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Comparison of Chirasil-DEX CB as gas chromatographic and ULMO as liquid chromatographic chiral stationary phase for enantioseparation of aryl- and heteroarylcarbinols

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Abstract

For a broad spectrum of simple chiral alcohols, incorporating a (substituted) (het)aryl building block, enantiomer separation characteristics are reported for both gas chromatography on a Chirasil-DEX phase, and liquid chromatography on an (*S,S*)-ULMO phase. On this chiral Pirkle-type phase, homochiral enantiomers (mostly *R*) are eluted first without exception. The elution order *R* before *S* appears conserved as a rule also for gas chromatographic separations on Chirasil-DEX, though with some remarkable exceptions indicating a change in the dominant discriminative mechanism. This was shown in the homologous series 1-phenylethanol to 1-phenylhexanol having the point of reversal at C4, while the *o*-methoxy analogues elute from C1 to C4 already in the reversed order.

Keywords: Chiral stationary phases, GC; Chiral stationary phases, LC; Enantiomer separation; Arylcarbinols; Heteroarylcarbinols; 1,2-Dimethoxyethane; 1-Phenyl-2-propanol; 1-Phenyl-2-butanol

1. Introduction

β-Cyclodextrin-modified capillary columns are being widely used for gas chromatographic (GC) analysis of underivatized chiral aryl- and heteroarylcarbinols [1–3]. Liquid chromatographic (LC) analysis of the same type of analytes has also been reported with numerous chiral stationary phases [4–10], in certain cases also β-cyclodextrin was used as chiral LC selector [11,12]. We have reported, that a Pirkle-type chiral stationary phase (CSP), based on *N*-(3,5-dinitrobenzoyl)-1,2-diphenyl-ethane-1,2-diamine (DNB-DPEDA, Fig. 1), can cleanly separate a large number of aryl alcohols using 0.5% 2-propanol and *n*-heptane as the mobile phase [13,14]. This CSP was commercialized [15] and has been optimized. Resolution and separation factors for aryl alcohols are improved compared with our CSP I grafted on Lichrospher Si 100 [16], especially when 1.5% 1,2-dimethoxyethane was used as the polar modifier.

This work presents GC/Chirasil-DEX (Fig. 1) and LC/ULMO derived data of 30 analytes belonging to the classes of (substituted) 1-phenyl-1-alkanols, 1-

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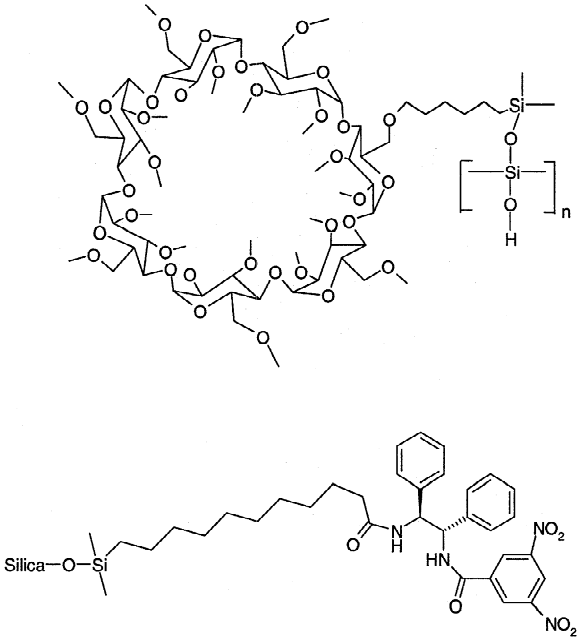


Fig. 1. Hexyl linked GC-selector Chirasil-DEX and undecanoyl linked LC selector (*S,S*)-ULMO.

phenyl-2-alkanols and heterocyclic substituted ethanols, where in most cases the enantiomers were resolved under equal conditions for each CSP. The GC-gradient was chosen to allow fast analysis combined with sufficient separation from ketone precursors as well as byproducts derived from enzymatic reduction studies.

2. Experimental

Analytes were purchased from Sigma–Aldrich or otherwise were prepared by chemical or enzymatic reduction of the corresponding ketones. Products were identified by comparison of NMR data. Elution order was established by comparing known optical rotation and/or elution order data, mainly from Refs. [1–3].

GLC measurements were carried out on a Varian 3800 gas chromatograph equipped with a flame ionization detector and Star Chromatography Workstation software. Column: CHROMPACK Chirasil-DEX CB (Varian Analytical Instruments, Walnut Creek, CA, USA, 25 m×0.32 mm I.D.×0.25 μm d_f, 1.0 bar H_2). The operating conditions for the capillary column were: injector temperature 220 °C, detector temperature 250 °C and column temperature programmed, if not otherwise stated, 10 min at 100 °C then 10 °C/min to 160 °C. Void time was determined with *n*-pentane. The combined gas chromatographic separation in Fig. 4 was taken on a 19 m×0.25 mm (I.D.) fused-silica coated with 0.25 μm Chirasil-DEX with an undecenyl-spacer. Column: 19 m×0.25 mm (I.D.) fused-silica coated with 0.25 μm Chirasil-DEX with an undecenyl-spacer; oven temperature, 110 °C; FID temperature, 250 °C; injector temperature, 200 °C; head pressure, 50 kPa [17].

HPLC analyses were performed on a Hewlett-Packard 1050 system combined with HP Chemstation as software tool. UV-detection at 215 nm. Column: *S,S*-ULMO 250×4.6 mm (REGIS, Chicago, IL, USA), 5 μm silica. Mobile phase: *n*-heptane–1,2-dimethoxyethane (98.5:1.5); 25 °C. Void volume was determined with 1,3,5-tri-*tert.*-butylbenzene.

3. Results and discussion

The power of enantiodiscrimination of cyclodextrin rests on inclusion forces fitting analytes into the conic ring structure, while Pirkle-type CSPs utilize mainly the π–π interaction of aromatic rings to discriminate in combination with hydrogen bonding and steric interactions.

Although the two selectors are completely different (Fig. 1), the resolution values and the time of analysis are comparable. In contrast to these parameters, separation factors α in GC and LC are not comparable since baseline separations in the capillary GC technique can be performed with weaker differences of intermolecular forces due to the higher number of theoretical plates. Further, in GC on Chirasil-DEX rather large differences in α do not really correlate with the resolution data (see tables).

3.1. Homologous 1-phenylalkanols (Table 1)

In general, enantiomers of 1-phenyl-1-alkanols could be separated within 5 to 10 min by each method. However, GC peaks of racemic 1-phenyl-1-butanol **1c** appeared broad and only partly separated

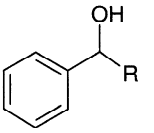


Table 1
GC (first row) vs. HPLC data for phenylcarbinols taken under standard conditions[a]

Compound no.	R		t_1 (min)	k'_1	α	Res	m.r.
1a	Methyl	GC	5.53	12.80	1.09	1.42	*S*
		HPLC	9.85	2.29	1.26	3.61	*S*
1b	Ethyl		7.17	16.90	1.02	1.80	*S*
			9.17	2.06	1.44	9.90	*S*
1c	*n*-Propyl		7.97	18.93	1.01	0.20	n.s.
			8.71	1.90	1.46	7.05	*S*
1d	*n*-Butyl		8.91	21.28	1.01	1.20	*R*
			5.30	1.65	1.45	5.33	*S*

m.r., Most retained enantiomer; n.s., no separation.

[a] GC: Varian GC 3800, split-injector, FID, Chirasil-DEX CB (Chrompak) 25 m×0.32 mm×0.25 μm, 1.0 bar H_2. Standard condition: 10 min at 100 °C then 10°/min to 160 °C. HPLC: (*S*,*S*)-ULMO (REGIS) 250×4.6 mm. Standard condition: 25 °C; mobile phase, *n*-heptane–1,2-dimethoxyethane (98.5:1.5); flow, 1 ml/min.

(res=0.20). Isothermic runs at 105, 110 and 115 °C did not significantly improve the resolution. Consequently, authors using GC excluded **1c**. As previously observed by others [1], 1-phenyl-1-pentanol was eluted in reversed order (*S*-alcohol before *R*-enantiomer) on Chirasil-DEX columns. Hence the point of inversion is given with **1c** (see also Fig. 4).

3.2. Ring substituted 1-phenylethanols (Table 2)

Good to excellent separations of ring-substituted 1-phenylethanols were achieved with both methods. Interestingly, by comparing both methods, in many cases no significant difference in analysis time, resolution and peak shape was found (see Fig. 2).

The influence of substituents of 1-phenylethanol on α and resolution was found to be significant. Chirasil-DEX showed in most cases improved resolution for derivatives with less electron donating substituents on the phenyl moiety (e.g. methoxy vs. methyl and halogens). With ULMO, chiral recognition depends to a high extent on π-acid π-base interactions. As a consequence, resolution of methoxyphenyl derivatives **5**–**7** and hydroxy compound **13** is better than with GC, while there is no obvious difference for methylated and halogenated arylalcohols. This preference of larger π electron systems is more distinct for naphthyl and anthryl analogues [13]. The strong interaction of aryl residues with the 3,5-dinitrobenzoylamido function is also the reason why *S*-enantiomers were generally more retained on *S*,*S*-ULMO. By coincidence this *S*-preference for most of the investigated alcohols is also observed on Chirasil-DEX. As previously observed [1], there is a notable exception: the *S*-enantiomer of *o*-methoxy-1-phenylethanol (**5**) is eluted first. A closer look at this behaviour is given in Section 3.5.

3.3. Heterocyclic 1-substituted ethanols (Table 3)

Heterocyclic 1-substituted ethanols can be distinguished in two groups of analytes: furanyl and thienyl ethanols (**18**–**20**) behave chromatographically similar to phenylcarbinols. To maintain excellent peak separation by applying GC, temperature programs had to be changed towards lower temperatures. Resolution values are comparable and elution order is consistent with the data from substituted 1-phenylethanols (Table 2); the *S*-alcohols were again the most retained enantiomers (Fig. 3).

N-Heterocyclic carbinols are the exclusive domain of Chirasil-DEX [2]. Elution is not possible in LC under normal-phase conditions using unpolar solvents as required for the weak carbinol interactions. 2-(*N*-Methylpyrrolyl)-1-ethanol (**21**), 1-(3- and 4-pyridyl)-1-ethanol (**23** and **24**) could be separated sufficiently on Chirasil-DEX and with peak shapes as achieved with nonpolar substituted 1-phenylethanols. This is one of the real advantages to normal-phase HPLC. However, 2-pyridyl-1-ethanol (**22**) remained only partly separated on the Chirasil-DEX column.

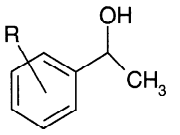


Table 2
GC (first row) vs. HPLC data for substituted 1-phenylethanols taken under standard conditions[a]

Compound no.	R		t_1 (min)	k'_1	α	Res	m.r.
1a	H	GC	5.53	12.80	1.09	1.42	*S*
		HPLC	9.85	2.29	1.26	3.61	*S*
2	*o*-Me		8.65	20.63	1.02	1.75	*S*
			8.63	1.88	1.29	4.97	*S*
3	*m*-Me		7.28	17.20	1.03	2.83	*S*
			8.81	1.94	1.26	4.43	*S*
4	*p*-Me		6.72	15.05	1.12	5.13	*S*
			9.17	2.06	1.21	3.94	*S*
5	*o*-MeO		8.66	20.65	1.02	1.73	*R*
			12.80	3.27	1.29	3.73	*S*
6	*m*-MeO		9.03	21.58	1.02	1.43	*S*
			14.80	3.96	1.34	4.07	*S*
7	*p*-MeO		8.85	21.13	1.02	1.13	*S*
			14.50	3.85	1.22	2.26	*S*
8	*o*-Cl		8.63	20.57	1.06	3.12	*S*
			7.75	1.58	1.12	2.14	*S*
9	*m*-Cl		8.76	20.90	1.03	1.30	*S*
			9.38	2.13	1.17	3.37	*S*
10	*p*-Cl		8.76	20.89	1.04	1.65	*S*
			9.54	2.18	1.15	3.07	*S*
11	*p*-F		6.00	14.02	1.11	1.97	*S*
			9.40	2.13	1.16	2.98	*S*
12	*p*-Br		9.88	23.70	1.02	2.36	*S*
			10.17	2.39	1.17	3.26	*S*
13	*p*-OH		26.63	65.58	1.01	1.52	*S*
		[b,c]	7.47	1.49	1.16	2.08	*S*
14	*p*-NO_2		14.25	34.60	1.07	1.93	*S*
		[b]	15.70	9.47	1.08	1.42	*S*
15	*p*-Phenyl	[d]	6.70	15.72	1.06	2.52	n.d.
			7.14	3.76	1.21	3.10	*S*
16	*p*-Benzyloxy		n.e.				
			9.30	5.21	1.21	3.43	*S*
17	*m*-CF_3		6.39	14.99	1.08	3.02	*S*
			7.97	1.66	1.14	2.44	*S*

n.d., Not determined; n.e., not eluted.
[a] See Table 1.
[b] Flow 2 ml/min.
[c] 5% 2-propanol/0.1% TFA.
[d] 170 °C isotherm.

3.4. 1-Aryl-2-alkanols (Table 4)

Separation conditions and retention times of 1-aryl-2-alkanols were very similar to the data of 1-aryl-1-alkanols. Due to the fact that π–π interaction is the most important driving force for chiral recognition on the ULMO-selector, homochiral enantiomers always had an identical elution order in LC. The observed tendency (Table 2) for Chirasil-DEX to poorly resolve methoxy derivatives was also found with 1-aryl-2-alkanols **28** and **29**. Interestingly, non-substituted **27** could be separated, but it showed a reversed elution order compared with most 1-aryl-1-ethanols.

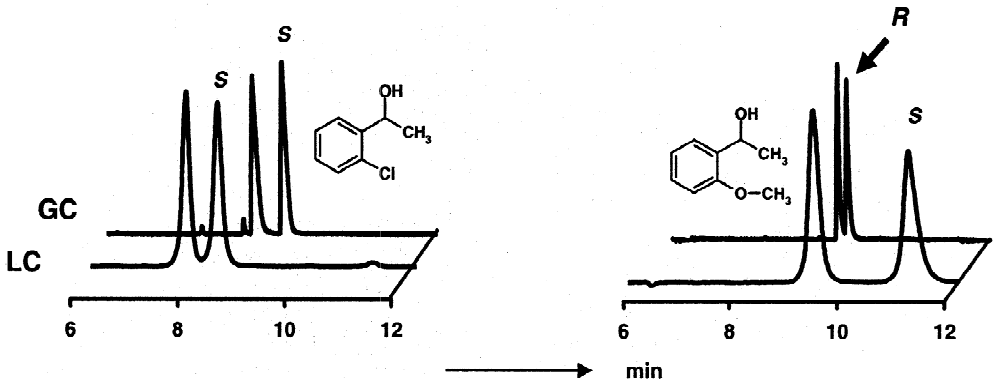


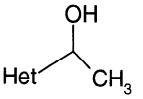
Fig. 2. Comparison of HPLC and GC separation of selected substituted 1-phenylethanols.

3.5. A Chirasil-DEX variation with an 11 carbon linker

After preparation of the manuscript, a new variation of Chirasil-DEX with a longer linker group [17] was checked with key alcohols of this work in one isocratic run.

In the homologous series it can be observed that 1-phenylbutanol marks the turn of the elution order. *o*-Methoxy derivative **5** is now even better separated and as with the commercial Chirasil-DEX CB column again *R* is most retained. The very large separation factor of the butanol analogue in Fig. 4 shows that the ''long-chain'' elution order effect, observed in the unsubstituted series, must be already dominant with *o*-methoxyphenyl-1-ethanol (**5**). Since

Table 3
GC (first row) vs. HPLC data for 1-hetarylethanols



Compound no.	Het		t_1 (min)	k'_1	α	Res	m.r.
18	2-Furanyl	GC[a]	10.22	24.55	1.02	1.93	*S*
		HPLC	6.10	1.05	1.10	4.02	*S*
19	2-Thiophenyl	[b]	10.65	25.37	1.03	1.83	*S*
			9.60	2.21	1.12	2.31	*S*
20	3-Thiophenyl	[b]	11.03	26.57	1.02	1.75	*S*
			10.30	2.42	1.13	2.71	*S*
21	2-*N*-Me-pyrrol		10.70	25.75	1.02	1.44	
			n.e.				
22	2-Pyridinyl	[c]	6.12	14.25	1.01	0.20	
			n.e.				
23	3-Pyridinyl	[c]	9.83	23.58	1.02	1.77	*S*
			n.e.				
24	4-Pyridinyl	[c]	10.17	24.42	1.02	2.23	*S*
			n.e.				

HPLC: see Table 1; n.e., not eluted.
[a] 8 min at 60 °C, 15°/min to 100 °C.
[b] 7 min at 80 °C, 10 °C/min to 130 °C.
[c] 5 min at 90 °C, 10 °C/min to 150 °C.

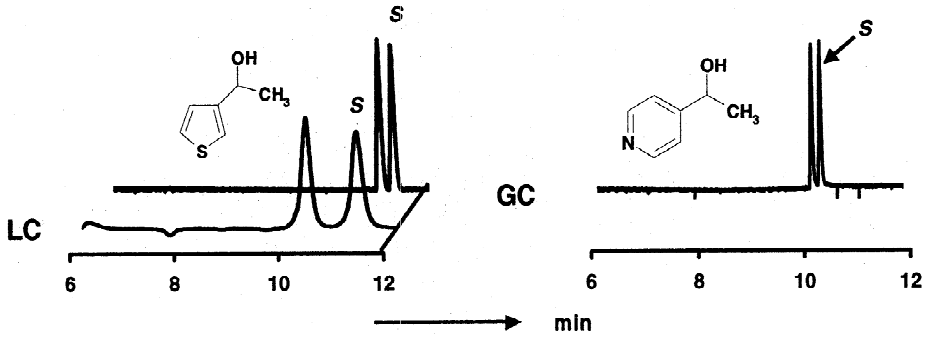


Fig. 3. Comparison of HPLC and GC separation of selected 1-hetarylethanols.

in GC very small differences in the binding forces may be utilized to discriminate enantiomers, a closer interpretation of the separation mechanism is not possible. However, if one looks at this result in combination with the observation that the *R*-enantiomer of benzyl-methylcarbinol (**27**) is also eluted first (Table 4), the series of phenyl- and hetaryl-1-ethanols seems to be rather unique in retaining the *S*-enantiomer.

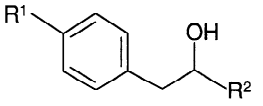
4. Conclusions

Without time-consuming development of methods and using standard protocols, Chirasil-DEX and ULMO provide comparable broadly applicable GC and LC tools for the enantioseparation of 1- and 2-arylalkanols. Concerning N-heterocyclic substituted alkanols, the GC method is superior and almost as efficient as for simple aryl compounds. ULMO has a significant advantage for compounds having π-basic substituents. Additionally the elution order in Pirkle-type enantioselective LC is highly predictable, since a major force for the chiral discrimination mechanism is a π–π interaction involving the 3,5-dinitrobenzoylamido group of the selector and the aromatic ring of the analytes.

Acknowledgements

The combined separation of 1-arylalkanols on a new variation of Chirasil-DEX in Fig. 4 was kindly supplied by Prof. Volker Schurig and Dr. Zhengjin Jiang, University Tübingen, Germany.

Table 4
GC (first row) vs. HPLC data for benzylcarbinols taken under standard conditions[a]



Compound no.	R^1	R^2		t_1 (min)	k'_1	α	Res	m.r.
27	H	Me	GC	8.62	14.08	1.02	1.21	*R*
			HPLC	8.34	1.72	1.19	2.40	*S*
28	MeO	Me		n.s.				
				14.18	5.33	1.28	4.62	*S*
29	MeO	Et		n.s.				
				9.11	2.04	1.49	6.81	*S*

[a] See Table 1; n.s., no separation.

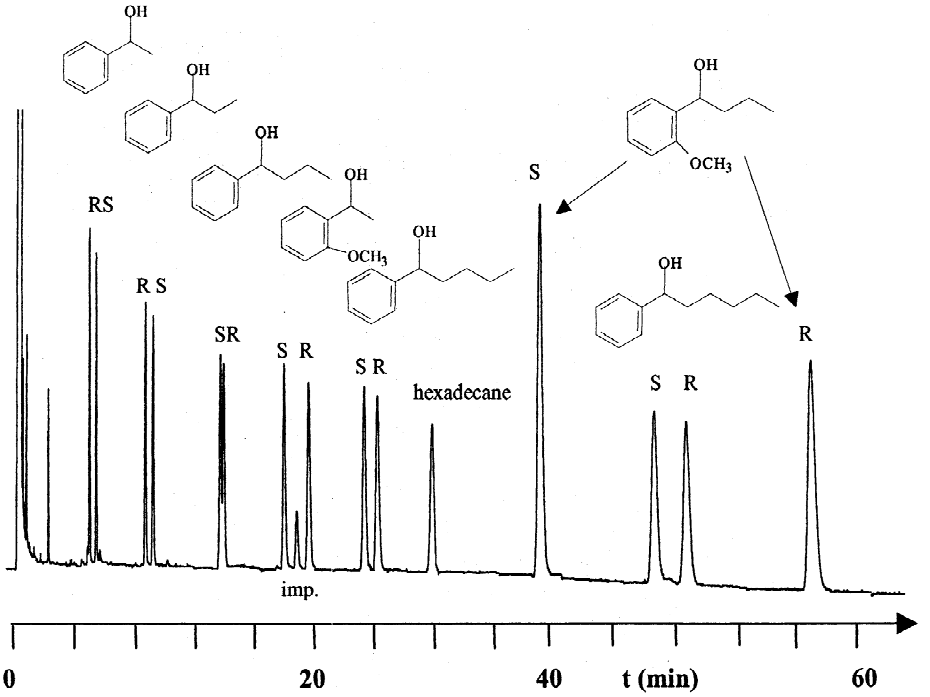


Fig. 4. Isocratic GC separation of a series of 1-aryl-alkanols on a modified β-cyclodextrin column [17] shows clearly the minimum for 1-phenylbutanol followed by a change in the order of elution.

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