-basicity and steric bulkiness determine the magnitude of enantioselectivity. For simple structured arylalkylcarbinols a correlation is found between elution order and absolute configuration of the analyte. A rationale for molecular recognition of carbinol type analytes on DNB-DPEDA-derived CSPs is advanced. Their general applicability is demonstrated for a number of chiral auxiliaries, solvating agents and drug intermediates of carbinol structure.

Keywords: Chiral stationary phases; LC; Enantiomer separation; Diphenylethanediamine; Alcohols; Arylalkylcarbinols; Arylcyclohexanols; Carbinols

1. Introduction

Enantiomerically pure arylalkylcarbinols have proved to be useful in many fields of enantioselective synthesis and analysis. Moreover, the simplicity of their molecular architecture predestinates them to serve as model probes for studying the mechanistic principles of stereodiscrimination by spectroscopic [2] and, more frequently, chromatographic techniques [3,4]. Since many applications demand materials of accurately established optical purity, analytical methods to resolve the enantiomers of aromatic alcohols on various chiral stationary phases (CSPs) have been developed. Typically, high-performance liquid chromatographic (HPLC) and gas chromatographic (GC) methods require the preformation of covalent derivatives (e.g., carbamates or

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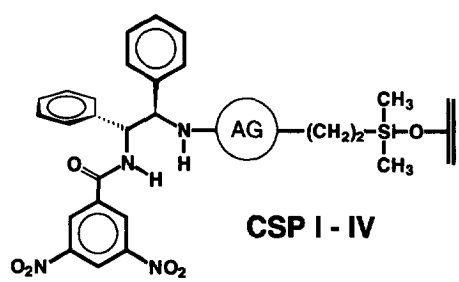
esters) for introduction of additional interaction sites [5] or enhancement of volatility [6]. The derivatization steps are often tedious and time consuming and therefore it is highly attractive to use CSPs capable of separating directly underivatized arylalkylcarbinols. In liquid chromatography these CSPs include donor–acceptor CSPs [3], phases derived from (chemically modified) biopolymers [7,8], and synthetically generated polymeric chiral sorbents. Gas chromatographic techniques employ CSPs based on chiral polysiloxanes [9].

This study introduces derivatives of (*R,R*)-N-3,5-dinitrobenzoyl - 1,2 - diphenylethane - 1,2 - diamine [(*R,R*)-DNB-DPEDA], a chiral selector of established broad applicability [1], as efficient tool for the analytical separation of different classes of *underivatized* chiral arylalkylcarbinols. Previously published CSP I ([10], Fig. 1), which contains this selector immobilized to silica via an undecanoyl anchor, was found to exhibit even with simple phenylcarbinols useful levels of enantioselectivity in combination with reasonably short elution times and excellent band shapes. This prompted us to investigate in more detail the features which are responsible for chiral recognition of aromatic alcohols on this promising selector. For this purpose three conformationally 'stiffer' versions (CSP II–IV) were prepared, differing from CSP I in the mode by which (*R,R*)-DNB-DPEDA is attached to silica (Fig. 1). These modifications involved the introduction of shorter tethers and/or incorporation of a urea linkage. Improvements of brush-type CSPs by similar variations of the anchor group have been demonstrated previously [11–13]. For evaluation of the resultant CSP I–IV a representative number of differently structured carbinols was synthesized and tested at identical chromatographic conditions. Based on the results both the nature and the steric arrangement of the interaction sites involved in the stereodiscriminating process shall be discussed. Changes in the enantioseparation characteristics of the CSPs induced by structural modification of the anchoring group will be considered. The results, including the observed elution order for representative analytes, are utilized as a guide to develop an interaction model to rationalize chiral recognition of arylalkylcarbinols on DNB-DPEDA-derived selectors.

2. Experimental

2.1. Reagents

10-Undecenoyl chloride, allyl acetic acid, allyl isocyanate, 1,3-diisopropylcarbodiimide, hydrogen hexachloro-(IV)-platinate hydrate, dimethylchlorosilane and hexamethyldisilazane were all from Aldrich (Steinheim, Germany) and were used as received. Mono-N-3, 5-dinitrobenzoyl-1, 2-diphenylethane-1, 2-diamine was prepared analogous to the (*S,S*)-enantiomer [10] from (*R,R*)-diphenylethane-1,2-diamine purchased from Fluka (Buchs, Switzerland). 9-Decenyl isocyanate was synthesized via Curtius degradation from 10-undecenyl chloride analogous to a literature procedure reported for the synthesis of undecenyl isocyanate [14]. Lichrospher SI 100, 5 μm (Merck, Darmstadt, Germany) was used as a support for grafting the chiral selectors after hydrosilylation.



ANCHORING GROUP AG	CSPs
CO-(CH2)8	CSP I
CO-(CH2)2	CSP II
CONH-(CH2)8	CSP III
CONH-CH2	CSP IV

Fig. 1. Structure of the four investigated CSPs.

2.2. Chromatography

HPLC measurements were performed on a Hewlett-Packard HP Series 1050 liquid chromatograph and with HP Chemstation as the software. Mobile phases were mixed from isopropanol and *n*-heptane of gradient grade (Merck). 1,3,5-Tri-*tert.*-butylbenzene was used as void volume marker [15].

2.3. Analytes

Compounds **5–12**, **18**, **20–24**, **25–35**, **50**, **80–82** were prepared by sodium borohydride reduction from the corresponding ketones which were commercially available (Aldrich) or synthesized via Friedl–Crafts acylation. Carbinols **37**, **38**, **40–45** and **51–56** were synthesized from the corresponding epoxides with Cu(I) doped Grignard reagents analogous to **51** [16]. Addition of Grignard reagents to benzaldehydes or ketones was used to obtain alcohols **15**, **17**, **36**, **39**, **46–49**, **57–61** and **64–70**. Ether **71** was obtained from the sodium salt of **70** with iodomethane in DMF. Acetate **72** was prepared by acylation of **70** with acetic acid anhydride in pyridine. Diol **73** was prepared according to the literature [17]. Alcohols **14**, **16**, **78** and **79** were purchased from Aldrich. Alcohols **19**, **62**, **63** and **13**, **76** were generously donated by Prof. K. Faber and Prof. H. Hönig (Technical University of Graz). Synthesis of **74** and **75** will be published elsewhere [18]. Optically pure carbinols **5**, **14**, **51**, **78**, **79** were purchased from Aldrich. Optically enriched samples of analytes **6–8**, **10**, **11**, **16**, **20**, **21**, **25**, **29**, **30**, **33**, **34**, **53**, **56**, **70** were obtained by separation of the racemates (sample loading: 3–25 mg) on analytical columns packed with CSP I or CSP IV. The absolute configuration of the enriched enantiomers was determined by comparing the sign of the optical rotation with literature data.

2.4. Check of optical purity of chiral selectors

The optical purity of **1–4** was checked on a D-(2-naphthyl)alanine-derived CSP (250×4.1 mm I.D.; Regis, Morton Grove, IL, USA) at 25°C column temperature using *n*-heptane–isopropanol (70:30, v/v) as mobile phase at a flow-rate of 1 ml/min and UV detection at 254 nm.

2.5. *N'*-Undec-10-enoyl-(*R,R*)-*N*-DNB-DPEDA (**1**)

An amount of 7.00 g (34.5 mmol) of 10-undecenoyl chloride was added dropwise to a cooled solution (ice water bath) of 11.50 g (28.3 mmol) of (*R,R*)-DNB-DPEDA in 100 ml of pyridine. The reaction mixture was allowed to stand at 4°C for 24 h. The reddish solution was diluted with 300 ml dichloromethane and poured into 200 ml ice water. The magnetically stirred mixture was adjusted to pH 2 by careful addition of concentrated hydrochloric acid (about 150 ml). The layers were separated and the aqueous phase was extracted with more dichloromethane (2×50 ml). The organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Drying the residue in high vacuo at 60°C afforded 18.90 g of a brownish crystalline powder. After flash chromatography (300 g silica, eluent: dichloromethane) 15.12 g (93%) of a yellowish, glassy solid was obtained: m.p. 216–218°C; $[\alpha]_{546} = -74.3$, $[\alpha]_{436} = -143$ ($c = 1$, THF); (*S,S*)-enantiomer, $k' = 1.61$; (*R,R*)-enantiomer, $k' = 1.88$; $\alpha = 1.17$, e.e. >98%. The ^{1}H NMR and IR spectra were identical with those reported for the (*S,S*)-enantiomer [10].

2.6. *N'*-Pent-4-enoyl-*N*-DNB-(*R,R*)-DPEDA (**2**)

An amount of 2.05 g (5.04 mmol) DNB-(*R,R*)-DPEDA was added to a solution of 0.80 g (8.0 mmol) allylic acetic acid and 0.90 g (7.1 mmol) of 1,3-diisopropylcarbodiimide in 25 ml THF. The mixture was heated on the water bath to form a yellowish solution. The magnetically stirred solution was kept for 14 h at 50°C under argon. Subsequently the solvent was removed under reduced pressure. The resultant solid was subjected to flash chromatography [50 g silica gel, eluent: dichloromethane–methanol (99:1)]. The resultant slightly yellowish oil was stirred with methanol (20 ml) for 0.5 h to form a white precipitate. This was isolated by filtration, washed with cold methanol (2×10 ml) and dried in high vacuo at 50°C to yield 1.42 g (57%) of **2** as a white, crystalline powder: m.p. 240–245°C (dec.); ^{1}H NMR (DMSO-d_6) 360 MHz δ 2.15 (m, 4H), 4.80 (m, 2H), 5.40 (m, 2H), 5.65 (m, 1H), 7.30 (m, 10H), 8.67 (m, 1H), 9.00 (m, 3H) and 9.68 ppm (m, 1H);

IR(KBr): 3320, 3080, 1650, 1545, 1350 cm^{-1}; $C_{26}H_{24}N4O_6$; elemental analysis: calc. C, 63.93; H, 4.95; N, 11.47; found: C, 64.07; H, 4.95; N, 11.55; $[\alpha]_{546}=-86.0$, $[\alpha]_{436}=-162.4$ ($c=1$, THF); check of optical purity: (*S,S*)-enantiomer, $k'=2.06$; (*R,R*)-enantiomer, $k'=2.29$; $\alpha=1.11$; e.e. >98%.

2.7. *N'-(Dec-9-enyl)carbaminoyl-N-DNB-(R,R)-DPEDA (3)*

An amount of 1.10 g (6.0 mmol) 9-decenyl isocyanate was added to a solution of 2.05 (5.0 mmol) DNB-(*R,R*)-DPEDA in 20 ml THF. The mixture was stirred at 50°C for 14 h under argon. Removal of the solvent gave 3.10 g yellowish, crystalline powder, which was subjected to flash chromatography (60 g silica, eluent: dichloromethane). After drying in high vacuo at 50°C 2.79 g (94%) of **3** was obtained as a yellowish crystalline powder: m.p. 191–195°C (dec.); ^1H NMR ($CDCl_3$) 360 MHz δ 1.25 (m, 12H), 2.00 (m, 2H), 3.23(m, 2H), 4.90 (m, 2H), 5.10 (m, 2H), 5.35 (m, 1H), 5.80 (m, 1H), 6.95 (m, 1H), 7.10 (m, 10H), 9.10 (m, 3H) and 10.12 ppm (m, 1H); IR(KBr): 3300, 3090, 2915, 2860, 1640, 1545, 1340 cm^{-1}; $C_{32}H_{37}N_5O_6$; calc.: C, 65.40; H, 6.35; N, 11.92; found: C, 65.36; H, 6.25; N, 12.01; $[\alpha]_{546}=+10.7$, $[\alpha]_{436}=+29.5$ ($c=1.2$, THF); (*S,S*)-enantiomer, $k'=1.78$; (*R,R*)-enantiomer, $k'=1.32$; $\alpha=1.30$; e.e. >98%.

2.8. *N'-Allylcarbaminoyl-N-DNB-(R,R)-DPEDA (4)*

An amount of 500 mg (6.0 mmol) of allyl isocyanate was added to a solution of 2.18 g (5.3 mmol) DNB-(*R,R*)-DPEDA in 17 ml THF and the reaction mixture was stirred at 50°C for 12 h under argon. The solvent was removed under reduced pressure. The residue was suspended in 30 ml methanol, refluxed with magnetical stirring for 10 min and allowed to stand at ambient temperature for 0.5 h. The precipitate was isolated by filtration, washed with hot methanol (3×10 ml) and dried in high vacuo at 50°C to yield 2.45 g (93%) of **4** as a white crystalline powder: m.p. 210–215°C (dec.); ^1H NMR (DMSO-d_6) 360 MHz δ 3.35 (m, 2H), 4.90 (m, 2H), 5.20 (dd, 1H), 5.35 (dd, 1H), 5.70 (m, 1H), 6.12 (t, 1H), 6.85 (d,1H), 7.20 (m, 10H), 9.05 (m, 3H) and 9.85 ppm (d, 1H); IR(KBr): 3320, 3090, 2915, 2860, 1640, 1545, 1350 cm^{-1}; $C_{25}H_{23}N_5O_6$; calc.: C, 61.34; H, 4.74; N, 14.31; found: C, 61.06; H, 4.74; N, 14.18; $[\alpha]_{546}=-14.4$, $[\alpha]_{436}=-19.4$ ($c=1$, THF); check of optical purity: (*S,S*)-enantiomer, $k'=1.78$; (*R,R*)-enantiomer, $k'=1.32$; $\alpha=1.30$; e.e. >98%.

2.9. *CSP I–IV*

2.9.1. *Hydrosilylation*

An amount of 17 ml of chlorodimethylsilane and a solution of 10 mg of hydrogen hexachloro(IV) platinate in 0.2 ml of isopropanol were added to a solution of 3.5 mmol of selector **1–4** in 25 ml of dichloromethane (selector **1** and **3**) or THF (selector **2** and **4**). The mixture was refluxed under argon until the ^1H NMR ($CDCl_3$) spectrum of a sample indicated complete conversion (2–4 h). The solvent and excess chlorodimethylsilane were removed under reduced pressure. The residue was dissolved in 20 ml of dichloromethane and evaporated. In order to remove traces of dimethylchlorosilane this redissolving–evaporating procedure was repeated three times. Subsequently the resultant orange, glassy residue was dried in high vacuo at room temperature for 0.5 h.

2.9.2. *Grafting*

From a mechanically stirred slurry of 3.00 g silica in 90 ml of dry pyridine a 40-ml volume was distilled off at ambient pressure to remove traces of water azeotropically. The silica slurry was allowed to cool to room temperature and the corresponding hydrosilylated selector, dissolved in 20 ml of dichloromethane, was added. The mechanically gently stirred mixture was maintained under dry argon at 85–90°C (internal temperature) for 8 h. The modified silicas were isolated by filtration, washed with pyridine (3×30 ml), methanol (6×50 ml), acetone (2×50 ml), ether (2×50 ml), petroleum ether (2×50 ml) and dried at 60°C in high vacuo. Elemental analysis: CSP I: C, 16.68; H, 2.25; N, 2.21; loading: 395 μmol/g (based on N), 409 μmol/g (based on C); CSP II: C, 8.56; H, 1.25; N, 1.50; loading: 267 μmol/g (based on N), 255 μmol/g (based on C); CSP III: C, 14.09; H, 2.02; N, 2.04; loading: 292 μmol/g (based on N), 345 μmol/g (based on C); CSP IV: C, 9.34; H, 1.34; N 1.70; loading: 242 μmol/g (based on N), 288 μmol/g (based on C). Subsequently the CSPs were packed into 250×4.0

mm I.D. stainless-steel columns. All CSPs were endcapped by passing at 35°C a solution of 7 ml of hexamethyldisilazane in dry dichloromethane (100 ml) through the dichloromethane equilibrated columns (flow-rate: 1 ml/min).

3. Results and discussion

3.1. Synthesis

A series of four DNB-DPEDA-based brush-type CSPs differing in tether length and chemical nature of the linkage was prepared (Fig. 2). Conversion of the amino function of DNB-(*R,R*)-DPEDA with activated carboxylic acid derivatives or isocyanates of different chain length afforded amides and ureas **1–4** bearing a terminal olefinic group. Optical purity

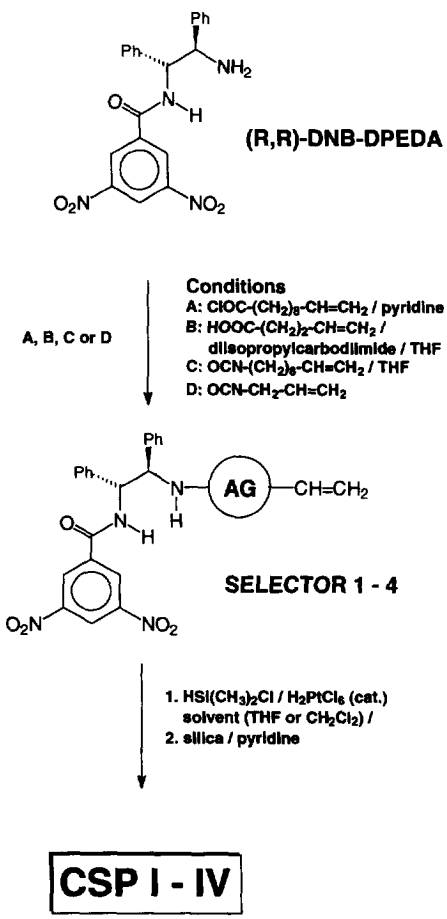


Fig. 2. Synthesis of CSP I–IV.

(>98% e.e.) of these selectors was confirmed by HPLC on a π-basic N-(2-naphthyl)alanine CSP. Hydrosilylation of **1–4** with dimethylchlorosilane-Speyer's catalyst followed by attachment of the resultant chlorosilanes to spherical silica gave CSPs I–IV. For removal of residual silanol groups as a potential source of non-enantioselective interactions [19] the CSPs were carefully endcapped with hexamethyldisilazane after packing. Compared to the non-endcapped versions these 'deactivated' phases were found to exhibit both higher levels of enantioselectivity and significantly reduced capacity factors for arylcarbinols.

3.2. Selection of the mobile phase and the analytes

In order to explore the scope of applicability a broad assortment of chiral aromatic alcohols were chromatographed on CSP I–IV in mobile phases of low polarity (0.5–5% polar modifier in heptane). Interestingly, for most test analytes similar levels of enantioselectivity were observed with a range of mobile phase additives (methanol, ethanol, isopropanol, *tert.*-butanol, dichloromethane, ethyl acetate, tetrahydrofuran, dioxane and dimethoxyethane). However, the superior peak shapes observed with isopropanol recommended this alcohol as modifier. With a mixture of 0.5% isopropanol in heptane almost all analytes documented in Table 1 were baseline separated at least on one of the investigated CSPs.

The palette of analytes includes arylalkylcarbinols, (arylmethyl)alkylcarbinols, (2-arylethyl)alkylcarbinols, *trans*-2-arylcyclohexanols, tertiary arylcarbinols and some candidates containing either additional functional groups (azido, ester, hydroxyl, halogeno functionality) or special structural features. The obtained results are summarized in Table 1 and Table 2, and shall be discussed in terms of enantioselectivity and retention behavior within the individual classes. Significant differences in the performances of CSP I–IV will be emphasized.

3.3. Enantioseparation of arylalkylcarbinols on CSP I–IV

3.3.1. Phenylalkylcarbinols

Within the class of 1-phenylalkanols growing length of the alkyl chain (entries **5–8**) leads clearly

Table 1
Enantioseparation of various classes of arylalkylcarbinols on CSP I–IV

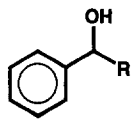
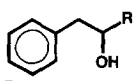
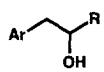
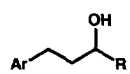
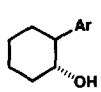
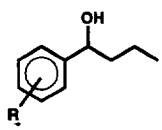
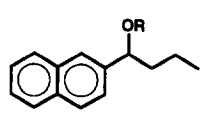
Entry	Compounds	CSPs											
		CSP I			CSP II			CSP III			CSP IV		
		k_1'	α	mre	k_1'	α	mre	k_1'	α	mre	k_1'	α	mre
													
	R												
5	methyl	3.85	1.12	*R*	4.74	1.11	*R*	4.00	1.13	*R*	4.62	1.16	*R*
6	ethyl	2.79	1.20	*R*	3.51	1.19	*R*	3.13	1.19	*R*	3.65	1.23	*R*
7	propyl	2.45	1.22	*R*	3.15	1.20	*R*	2.84	1.21	*R*	3.41	1.24	*R*
8	butyl	2.33	1.24	*R*	3.00	1.20	*R*	2.73	1.22	*R*	3.32	1.24	*R*
9	iso-propyl	1.93	1.30		2.43	1.27		2.25	1.27		2.66	1.32	
10	*tert.* butyl	1.39	1.47	*R*	1.61	1.46	*R*	1.66	1.35	*R*	2.03	1.37	*R*
11	cyclohexyl	2.08	1.33	*R*	2.49	1.29	*R*	2.47	1.28	*R*	2.88	1.34	*R*
12	CH_2Br	2.56	1.12		3.26	1.13		3.10	1.10		3.47	1.14	
13	CH_2N_3	4.16	1.11		5.49	1.11		4.88	1.09		5.76	1.11	
14	CF_3	3.76	1.16	*S*	4.47	1.15	*S*	5.96	1.13	*S*	6.84	1.18	*S*
15	CCl_3	2.91	1.30		3.23	1.31		4.70	1.19		4.85	1.30	
16	COPh	4.30	1.18	*R*	4.32	1.17	*R*	4.89	1.17	*R*	5.24	1.18	*R*
17	CH_2CH_2Ph	3.70	1.20		4.38	1.17		4.72	1.17		4.95	1.17	
18	CH=CHPh	6.74	n.r.		7.80	n.r.		9.35	n.r.		9.67	n.r.	
19	C≡CPh	7.59	1.02		8.59	1.07		10.7	1.03		10.9	1.06	
20		5.99	1.14	*S*	7.58	1.14	*S*	6.93	1.09	*S*	7.16	1.15	*S*
21		4.29	1.16	*S*	5.14	1.15	*S*	4.95	1.09	*S*	5.50	1.16	*S*
													
	Ar												
22	4-nitrophenyl	18.0	n.r.		16.2	1.03		15.7	1.06		15.2	1.07	
23	4-bromophenyl	4.95	1.09		5.82	1.10		5.05	1.11		5.37	1.14	
24	4-benzyloxyphenyl	7.47	1.11		9.86	1.12		8.90	1.13		9.58	1.17	
25	mesityl	2.58	1.12	*R*	3.25	1.09	*R*	3.04	1.13	*R*	3.20	1.18	*R*
26	4-biphenyl	5.97	1.11		7.31	1.12		7.11	1.13		7.02	1.17	
27	tolyl	3.66	1.13		4.96	1.13		3.95	1.15		4.80	1.18	
28	4-methoxyphenyl	3.16	1.21		3.26	1.27		2.73	1.19		2.67	1.25	
29	1-naphthyl	7.23	1.19	*R*	8.96	1.15	*R*	8.92	1.14	*R*	9.54	1.19	*R*
30	2-naphthyl	7.62	1.29	*R*	9.76	1.29	*R*	9.14	1.29	*R*	10.6	1.36	*R*

Table 1 (*continued*)

Entry	Compounds		CSPs											
			CSP I			CSP II			CSP III			CSP IV		
			k_1'	α	mre	k_1'	α	mre	k_1'	α	mre	k_1'	α	mre
31	2-(6-methoxy)-naphthyl		6.34	1.32		7.13	1.30		8.51	1.31		7.75	1.37	
32	1-(6-methoxy)-naphthyl		5.35	1.43		6.14	1.39		5.64	1.50		7.97	1.60	
33	9-anthryl		7.88	1.83	*R*	9.53	1.94	*R*	11.5	1.71	*R*	12.3	1.89	*R*
	 R													
34	methyl		2.77	1.09	*R*	3.28	1.11	*R*	2.90	1.12	*R*	2.93	1.16	*R*
35	ethyl		1.73	1.13		2.01	1.17		1.93	1.18		1.99	1.24	
36	pentyl		1.24	1.20		1.45	1.27		1.55	1.25		1.67	1.24	
37	hexyl		1.10	1.20		1.42	1.26		1.50	1.25		1.61	1.24	
38	decyl		1.01	1.17		1.36	1.18		1.32	1.25		1.43	1.24	
39	iso-propyl		1.08	1.27		1.23	1.41		1.27	1.36		1.32	1.50	
	 Ar	R												
40	4-methoxyphenyl	ethyl	3.30	1.23		4.21	1.36		3.32	1.36		4.04	1.51	
41	4-methoxyphenyl	hexyl	2.51	1.28		3.29	1.37		2.70	1.42		3.45	1.47	
42	1-naphthyl	ethyl	3.17	1.43		3.86	1.63		3.45	1.58		4.44	1.90	
43	1-naphthyl	hexyl	2.36	1.58		3.01	1.73		2.85	1.68		3.69	1.81	
44	2-naphthyl	ethyl	4.06	2.21		5.46	2.77		4.63	2.27		6.29	2.79	
45	2-naphthyl	hexyl	3.36	2.51		4.42	2.82		3.96	2.44		5.45	2.63	
	 Ar	R												
46	1-naphthyl	ethyl	4.58	n.r.		6.46	n.r.		4.48	1.05		5.67	1.09	
47	1-naphthyl	pentyl	3.62	n.r.		5.96	n.r.		3.82	1.06		4.83	1.09	
48	2-naphthyl	ethyl	4.78	n.r.		7.17	1.03		4.59	1.04		5.77	1.07	
49	2-naphthyl	pentyl	3.67	n.r.		5.22	1.03		3.90	1.05		4.82	1.07	
50	PhCH=CHCHOHCH$_3$		5.60	1.06		7.07	1.06		6.32	1.09		6.62	1.08	
	 Ar													
51	phenyl		2.26	1.23	1*R*,2*S*	2.80	1.30	1*R*,2*S*	2.55	1.29	1*R*,2*S*	2.65	1.38	1*R*,2*S*

(continued on p. 222)

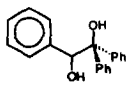
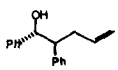
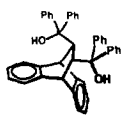
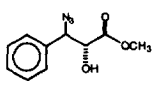
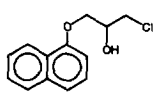
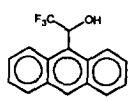
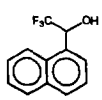
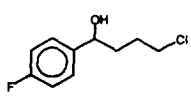
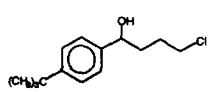
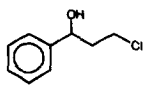
Table 1 (*continued*)

Entry	Compounds		CSPs											
			CSP I			CSP II			CSP III			CSP IV		
			k_1'	α	mre	k_1'	α	mre	k_1'	α	mre	k_1'	α	mre
52	4-t.butylphenyl		1.35	1.18		1.77	1.19		1.55	1.16		1.94	1.17	
53	4-methoxyphenyl		3.85	1.46	1*R*,2*S*	4.88	1.60	1*R*,2*S*	4.00	1.59	1*R*,2*S*	4.43	1.76	1*R*,2*S*
54	4-biphenyl		4.07	1.49		4.69	1.67		4.90	1.59		5.22	1.79	
55	2-naphthyl		5.67	2.40		8.06	2.90		7.09	2.38		8.26	2.92	
56	1-naphthyl		6.04	n.r.	1*S*,2*R*	8.06	1.09	1*S*,2*R*	7.27	1.16	1*S*,2*R*	8.59	1.12	1*S*,2*R*
														
	Ar	R												
57[b]	phenyl	propyl	1.49	1.08	*R*	2.66	1.06	*R*	1.98	1.07	*R*	2.61	1.08	*R*
58	4-methoxyphenyl	propyl	2.73	1.12		3.52	1.11		2.87	1.11		3.66	1.14	
59	2-naphthyl	propyl	2.79	1.25		3.55	1.26		3.33	1.23		4.35	1.31	
60	1-naphthyl	propyl	2.15	1.95		2.62	2.07		2.50	1.94		3.11	2.10	
61	1-naphthyl	pentyl	1.88	2.02		2.41	2.12		2.23	2.02		4.55	2.16	
62	phenyl	C≡CH	2.77	1.13		3.50	1.10		3.37	1.09		4.17	1.11	
63	phenyl	C=CPh	3.51	1.22		4.30	1.25		4.35	1.17		5.26	1.27	
														
	R													
64	2-methoxy		3.49	1.25		4.38	1.19		3.53	1.20		4.50	1.26	
65	3-methoxy		4.21	1.26		5.67	1.25		4.59	1.28		5.69	1.33	
66	4-methoxy		4.67	1.21		5.85	1.21		4.80	1.22		5.81	1.28	
67	2-methyl		1.60	1.26		1.91	1.21		1.99	1.21		2.16	1.27	
68	3-methyl		1.61	1.27		1.97	1.25		2.02	1.25		2.18	1.29	
69	4-methyl		1.70	1.22		2.09	1.22		2.13	1.21		2.32	1.26	
														
70	R: H		5.08	1.49	*R*	6.42	1.52	*R*	6.49	1.47	*R*	7.25	1.57	*R*
71	R: OCH_3		0.34	n.r.		0.30	n.r.		0.32	n.r.		0.26	n.r.	
72	R: $COCH_3$		1.33	n.r.		1.41	1.53		1.22	1.05		1.25	1.26	

HPLC conditions: column dimension, 250×4.0 mm I.D.; mobile phase, 0.5% 2-propanol in *n*-heptane.
[a] 2% 2-propanol; flow-rate, 2 ml/min ([b] 0.5 ml/min); UV detection, 230 nm; column temperature, 25°C; mre: indicates the enantiomer most retained.

to an increase in enantioselectivity, (methylcarbinol **5** vs butylcarbinol **8**: $\alpha = 1.12/1.24$) accompanied by significantly decreasing capacity factors (3.85/2.32). A similar behavior is found for carbinols bearing a highly branched alkyl substituent (compare entries **7/9**, **8/10**,**11**). Selectands formally derived from

Table 2
Separation of chiral drug intermediates, solvating agents and auxiliaries

Entry	Compounds	CSPs											
		CSP I			CSP II			CSP III			CSP IV		
		k_1'	α	mre	k_1'	α	mre	k_1'	α	mre	k_1'	α	mre
73[a]		4.95	1.07		5.67	1.11		7.88	n.r.			n.r.	
74		2.23	1.36		2.97	1.28		2.53	1.19		3.07	1.25	
75[c]		1.72	1.07		1.76	n.r.		1.86	1.03		1.89	1.13	
76[a]		3.72	1.11		4.92	1.08		4.56	1.08		4.62	1.12	
77		4.85	1.16		11.11	1.25		11.87	1.15		13.09	1.22	
78[b]		4.35	2.04	*S*	4.02	2.27	*S*	8.81	1.84	*S*	6.69	2.17	*S*
79		6.95	1.48	*S*	4.02	1.58	*S*	11.51	1.40	*S*	12.17	1.55	*S*
80		2.87	1.11		3.01	1.10		3.64	1.11		3.39	1.13	
81		1.88	1.15		2.10	1.19		2.49	1.16		2.48	1.21	
82		2.55	1.11		2.89	1.10		3.27	1.10		3.11	1.12	

HPLC conditions: column dimension, 250×4.0 mm I.D.; mobile phase, 0.5% 2-propanol in *n*-heptane. ([a] 1% 2-propanol; [b] 2% 2-propanol); flow-rate, 1 ml/min ([c] 0.5 ml/min); UV detection, 230 nm; column temperature, 25°C; mre: indicates the enantiomer most retained.

phenylethanol **5** by introduction of hetero atoms in the side chain (entries **12–15**) exhibit less a clear trend. No change could be observed for the mono-substituted selectands **12** and **13**. Interestingly, compared with phenylethanol **5** the bromo alcohol **12** is less strongly retained, while the azido derivative **13** exhibits increased retention. Relative to the unsubstituted phenylethanol **5** the trifluoro derivative **14** and especially trichloro derivative **15** show increased enantioselectivity. As observed with azido derivative **13** stronger retention on CSP I–IV seems to be significant for arylcarbinols containing additional multibonds (**18**, **19**). Considering the presence of both π-basic and π-acidic interaction sites in the studied selector, this effect may be deduced to non-enantioselective $\pi-\pi$ interactions. More evidence for this trend is found when the retention behavior of the unsaturated alcohols **18** and **19** is contrasted to that of the saturated carbinol **17**, all of them being derived from an identical carbon skeleton. Interestingly, the saturated compound **17** is separated well, no enantioselectivity could be observed for the significantly stronger retained alkene type **18** while alkine alcohol **19** shows only peak splitting in combination with the strongest retention in this series. The small α-values observed for selectands **18** and **19** in contrast to **17** are the consequence of their rigid architecture. The enantiomers of cyclic alcohols condensed to a phenyl ring (entries **20** and **21**) were less well separated than the structurally related versions bearing flexible alkyl chains (entries **6** and **7**). Remarkably, despite the closely related structure, these rigid alcohols show relative to phenylcarbinols with 'flexible' chiral centers an inverted elution order. This is also observed for benzoin **16**, which contains a benzoyl group instead of an alkyl chain. [Note: Structurally seen (*S*)-benzoin is related to the (*R*)-enantiomers of 1-phenylalkanols; the different designation is due the CIP-rules].

The chromatographic data for 1-phenylalcohols **1–18** show that not enantioselectivity but retention behavior is effected significantly by the different modes of selector immobilization. Under identical conditions CSP II and CSP IV, immobilized via short spacer, exhibit about 20% larger capacity factors than their more flexibly tethered analogues CSP I and CSP III. However, there is no evidence for consequential changes (e.g., different elution order for an individual analyte) in the stereodiscriminating process (Table 1).

3.3.2. 1-Arylethanols

In order to specify the role of the aromatic substituent in chiral recognition of arylalkylcarbinols, the chromatographic behavior of a number of 1-arylethanols (entries **5**, **22–33**) was studied on CSP I–IV. In accordance with the π-acidic nature of the selector, increasing π-basicity of the aromatic moiety should result in increased enantioselectivity. Analytes bearing aryl moieties with electron withdrawing substituents (nitro and bromo moieties in entries **22**, **23**) are less well resolved relative to unsubstituted 1-phenylethanol **5**. Surprisingly, almost no improvement of enantioselectivity relative to **5** is observed for *para*-substituted selectands **24** and **26** containing as additional π-basic functionality a benzyloxy and phenyl substituent. Remarkably, in terms of enantioselectivity the position of small substituents on the phenyl ring is not crucial, as shown in the series **64–70**; the $\pi-\pi$ stacking seems to be rather flexible. However, steric hindrance at the 'active site' of the selector must account for the fact that the considerably more π-basic mesityl derivative **25** shows an α-value comparable to that of the less π-basic phenylethanol **5**.

The $\pi-\pi$ stacking plays a major role in the chiral recognition process on the investigated phases. Consequently, significantly larger enantioseparation factors are observed for naphthyl alcohols **29–32**. However, again steric effects influence separation and capacity factors. The 2-naphthylalcohol **31** is significantly better resolved than the 1-naphthyl isomer **30** of similar π-basicity, whereas for the 6-methoxy substituted analogues **32** and **33** the inverse situation is found.

A case of extreme retention behavior is observed with nitro derivative **22**. In accordance with its weak π-basicity this solute shows the expected low level of enantioselectivity, but it is also by far the most retained alcohol investigated in this study. These effects can only be rationalized by very strong non-stereoselective $\pi-\pi$-interactions, in which the selector's second benzene ring close to the linker domain (Fig. 1) might be somehow involved.

In contrast to the series of unsubstituted phenyl

alcohols **5–19**, the ring substituted analogues **22–33** show in terms of enantioselectivity a dissimilar behavior on all four CSPs. In general CSP IV exhibits in comparison to CSP I–III 20–30% improved α-values. Consequently, on CSP IV baseline separation for the enantiomers of nitrophenyl alcohol **22** can be established, whereas at identical conditions CSP II and CSP III show only modest and CSP I even no resolution. The improved enantioselectivity of CSP IV must be a consequence of the conformationally 'stiffer' selector immobilization, which leads to a more rigid, but (in the most cases) more effective arrangement of the interaction sites.

3.3.3. (Arylmethyl)carbinols

Analytes **34–45** are formally derived from arylcarbinols by insertion of a methylene group between an aromatic ring and the stereogenic center and therefore expose a greater amount of conformational mobility. Although this loss in steric rigidity was believed to lead to a seriously diminished magnitude of chiral resolution, the enantiomeric pairs of all investigated candidates were excellently separated. CSP IV is again superior to the other three versions. For the unsubstituted phenyl derivatives **34–39** separation factors range from 1.16 (entry **34**) to 1.50 (entry **39**). As expected, increasing π-basicity of the aromatic portions in (arylmethyl)carbinols was found to lead to an increase in the magnitudes of α-values (entries **40–45**). The general trends for enantioselectivity and retention are similar to those observed for the class of 1-arylalcohols: increasing chain length and a highly branched substituent at the chiral center lead to improved enantiomeric separation and reduced retention. However, this statement must be modified for the amide-linked CSP I and CSP II. They do display generally reduced levels of enantioselectivity for higher homologues (entry **38**). Presently, we cannot explain this behavior.

3.3.4. (2-Arylethyl)carbinols

Encouraged by the observation of excellent enantiodiscrimination potential for (arylmethyl)alcohols, some π-basic representatives of conformationally even more flexible (2-arylethyl)carbinols (entries **46–49**) were tested. In spite of the rather small α-values observed for this class of selectands, the results are useful to demonstrate the higher stereodiscriminating potential of the urea-linked CSP III and especially CSP IV relative to the amide-linked versions. Under identical chromatographic conditions CSP I and CSP II show only peak splitting or even no resolution for these alcohols. However, on CSP III all of them are partially resolved, while on CSP IV baseline separation can be established. The extreme decrease in enantioselectivity for (2-arylethyl)carbinols compared to (arylmethyl)carbinols is a consequence of the unfavorable remote position of the hydroxyl group from the aromatic ring. In addition, the high conformational mobility of the aryl portion caused by insertion of a second methylene group between the latter and the stereogenic center may complicate chiral recognition. This assumption is supported by results found for the structurally closely related analyte **50**, in which the conformational mobility was reduced by replacing the ethylene group between chiral center and aryl moiety by a double bond. In spite of the moderately π-basic phenyl group present in this solute, on all CSPs appreciable levels of enantioselectivity can be obtained. Baseline separation of the enantiomers of **50** can be observed on CSP III and IV.

3.3.5. trans-2-Arylcyclohexanols

The synthetically useful optical isomers of *trans*-2-arylcyclohexanols represent a challenging goal for direct enantioseparation. These selectands can be classified as (arylmethyl)carbinols (entries **51–56**), but differ from the latter due to their cyclic framework in structural rigidity of the alkyl substituent and branching at the second stereogenic center bearing the aryl moiety. Excellent resolution of the enantiomers of the phenyl, 4-methoxyphenyl, 4-biphenyl and 2-naphthyl derivatives (entries **51, 53, 54** and **55**) can be obtained. However, the sterically more demanding 4-*tert.*-butylphenyl and the 1-naphthyl analogues (entries **52** and **56**) expose unexpected low levels of enantioselectivity. The contrasting results for the isomeric naphthylalcohols **55** and **56** bearing aryl substituents of comparable π-basicity (e.g., CSP I: $\alpha = 1.00$ versus 2.40) suggest different mechanisms for enantiodiscrimination. In accordance with this assumption a different elution order was found for the well separated derivatives (**51**, **53**) and for the weakly recognized 1-naphthyl analogue. Again, CSP IV shows for the 'normal' candidates of this class the

highest levels of enantioselectivity, while the enantiomers of the 4-*tert.*-butylphenyl and 1-naphthyl derivative are separated slightly better on CSP II and CSP III.

3.3.6. Tertiary carbinols

Direct separation of underivatized tertiary carbinols has not been published frequently. A number of aryl-methyl-alkylcarbinols can be separated on CSP I–IV. Again CSP IV gives the best separation factors in combination with larger retention times. The tertiary phenyl carbinol **57** shows relative to the corresponding secondary alcohol **7** reduced enantioselectivity on CSP IV (α = 1.08 vs. 1.24). However, the introduction of sterically 'stiffer' substituents (e.g. an acetylene bond in entries **62**, **63**) in the side chain of tertiary arylcarbinols effects an increase both in the magnitude of chiral resolution and retention. In contrast to secondary naphthyl alcohols (e.g. 1- and 2-naphthylethanol, entries **29** and **30**), within the class of the related tertiary alcohols the 1-naphthyl derivative **60** exposes a larger enantioseparation factor in combination with less retention than the 2-naphthyl isomer **59**.

3.4. Role of the hydroxyl function in chiral recognition

As shown in Fig. 3 for all investigated arylalkylcarbinols a reduced isopropanol content in the mobile phase was found to increase significantly the magnitude of enantioselectivity. A plot of α vs. % isopropanol reveals in all investigated cases nonlinear relationships. Similar curves are found in a plot $\ln k'_1$ vs. % isopropanol (Fig. 4). This emphasizes the role of the modifier as a competitor of the selectand for hydrogen bonding sites at the chiral selector [20]. Alternatively, the high propensity of isopropanol to act as an efficient proton acceptor [21] may lead to predominant hydrogen bonding interaction with the protic selectands, weakening the potential of the latter to form enantioselective hydrogen bonds to the selector. However, clear evidence for the contribution of the analyte's hydroxyl group as hydrogen bond donor to enantiodiscrimination on CSP I–IV is provided by the chromatographic results for carbinol **70** and its methyl ether **71**. The enantiomers of alcohol **70** were excellently separated on all

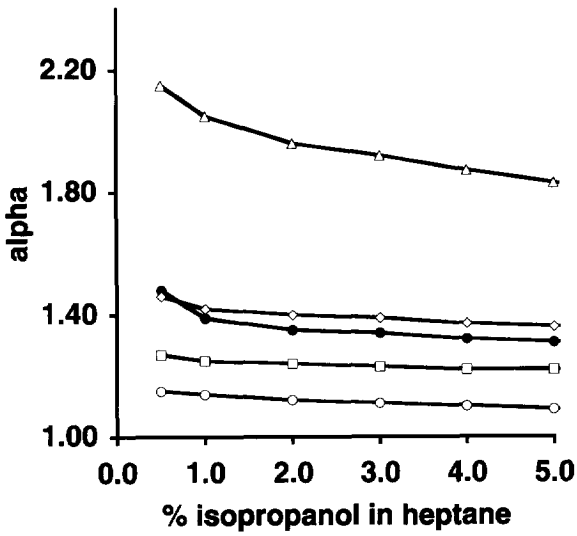


Fig. 3. Effect of the isopropanol concentration in *n*-heptane on the enantioseparation factor α of arylcarbinols. (△) compound **78**, (◇) compound **79**, (○) compound **14**, (□) compound **51**, (●) compound **10**. Experimental conditions: column, CSP I (250×4 mm I.D.); flow-rate, 1 ml/min; UV detection, 254 nm; T = 25°C.

phases, while the replacement of the hydroxyl function by a methoxy group led to the collapse of chiral recognition. The enantiomeric resolution of the cor-

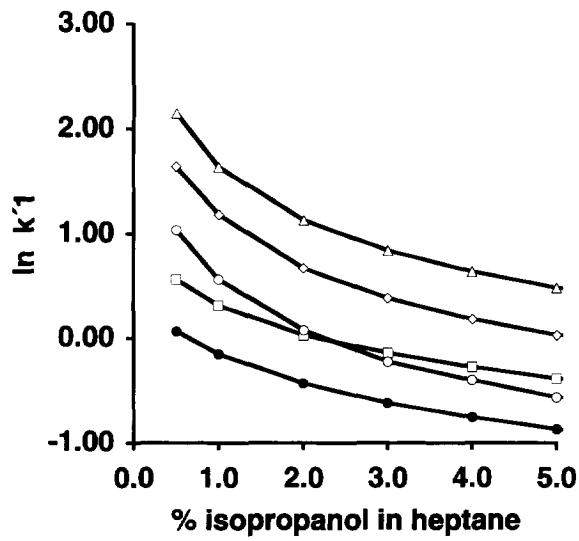


Fig. 4. Effect of the isopropanol concentration in *n*-heptane on the natural logarithm of the capacity factor k' of the less retained enantiomer. The symbols and the experimental conditions are the same as in Fig. 3.

responding acetate **72** on CSP II–IV (but not on CSP I) is not necessarily in contradiction with this concept. In this selectand the lack of a hydrogen bond donor (hydroxyl group) is obviously compensated by the carbonyl group, a hydrogen bond acceptor capable of undergoing stereoselective interactions with a hydrogen bond donor site (e.g. NH function of the 3,5-dinitrobenzoylamido group) at the selector.

3.5. Mechanism of chiral recognition for arylalkylcarbinols on DNB-DPEDA-derived CSPs

According to the 'three-point-interaction rule', in terms of affinity, for enantiodifferentiation a minimum of three simultaneous 'interactions' has to be existent between selector and at least one of the optical isomers and, in addition, at least one of these interactions must be stereochemically dependent [22,23].

As pointed out in the discussion of the data in Table 1, the structural variables of arylalcohols determining the magnitude of enantioselectivity on our (*R,R*)-DNB-DPEDA-derived phases are π-basicity, steric bulkiness of the alkyl substituents and the presence of a hydroxyl function. On this basis we suggest the following simultaneous interactions (Fig. 5, Model A) for enantiodiscrimination of arylalkylcarbinols on CSP I–IV: (i) face to face $\pi-\pi$ stacking between the π-basic aromatic portion of the solute and the π-acidic 3,5-dinitrobenzoyl (DNB) function of the selector; (ii) hydrogen bonding interaction between the selectands hydroxyl function and the carbonyl group of the DNB moiety, and (iii) sterically repulsive interaction occurring between the alkyl substituent of the arylcarbinol and the phenyl ring (phenyl ring 1) at the selector's stereogenic center bearing the DNB group.

Interestingly, a comparative study of the enantiomeric version of CSP I and its (*S,R*)-DPEDA analogue [1] has revealed significant differences in the enantioseparation behavior of these phases for arylcarbinols: e.g., the anthryl alcohol **78** is resolved on (*S,S*)-CSP I with $\alpha = 1.80$, while at identical conditions on the diastereomeric version a value of 1.16 is observed. Evidently, the stereochemistry of the phenyl ring at the second chiral center (phenyl ring 2) in DNB-DPEDA-type selectors controls the

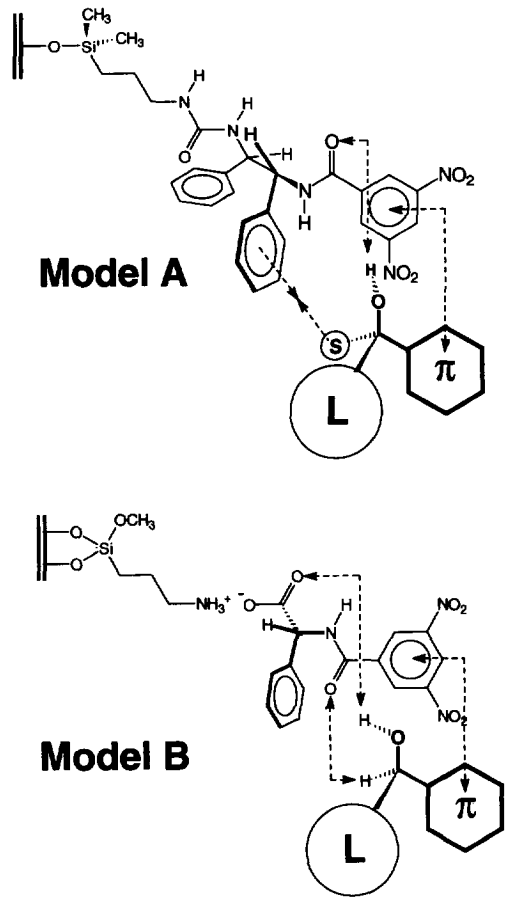


Fig. 5. Models of a chiral recognition mechanisms for arylalkylcarbinols on CSP I–IV (Model A) and on ionically bonded (*R*)-N-3,5-(dinitrobenzoyl)phenylglycine (Model B). In both cases the most stable selector–solute adsorbate is shown. 'L' stands for the larger, 'S' for the smaller substituent at the chiral center of the carbinol.

orientation of phenyl ring 1 relative to the π-acidic function, and therefore determines the magnitude of sterically repulsive interactions.

A chiral recognition model involving similar interactions has been advanced for the stereodiscrimination of 1-arylalcohols on a CSP derived from ionically bonded N-DNB-(*R*)-phenylglycine ([3], Fig. 5, Model B). In contrast to this rationale we have little evidence for a participation of the selectand's carbinyl hydrogen in the chiral recognition process on CSP I–IV. This is emphasized by the fact that the enantiomers of tertiary arylcarbinol **57**, which do lack the carbinyl hydrogen, were readily

separated on all CSPs in the elution order predicted by our less complex interaction model. The arylcarbinol displaying the steric requirements shown in Fig. 5, Model A experiences less steric repulsion than its enantiomer (interchange the large and small substituent 'L' and 'S') and is consequently expected to form a more stable adsorbate with the selector. Therefore it should be the most retained enantiomer. As can seen from Table 1, the elution order documented for simple 1-arylalcohols, benzylalcohol **34** and tertiary carbinol **57** is consistent with this interaction model. Carbinols, in which the hydroxyl group is bonded to a rigid framework (entries **20**, **21**), or is flanked by a strong hydrogen acceptor (benzoin **16**) are notable exceptions.

The elution order on all four CSPs was in all investigated cases identical, proposing closely related mechanisms for enantiodiscrimination on these phases. The 'active site' responsible for chiral recognition of arylalkylcarbinols is located at the DNB-modified chiral center of (*R,R*)-DNB-DPEDA and represents a domain, which seems to be only moderately affected by the different modes of selector immobilization. However, as reflected by different α-values observed for individual analytes, the incorporation of the different anchoring groups must induce small changes in the steric arrangement of the crucial interaction sites. In addition, the introduction of the rigid urea linkage certainly leads, in peculiar in combination with a short tether, to considerable restrictions in the conformationally flexibility of the complete selector environment. As shown in previous studies, the reduction of conformational flexibility of diamine-based selectors can be used with advantage to improve enantioselectivity for special classes of analytes [24]. This is also the case with CSP IV and arylalcohols. Thus, among the investigated phases the conformationally most rigid CSP IV displays for many of the analytes the highest level of enantioselectivity.

3.6. Applications

As demonstrated in the previous sections, CSP I–IV expose for chiral arylalkylcarbinols considerable levels of enantioselectivity in combination with good band shapes and short elution times. These attractive features recommend DNB-DPEDA-derived phases for facile, accurate and fast determination of the optical purity of even moderately π-basic carbinols. A typical separation example of four enantiomeric pairs of phenylalcohols is shown in Fig. 6.

As useful as the results from simple arylalcohols on CSP I–IV for the understanding of chiral recognition are, the analytical challenges encountered in contemporary research in stereochemistry often involve more complicated structures. Many synthetically and spectroscopically useful chiral arylalkylcarbinols contain other functionalities in addition to those essential for chiral recognition on our phases. These additional structure elements such as azido, halogeno, hydroxy, ester groups or sterically highly demanding frameworks can evoke both strong non-enantioselective retention [25] and/or restricted access to the 'active site' of the selector and therefore can lead to reduced enantioselectivity. However, the capability of CSP I–IV to separate the enantiomers even of multifunctionalized or sterically highly demanding arylcarbinols is demonstrated by the data in Table 2. Structures **73–82** are examples of chiral auxiliaries (**73**, **75**), solvating agents (**78**, **79** [26,27]), drug intermediates (**77**, **80–82** [28]), and other building blocks (**74**, **76**).

The considerably high preparative capacity of our selector is documented by the fact that most of the optically enriched samples used for determination of the elution order were obtained from racemates by semipreparative separations (3–25 mg sample loading) on analytical columns packed with CSP I and CSP IV.

4. Conclusions

The successful enantioseparation of a broad assortment of structurally different arylalkylcarbinols on CSP I–IV provided data which indicate clearly that the enantioselectivity is determined by π-basicity of the aromatic moiety and steric bulkiness of the alkyl substituent of the analyte. In addition, the hydroxyl function of the analyte was shown to be essential for enantiodiscrimination. These results and the elution order found for representative analytes were used to develop an interaction model to rationalize chiral recognition of arylalkylcarbinols on DNB-DPEDA-derived phases. The evaluation of the differently

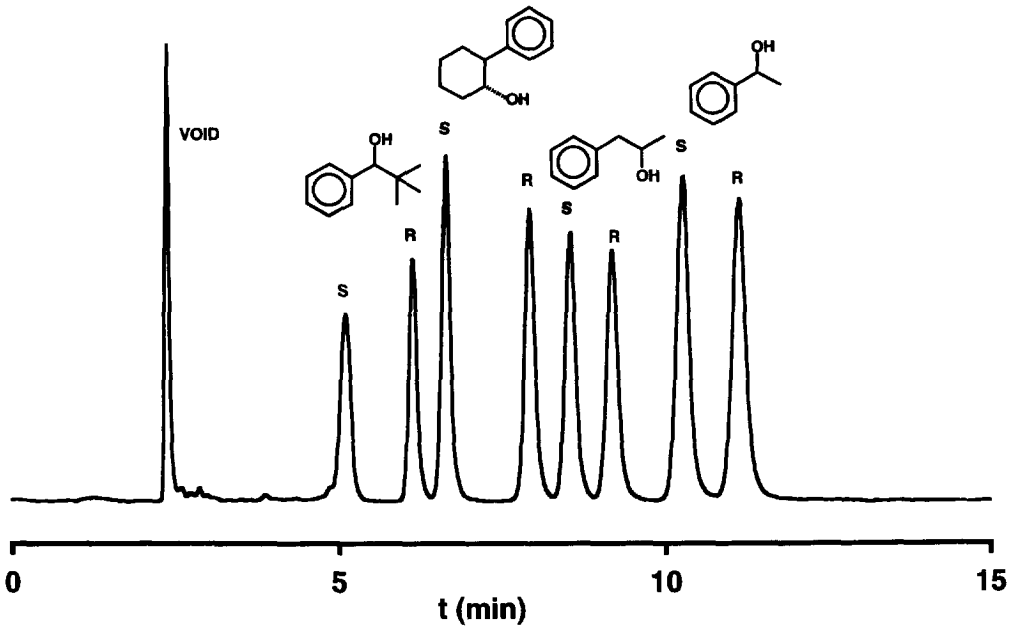


Fig. 6. Single run separation of the enantiomers of four phenylcarbinols. Experimental conditions: column, CSP II (250×4 mm I.D.); mobile phase, 0.5% isopropanol in *n*-heptane; flow-rate, 1 ml/min; UV detection, 254 nm; $T = 25°C$.

immobilized versions of selector revealed that the incorporation of a conformationally rigid anchoring group results in a CSP exposing significantly improved enantioselectivity.

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