ELSEVIER

Journal of Chromatography A, 946 (2002) 197–208

JOURNAL OF CHROMATOGRAPHY A

www.elsevier.com/locate/chroma

Separation of racemic sulfoxides and sulfinate esters on four derivatized cyclodextrin chiral stationary phases using capillary gas chromatography

Jared L. Anderson, Jie Ding, Ryan D. McCulla, William S. Jenks, Daniel W. Armstrong*

Department of Chemistry, Iowa State University, Ames, IA 50011, USA

Received 20 August 2001; received in revised form 15 November 2001; accepted 15 November 2001

Abstract

The separation of 17 chiral sulfoxides and eight chiral sulfinate esters by gas chromatography (GC) on four derivatized cyclodextrin chiral stationary phases (CSPs) (Chiraldex™ G-TA, G-BP, G-PN, B-DM) is presented. Many of these compounds are structural isomers or part of a homologous series. Differences in enantioselectivity of the methyl phenyl sulfoxide isomers on the derivatized gamma cyclodextrin and the heptakis 2,6-di-*O*-methyl-β-cyclodextrin (i.e. B-DM) CSPs are discussed. Under the conditions of this study, the molecular mass cut-off for the GC separation of these compounds was approximately 230. Compounds of higher molecular mass were not eluted from the CSPs at reasonable times and temperatures, but these higher molecular mass enantiomers can be separated by liquid chromatography and capillary electrophoresis. The enantiomeric separation and elution order of a sulfinate ester containing two stereogenic centers as well as 15 chiral sulfoxides is presented. The G-TA and B-DM CSPs generally gave opposite elution orders for most of the compounds studied.

Keywords: Derivatization, GC; Chiral stationary phases, GC; Enantiomer separation; Sulfoxides; Sulfinate esters; Cyclodextrins

1. Introduction

Gas chromatography (GC) has proven to be a reliable analytical method for the separation of chiral analytes. Its advantages include simplicity, speed, reproducibility, sensitivity, and ease of detection [1,2]. The high efficiency of capillary gas chromatography is advantageous as it allows the baseline separation of enantiomers even if they have low selectivity factors [3–7]. The need to obtain chiral sulfoxides of high enantiomeric purity has been a focus of recent research [8].

The first synthesis of chiral sulfoxides was reported in 1926 [9]. Since then, chiral sulfoxides have been used as important bioactive compounds [10–14]. Among the bioactive sulfoxides of interest is *N*-(2-chloro-5-methylthiophenyl)-*N′*-(3-methylsulfinylphenyl)-*N′*-methylguanidine (CNS 5655). The (+)-enantiomer of CNS 5655 exhibits similar neuroprotective characteristics as the racemate whereas the (−)-enantiomer demonstrates little neuroprotection [10]. Chiral sulfoxides are also used extensively as intermediates in synthetic reactions [15,16]. For example, enantiomerically pure myoinositol deriva-

*Corresponding author. Tel.: +1-515-294-1394; fax: +1-515-294-0838.

E-mail address: sec4dwa@iastate.edu (D.W. Armstrong).

0021-9673/02/$ – see front matter
PII: S0021-9673(01)01526-6

tives, which have been shown to play a role in cell–cell communication, have been synthesized using chiral sulfoxides [12]. Chiral sulfoxides are frequently used in asymmetric synthesis [17–20]. Recently, it was demonstrated that chiral 2-(phosphinoamido)phenyl sulfoxides serve as efficient chiral ligands in the palladium-catalyzed allylic alkylation [18].

The enantiomeric separation of racemic sulfoxides is of analytical and preparative interest. The first liquid chromatographic (LC) separation of chiral sulfoxides on α-lactose was reported by Farina and co-workers in 1959 [21]. Since then, a number of papers have described the resolution of chiral sulfoxides on numerous LC chiral stationary phases (CSPs) [22]. Recently, Armstrong and co-workers successfully separated nearly 40 racemic sulfoxides and sulfinate esters using derivatized cyclodextrins and macrocyclic antibiotic CSPs using both normal and reversed-phase LC [23,24].

The first successful gas chromatographic separation of five chiral sulfoxides on the Chirasil-Val stationary phase was described by Bayer et al. in 1985 [25]. However, few papers have demonstrated the resolution of chiral sulfoxides on derivatized cyclodextrin CSPs [25,26] and no papers have described the separation of an extensive collection of structurally related chiral sulfoxides and sulfinate esters.

In the present study, we illustrate the use of derivatized cyclodextrins as CSPs for the enantiomeric separation of 17 chiral sulfoxides and eight chiral sulfinate esters. Several of the racemates studied are also structural isomers of one another or part of a homologous series. One compound, a sulfinate ester, had two stereogenic centers. Circular dichroism (CD) and synthesis of enantiomerically enriched standards was also used to identify the absolute configuration and the enantiomer elution order of these compounds. Reversal of enantioselectivity was observed for most compounds on at least two of the four CSPs used in the study.

2. Experimental

2.1. Apparatus

All GC analyses were performed using a Hewlett-Packard (HP) Model 5890A Series II gas chromatograph equipped with a split capillary inlet system and flame ionization detection interfaced to a HP 3396 Series II integrator. The injector and detector temperatures were 220 and 250 °C, respectively. Helium was used as the carrier gas with an inlet pressure of 80 kPa, linear velocity of 1.6 ml/min, and split ratio of 100:1. Four capillary GC columns were obtained from Advanced Separation Technologies, Inc. Astec (Whippany, NJ): Chiraldex™ G-TA (2,6-di-*O*-pentyl-3-trifluoroacetyl-γ-cyclodextrin), 30 m×0.25 mm I.D.; Chiraldex™ G-PN (2,6-di-*O*-pentyl-3-propionyl-γ-cyclodextrin), 20 m×0.25 mm I.D.; Chiraldex™ G-BP(2,6-di-*O*-pentyl-3-butyryl-γ-cyclodextrin), 20 m×0.25 mm I.D.; Chiraldex™ B-DM (di-*O*-dimethyl-β-cyclodextrin), 20 m×0.25 mm I.D. Fig. 1 illustrates the structures of these well-known CSPs.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Varian VXR 300 MHz instrument. The high-performance liquid chromatography (HPLC) apparatus consisted of an inline vacuum degasser, a quaternary pump, an auto sampler, a UV VWD detector (1050, Hewlett-Packard, Palo Alto, CA), and an integrator (3395, Hewlett-Packard). Chiral LC separations were obtained using the macrocyclic antibiotic Chirobiotic™ teicoplanin aglycone (TAG) CSP (Astec, Whippany, NJ) oper-

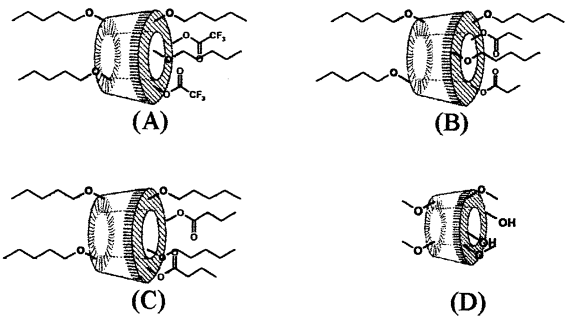


Fig. 1. Simplified schematics of the four derivatized cyclodextrin CSPs used in this study. (A) G-TA; (B) G-PN; (C) G-BP; (D) B-DM. Not all derivatized groups are shown in each structure. Note that the pentyl groups on A, B, and C are on the 2- and 6-hydroxyls while the 3-hydroxyl groups are esterified (for (A) there are trifluoroacetyl groups and for (B) and (C) the ester groups are propionyl and butyryl, respectively). For the B-DM CSP (D), the 2- and 6-hydroxyls are methylated while the 3-hydroxyls are largely unreacted. It should be noted that few derivatized cyclodextrins are pure compounds. They tend to be mixtures of closely related homologues and isomers [42].

ated in either the reverse phase ($MeOH/H_2O$) or normal-phase (Hexane/EtOH) mode, depending on which mode gave the best separation of the enantiomers. Fractions collected by reversed-phase HPLC were extracted with ether and concentrated by evaporation prior to analysis by GC. All LC separations involved injection of approximately 100 μl of concentrated analyte and were performed under isocratic conditions with a flow-rate of 1 ml/min and UV detection at 254 nm.

Circular dichroism spectra (200–300 nm) were recorded at 25 °C using a Jasco J-710 spectropolarimeter. Single enantiomer fractions collected by HPLC were analyzed directly by CD.

2.2. Chemicals and reagents

Methylene chloride and diethyl ether were purchased from Fisher Scientific (Fair Lawn, NJ). (*S*)-(+)-*p*-toluenesulfinamide was purchased from Aldrich (St Louis, MO). (*S*)-(−)-menthyl-*p*-toluenesulfinate was provided by William S. Jenks (Ames, IA).

Table 1 lists the 25 racemic analytes that were studied. Compounds **1**, **2**, and **5** are available commercially. Compounds **3** [27], **4** [28], **24** [29,30] and **25** [31] were prepared as previously described. Compounds **14–20** [32] were prepared by the method of Klunder and Sharpless [33].

Compounds **6–13** [34–38] were all prepared using the same synthetic method. The parent arenethiols were obtained commercially and transformed into the aryl methyl sulfides and then oxidized. The following is a general procedure. Sodium methoxide (20 mmol) was placed in a dry 100-ml round bottom flask, and fitted with rubber septum. The flask was charged with dry THF (60 ml) under ambient argon. To this was added 16 mmol of the arenethiol. After 15 min, 24 mmol of iodomethane was added. When the starting arenethiol was consumed, as judged by TLC, the solution was poured into a mixture of saturated aqueous sodium bicarbonate (50 ml) and hexane (50 ml). The organic layer was then washed twice with water, dried with anhydrous magnesium sulfate, and concentrated. Purification with flash chromatography (methylene chloride on silica) yielded the corresponding substituted thioanisole. Typical purified isolated yields were 70–80% for the unoptimized procedures. Care should be exercised with the arenethiols, which represent a significant stench hazard that can be minimized with the liberal use of commercial bleach solutions.

The thioanisole (7 mmol) was placed in a 250-ml round bottom flask with 80 ml of methylene chloride. The solution was cooled to −78 °C, and then mCPBA (7 mmol, as the commercial mixture with *meta*-chlorobenzoic acid) dissolved in 40-ml of methylene chloride was added dropwise. The reaction was allowed to proceed for 30 min before allowing it to warm to room temperature. The solution was then added to saturated aqueous sodium bicarbonate. After extractive work-up, the residual organic oil was purified by placing it on top of a 7-cm silica plug. Hexane (120 ml) was run through the plug. After the hexane wash, 100 ml of ethyl acetate was run through the plug and collected. The acetate was removed under reduced pressure, giving essentially pure sulfoxide. Isolated yields were typically in the range of 95%. All of these are known compounds and matched previously reported spectra when available.

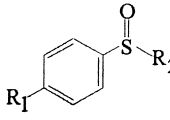
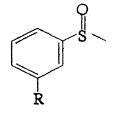
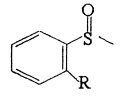
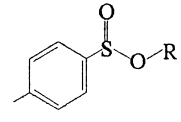
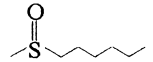
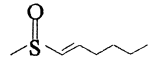
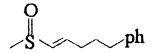
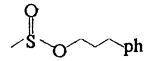
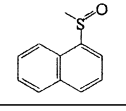
Compounds **22** and **23** were prepared using the same method [39]. Briefly, 1-hexene or 3-butenylbenzene was epoxidized with mCPBA. The epoxide was converted to the episulfide with KSCN and then oxidized to the episulfoxide with mCPBA. The episulfoxide is deprotonated and the resulting sulfenate is trapped with CH_3I. 1-Hexenyl methyl sulfoxide: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J=7.2 Hz), 1.2–1.4 (4H, m), 2.21 (2H, J=7.2 Hz), 2.59 (3H, s), 6.25 (1H, d, J=15 Hz), 6.45 (1H, dt, J=15 Hz, J=7.2 Hz). Methyl 3-phenyl-1-(E)-propenyl sulfoxide: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (3H, s), 2.5–2.6 (2H, m), 2.80 (2H, t, J=7.5 Hz), 6.25 (1H, d, J=15 Hz), 6.51 (1H, dt, J=15 Hz, J=6.9 Hz) 7.1–7.2 (3H, m), 7.2–7.4 (2H, m).

Electron impact mass spectrometry (EI/MS) was also used to characterize the structures of these sulfoxides.

2.3. Elution orders and absolute configuration assignments

A study of elution order and absolute configuration was conducted on 15 chiral sulfoxides. This entailed the collection of enantiomerically enriched

Table 1
Structures and retention data for 18 chiral sulfoxides and seven sulfinate esters on four different cyclodextrin-based GC-CSPs (see the experimental for the exact GC conditions)

No.	Structure	R–		G-TA							G-PN							G-BP							B-DM						
		R_1–	R_2–	T (°C)	k_1'	k_2'	a	R_s	n_1	n_2	T (°C)	k_1'	k_2'	a	R_s	n_1	n_2	T (°C)	k_1'	k_2'	a	R_s	n_1	n_2	T (°C)	k_1'	k_2'	a	R_s	n_1	n_2
1		H–	CH_3–	150	4.29	5.79	1.35	6.3	515	253	150	5.82	7.74	1.33	6.6	708	485	150	4.76	5.90	1.24	2.7	185	166	110	18.1	18.6	1.03	0.8	1111	642
2			CH_2=CH–	150	4.38	4.74	1.08	2.8	1174	823	150	6.30	6.74	1.07	2.3	1533	1203	150	5.03	5.33	1.06	1.3	763	517	120	12.1	12.4	1.02	0.4	726	219
3		CF_3–	CH_3–	140	5.30	5.41	1.02	1.1	2620	2124	130	10.8	11.1	1.03	1.2	1814	1452	120	15.0	15.6	1.04	0.7	398	278	120	12.9	14.1	1.09	2.9	1309	983
4		F–		150	3.39	3.80	1.12	3.7	1128	797	150	4.97	5.52	1.11	3.2	1173	940	150	4.03	4.35	1.08	1.2	330	249	120	11.8	12.5	1.06	1.7	389	299
5		CH_3–		150	6.65	7.10	1.07	2.0	809	535	150	8.19	8.68	1.06	1.9	1021	839	150	7.25	7.61	1.05	0.5	121	121	120	20.2	21.2	1.05	0.9	416	218
6		Cl–		150	8.27	8.62	1.04	1.4	1067	570	150	12.5	13.0	1.04	1.8	1915	1649	150	10.7	11.1	1.04	0.6	286	258	120	36.6	39.5	1.08	1.2	276	178
7		Br–		150	13.5	13.9	1.03	1.3	1598	771	150	21.3	21.9	1.03	1.3	1703	1483	150	17.2	17.7	1.03	0.5	306	157	120	66.3	71.6	1.08	1.2	196	193
8			CH_3–	150	6.13	8.79	1.44	6.2	280	166	150	7.66	11.0	1.44	10	1164	605	150	6.56	8.66	1.32	3.4	159	150	120	16.9	18.1	1.07	1.4	442	342
9			Cl–	150	7.57	12.7	1.68	8.5	357	129	150	11.2	19.4	1.74	20	2045	893	150	9.39	13.8	1.47	6.3	482	188	120	24.5	25.7	1.05	0.9	335	202
10			Br–	150	12.2	19.2	1.57	13.1	1795	304	150	18.5	29.3	1.58	15	1942	668	150	15.7	21.7	1.38	5.4	370	200	120	41.8	43.9	1.05	1.2	530	396
11			CH_3–	150	7.24	8.82	1.22	4.8	741	263	150	9.12	10.3	1.13	3.9	1123	924	150	7.86	8.49	1.08	1.1	203	172	120	18.7	24.5	1.31	7.8	818	705
12			Cl–	150	6.63	7.84	1.18	3.7	637	214	150	8.98	10.2	1.14	5.1	1690	1453	150	7.41	8.15	1.10	1.8	399	331	120	17.6	20.6	1.17	3.2	454	313
13			Br–	150	11.0	12.9	1.17	3.4	396	234	150	15.4	17.0	1.11	3.9	1381	1178	150	12.6	13.7	1.09	1.7	409	334	120	31.6	37.9	12.0	3.3	347	236
14			CH_3–	110	22.4	23.3	1.04	1.5	712	690	100	60.4	61.6	1.02	0.4	625	174	100	43.4	44.3	1.02	0.7	2696	747	120	11.8	12.9	1.09	3.5	1529	1275
15			CH_3CH_2–	110	28.5	31.9	1.12	4.1	940	673	110	38.4	43.4	1.13	4.8	1502	1171	110	29.8	32.5	1.09	2.9	1069	785	120	13.2	14.5	1.10	4.8	2909	1738
16			$CH_3(CH_2)_2$–	110	42.2	45.6	1.08	2.5	641	560	110	56.5	58.8	1.04	1.5	1648	1227	110	44.6	45.9	1.03	1.0	1440	724	120	20.5	21.9	1.07	3.2	2457	1813
17			$(CH_3)_2CH$–	110	27.0	30.2	1.12	4.3	1146	587	110	35.8	37.9	1.06	2.6	2289	1501	110	29.5	31.3	1.06	2.4	1857	1034	90	67.8	69.9	1.03	1.3	2785	1590
18			$CH_3(CH_2)_3$–	110	50.8	53.3	1.05	3.0	2456	1574	110	92.0	93.9	1.02	0.8	1780	615	100	43.3	44.2	1.02	0.7	1448	665	120	35.2	36.6	1.04	1.2	906	467
19			$(CH_3)_2CHCH_2$–	110	46.3	47.2	1.02	1.0	2600	1940	100	111	112	1.01	0.5	2957	1341	100	54.2	58.0	1.07	0.5	195	22	120	24.0	24.7	1.03	1.6	3623	2618
20			$CH_3CH_2CH(CH_3)$–	120	24.8	25.3	1.09	0.9	1794	1677	120	34.5	35.0	1.04	0.9	1957	6560	120	28.1	28.4	1.04	0.8	2994	3455	120	22.8	23.3				
						26.1		1.6					35.5		1.2					29.0		1.3					23.3				
						27.0	1.03	1.6	1364	841			35.8	1.01	0.7	5347	2537			29.3	1.02	0.5	3588	1938			23.3				
21				140	5.53	5.75	1.04	1.0	585	362	130	8.51	9.02	1.06	0.9	294	225	110	23	25.5	1.11	0.9	66	52	90	47.5	50.3	1.06	0.9	227	187
22			trans–	150	38.8	_	_	_	165	_	150	49.2	_	_	_	421	_	150	45.5	_	_	_	1780	_	155	21.4	22.0	1.03	0.8	1471	526
23			trans–	150	40.1	_	_	_	293	_	150	49.7	_	_	_	283	_	150	46.4	_	_	_	1218	_	150	27.1	27.9	1.03	1.0	1152	722
24				140	12.3	12.4	1.01	0.7	2430	1455	130	31.3	31.6	1.01	0.8	2810	1918	120	44.3	45.2	1.02	0.9	1925	1390	150	8.26	8.51	1.03	1.4	3203	2368
25				180	11.2	12.5	1.12	6.3	1993	1946	180	15.9	17.1	1.08	3.7	1876	1989	180	14.3	15.3	1.07	1.2	291	250	180	8.81	9.78	1.11	4.8	2533	1938

fractions by HPLC. Circular dichroism (CD) alone usually cannot be used to assign absolute configuration. However, Mislow and co-workers found that alkyl aryl sulfoxides exhibit a strong Cotton effect in the region below 250 nm [40]. They demonstrated that (*S*)-(+)-*p*-toluenesulfinamide and (*S*)-(–)-menthyl-*p*-toluenesulfinate are adequate standards in assigning absolute configuration to sulfinate esters and alkyl aryl sulfoxides. Therefore, a positive Cotton effect at 250 nm corresponded to the ''*R*'' configuration for all compounds presented in this study. Absolute configurations were assigned by matching the retention times of the single known configuration enantiomers to the retention times of the enantiomers in the racemate. In cases where the enantiomers are partially resolved, spiking the racemate with a single pure standard was performed to identify the enantiomer of interest.

2.4. Calculations

Void times (t_m) were estimated in gas chromatography by injection of methylene chloride. Retention factors (k'_1 and k'_2) were calculated according to the equation $k'=(t_r-t_m)/t_m$, enantioselectivities (α) according to $\alpha=k'_2/k'_1$ and the resolution factors (R_s) according to $R_s=1.18\times(t_2-t_1)/(W_{(0.5)1}+W_{(0.5)2})$ where t_2 and t_1 are the retention times of the first and second eluted enantiomers and $W_{(0.5)1}$ and $W_{(0.5)2}$ are the peak widths at half height of the corresponding peaks. Efficiencies (n_1 and n_2) were calculated by $n=N/L$ where N is defined by $N=5.54(t_r/(W_{(0.5)}))^2$ and L is the length of the capillary column.

3. Results and discussion

The separation data for the 17 chiral sulfoxides and eight chiral sulfinate esters is presented in Table 1. These compounds have been divided into five groups based upon their structural characteristics and were examined on four different chiral stationary phases.

3.1. Group I (chiral sulfoxides #1–7)

This group includes two racemic alkyl phenylsulfoxides and five racemic methyl *para*-substituted-phenylsulfoxides. The isothermal retention data obtained on β- and γ-cyclodextrin stationary phases varied greatly. Identical oven temperatures were used for the γ-cyclodextrin CSPs in order to evaluate the separation data under identical conditions. However, a lower temperature was required for the Chiraldex™ B-DM CSP in order to achieve any enantioselectivity. The three derivatized γ-cyclodextrin CSPs exhibited similar enantioselectivities. The enantiomers of the simplest sulfoxide **1** were baseline resolved in less than 15 min on the G-TA CSP.

Differences in enantioselectivity were observed with the Chiraldex™ B-DM CSP. The Chiraldex™ B-DM CSP exhibited only a partial separation of these enantiomers in 24 min. In comparing the G-PN and G-BP CSPs, the retention and separation factors were very similar. However, it should be pointed out that in all separations, the G-PN CSP exhibited higher efficiency and slightly higher resolution compared to the G-BP CSP.

A decrease in selectivity was observed on the three γ-cyclodextrin CSPs when the R_2-substituent was changed from methyl to vinyl. It has been shown previously in HPLC that enantioselectivity is enhanced when the stereogenic center is sandwiched between two π systems, resulting in a chiral molecule of some rigidity [41]. However, the opposite behavior is observed with the sulfoxides evaluated in this GC study. In this case, it appears that the additional double bond adjacent to the sulfur stereogenic center decreases the enantioselectivity on the γ-cyclodextrin CSPs.

A combination of size and polarity/electronegativity of the *para* substituent on methyl-phenyl-sulfoxides **3**–**7** appears to have an effect on enantioselectivity. For example, compound **1** contained an unsubstituted phenyl ring and it had the highest separation factor for this series of compounds. However, the opposite situation was encountered with the Chiraldex™ B-DM CSP; the compounds that had relatively large *para*-substituents were separated with higher selectivity. Therefore, it appears that the B-DM CSP has higher selectivity in separating the enantiomers of methyl-phenyl-sulfoxides with bulky, electronegative *para* substituents while the γ-cyclodextrin CSPs used in this study generally possess greater enantioselectivity for methyl-phenyl-sulfoxides with smaller *para* substituents.

3.2. Group II (chiral sulfoxides #8–13)

This group includes nine racemic *ortho*- and *meta*-substituted methyl-phenyl-sulfoxides. Noticeable differences exist between the enantioselectivities on the three γ-cyclodextrin CSPs and the Chiraldex™ B-DM CSP. The *meta*-substituted sulfoxides **8**, **9**, **10** always exhibited the best enantioselectivity on the derivatized γ-cyclodextrin CSPs, as shown in Fig. 2. The separations on the B-DM CSP produced broad, tailing peaks for the same compounds.

In the case of the Chiraldex™ B-DM CSP, *ortho*-substituted sulfoxides **11**, **12**, **13** produced the best separations. Selectivity appears to be influenced by the size and polarity of the *ortho* substituent. Setting selectivity aside and focusing merely on retention, there are similarities between the four CSPs. For *ortho*-substituted compounds, the chloro-substituted sulfoxide was always retained less than the methyl- and bromo-substituted sulfoxides. However, for both *para* and *meta* isomers, the methyl-substituted compounds were less retained (see compounds **1**–**10**).

3.3. Group III (chiral sulfinate esters #14–20)

This group includes seven racemic sulfinate esters. Compared to the sulfoxides discussed in Groups I and II, the liquid sulfinate esters could be separated at a much lower temperature. The Chiraldex™ G-TA and B-DM columns performed best in separating the

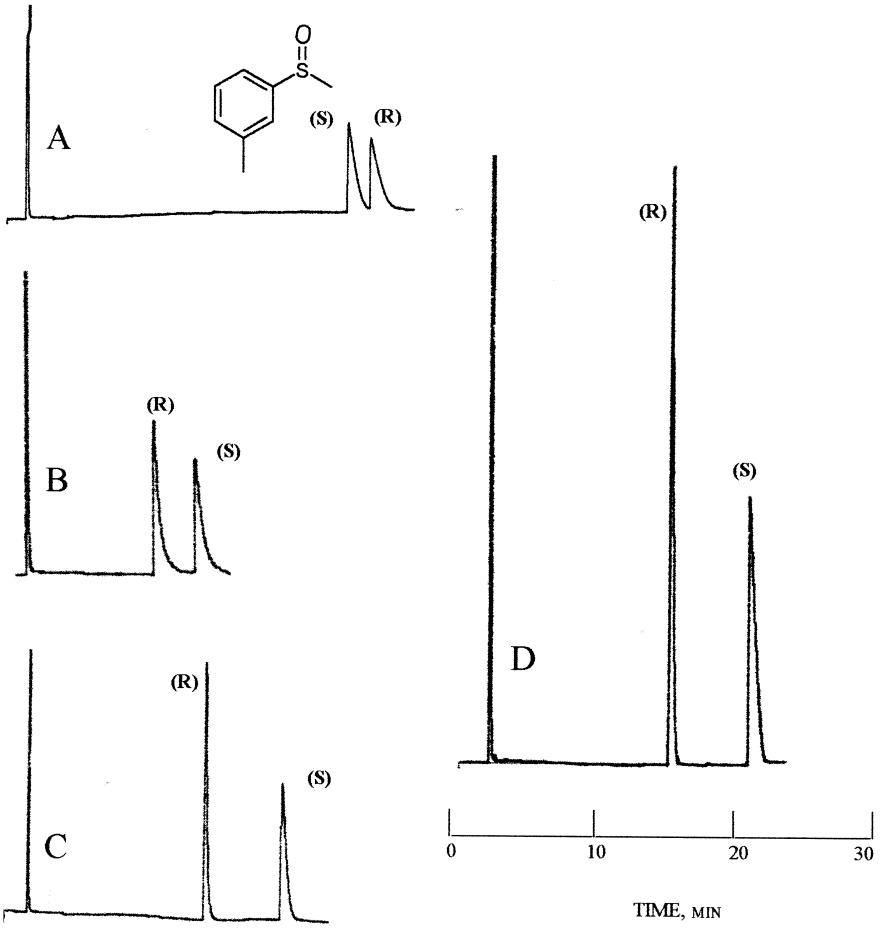


Fig. 2. Chromatogram of compound **8** (*meta*-methyl-methyl-phenyl sulfoxide) on (A) B-DM; (B) G-BP; (C) G-PN; (D) G-TA CSPs; *meta*-substituted sulfoxides exhibited higher selectivity with γ-cyclodextrins, but much lower enantioselectivity on the Chiraldex™ B-DM CSP. The elution order reversed on the B-DM CSP.

compounds of this group. Compound **20** presented an interesting case in that it possesses two stereogenic centers (i.e. the sulfur and a carbon in the branched alkyl side chain). As shown in Fig. 3, each derivatized γ-cyclodextrin CSP resolved the pair of diastereomers and enantiomers. The G-TA column, which was 30 m in length, produced the best separation of the four isomers with baseline separation of the enantiomers and only a slight overlap of the first two peaks, which are diastereomers. The Chiraldex™ G-PN and G-BP CSPs separated all four isomers with modest efficiency. The Chiraldex™ B-DM CSP, however, was only able to separate three of the four isomers.

Identification of the enantiomers and diastereomers was carried out by using pure (*R*)- and (*S*)-2-butanol and synthesizing two compounds with fixed configuration about the stereogenic center on the aliphatic chain. These compounds were then subjected to GC separation to determine the elution order with respect to the chiral side chain. Each peak from the racemate **20** was then collected using HPLC and analyzed by GC and circular dichroism to determine elution order and absolute configuration (see Experimental). It was found that the elution order for the G-TA, G-PN, and G-BP CSPs was: (*R*,*R*), (*R*,*S*), (*S*,*R*), and (*S*,*S*) where the first letter refers to the configuration about the sulfur stereogenic center and the latter gives configuration about the stereogenic carbon of the alkyl side chain. In the case of Chiraldex™ B-DM, it was observed that the CSP was not able to separate the (*S*,*R*) and (*S*,*S*) diastereomers.

The Chiraldex™ B-DM CSP exhibited the best selectivity for most sulfinate esters. In the case of the derivatized γ-cyclodextrins, the G-TA CSP demonstrated superior selectivity for most of these separations. The G-PN and G-BP CSPs possessed similar selectivities in nearly every case. We attribute this characteristic to the very similar functionality of the Chiraldex™ G-PN and G-BP CSPs. Clearly the G-TA is the most distinct of the three derivatized γ-cyclodextrin CSPs.

3.4. Group IV (chiral sulfoxides #21–23)

The group IV compounds consist of three sulfoxides with unique structures that do not easily fall under one of the previously mentioned groups. These sulfoxides presented an interesting case with the γ-cyclodextrin CSPs. Sulfoxide **21** was separated by all γ-cyclodextrin CSPs with modest enantioselectivity but lower efficiency. Although the retention of **21** is greater with the B-DM CSP, selectivity is nearly the same on all CSPs. This shows that retention and chiral selectivity are not necessarily proportional to each other. It can be observed in the separations of **22** and **23** that an additional *trans* double bond adjacent to the sulfur stereogenic center not only greatly increases retention but also decreases the enantioselectivity. This phenomenon of rigidity near the chiral center decreasing enantioselectivity was seen with gamma cyclodextrins in the Group I sulfoxides. However, this behavior is not observed with the B-DM CSP. This indicates that the size of the cyclodextrin also plays a role in the enantioselectivity and retention of these three sulfoxides.

3.5. Group V (chiral sulfoxides #24–25)

Group V consists of one chiral sulfinate ester and one chiral sulfoxide. Together, these compounds approach the molecular mass cut-off of ~230 encountered for the GC separation of sulfoxides. Higher molecular mass compounds could not be eluted from the CSPs at reasonable times and temperatures. The Chiraldex™ B-DM CSP was capable of resolving the enantiomers of compound **24** in fewer than 13 min with high efficiency. Sulfoxide **25** was easily separated by all CSPs, although at a higher temperature than all other sulfoxides and sulfinate esters previously evaluated. In the case of the 30-m G-TA CSP, the separation temperature was set at the highest suggested operating temperature of the column. Nevertheless, excellent enantioselectivity was obtained on all stationary phases. It may be possible to separate slightly higher molecular mass sulfoxides by using short columns, higher flow rates, and somewhat higher temperatures.

3.6. Elution order investigation

Fifteen of the chiral sulfoxides (Table 1) were selected to conduct a study of enantiomer elution order. Table 2 presents the results of this study. Reversing GC enantioselectivity has been previously reported for polar and nonpolar derivatized cyclo-

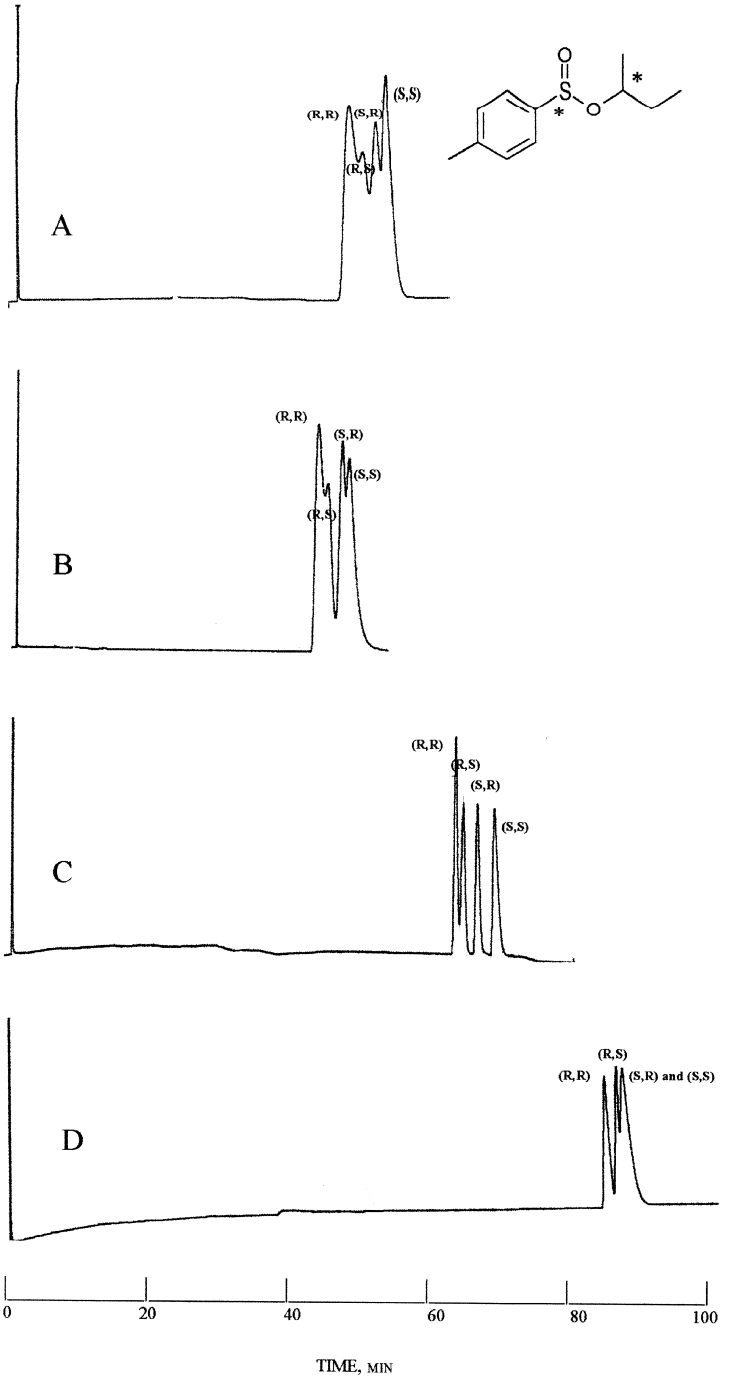


Fig. 3. Chromatograms of compound **20** (2-butyl *p*-toluenesulfinate) illustrating the separation on (A) G-PN; (B) G-BP; (C) G-TA; (D) B-DM CSPs. Peaks 1 and 2, 3 and 4 are diastereomers and peaks 2 and 3, 1 and 4 are enantiomers. Elution order and absolute configuration were determined by the collection of enantiomerically-enriched fractions by HPLC. Chiraldex™ G-TA exhibited the best selectivity in resolving all four peaks whereas B-DM resolved only three peaks.

Table 2
Elution order of enantiomers separated by GC on Chiraldex™ G-TA, G-PN, G-BP, B-DM CSPs

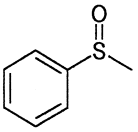
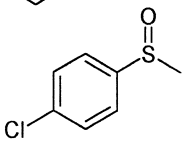
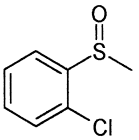
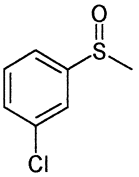
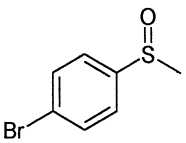
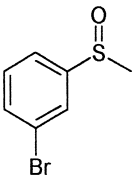
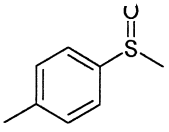
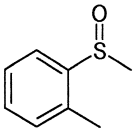
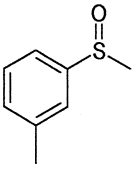
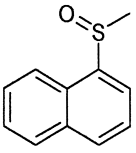
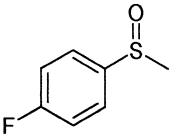
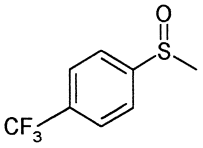
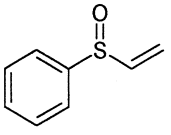
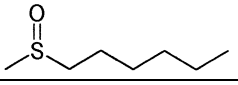
Number	Structure	G-TA	G-PN and G-BP	B-DM
1		(*R*), (*S*)	(*R*), (*S*)	(*S*), (*R*)
6		(*S*), (*R*)	(*R*), (*S*)	(*R*), (*S*)
12		(*S*), (*R*)	(*S*), (*R*)	(*S*), (*R*)
9		(*S*), (*R*)	(*R*), (*S*)	(*R*), (*S*)
7		(*R*), (*S*)	(*R*), (*S*)	(*S*), (*R*)
13		(*S*), (*R*)	(*S*), (*R*)	(*S*), (*R*)
10		(*R*), (*S*)	(*R*), (*S*)	(*S*), (*R*)
5		(*R*), (*S*)	(*R*), (*S*)	(*S*), (*R*)

Table 2. Continued

Number	Structure	G-TA	G-PN and G-BP	B-DM
11		(*R*), (*S*)	(*R*), (*S*)	(*S*), (*R*)
8		(*R*), (*S*)	(*R*), (*S*)	(*S*), (*R*)
25		(*S*), (*R*)	(*S*), (*R*)	(*R*), (*S*)
4		(*S*), (*R*)	(*R*), (*S*)	(*S*), (*R*)
3		(*R*), (*S*)	(*S*), (*R*)	(*S*), (*R*)
2		(*R*), (*S*)	(*R*), (*S*)	(*R*), (*S*)
21		(*S*), (*R*)	(*S*), (*R*)	–

Note that the prefix ''G'' denotes a derivatized γ-cyclodextrin and the prefix ''B'' denotes a derivatized β-cyclodextrin. See Fig. 1 for CSP structures.

dextrin CSPs [7]. Enantioselective reversals can occur on functionalized cyclodextrin-based CSPs either by changing the size of the cyclodextrin or by using a different derivative. Reversal of elution order was found for most sulfoxides on at least two of the four columns. All 15 chiral sulfoxides always had the same elution order on the G-PN and G-BP columns. Also, in the cases of the halogen-substituted methyl-phenyl-sulfoxides, the *para*- and *meta*-compounds always had the elution order of (*R*,*S*) while *ortho*-substituted compounds were (*S*,*R*) on these two CSPs.

In every case (Table 2) when a change in elution order occurred, it was on either the G-TA CSP or the B-DM CSP. Throughout this study, it was apparent that the separation trends on the B-DM column were different from those of the derivatized γ-cyclodextrin CSPs. These results on enantiomeric retention order confirm those observations. In addition, it is clear that the electronegative trifluoroacetyl substituents on the G-TA column give it a very different selectivity than other substituted γ-cyclodextrin CSPs. Thus, if one had to choose two CSPs that were broadly applicable and often gave the opposite elution order, the Chiraldex™ G-TA and B-DM columns would be good choices.

4. Concluding remarks

The Chiraldex™ G-PN and G-BP CSPs exhibited similar selectivity and resolution for nearly all of the chiral sulfoxides and sulfinate esters examined in this study. However, compared to the G-PN and G-BP CSPs, the G-TA CSP exhibited superior enantioselectivity for most sulfoxides and sulfinate esters. The size and polarity/electronegativity of sulfoxide substituents appear to affect their enantioselectivity on the derivatized γ-cyclodextrin and the B-DM CSPs evaluated in this study. The *meta*-substituted sulfoxides always exhibited the best selectivity on the γ-cyclodextrin CSPs. The B-DM CSP exhibited the best enantioselectivity for most of the sulfinate esters. The B-DM CSP possessed superior selectivity in separating the enantiomers of methyl-phenyl-sulfoxides with *ortho* substituents on the phenyl ring. Increased rigidity near the chiral center decreased enantioselectivity in γ-cyclodextrin-based CSPs but slightly increased enantioselectivity in the B-DM CSP. Reversal of enantiomer elution order appears to be a function of both the size of the cyclodextrin and the nature of the derivatizing groups. The G-TA and the B-DM CSPs usually gave the opposite enantiomeric elution order.

Acknowledgements

The authors wish to thank Dr Nenad Kostic for the use of his circular dichroism instrument.

References

[1] V. Schurig, J. Chromatogr. 441 (1988) 135.
[2] H. Frank, G.J. Nicholson, E. Bayer, J. Chromatogr. Sci. 15 (1977) 174.
[3] W.A. König, S. Lutz, M. Hagen, R. Krebber, G. Wenz, K. Baldenius, J. Ehlers, H.T. Dieck, J. High Resolut. Chromatogr. 12 (1989) 35.
[4] V. Schurig, H.P. Nowotny, J. Chromatogr. 441 (1988) 155.
[5] V. Schurig, H.P. Nowotny, D. Schmalzing, Angew. Chem. 101 (1989) 785.
[6] A. Berthod, W.Y. Li, D.W. Armstrong, Carbohydr. Res. 201 (1990) 175.
[7] D.W. Armstrong, W.Y. Li, J. Pitha, Anal. Chem. 62 (1990) 214.
[8] P.J. Stephens, A. Aamouche, F.J. Devlin, S. Superchi, M.I. Donnoli, C. Rosini, J. Org. Chem. 66 (2001) 3671.
[9] P.W.B. Harrison, J. Kenyon, H. Phillips, J. Chem. Soc. (1926) 2079.
[10] S. Padmanabhan, R.C. Lavin, G.J. Durant, Tetrahedron Asymmetry 11 (2000) 3455.
[11] H. Cotton, T. Elebring, M. Larsson, L. Li, H. Sorensen, S. von Unge, Tetrahedron Asymmetry 11 (2000) 3819.
[12] F. Colobert, A. Tito, N. Khiar, D. Denni, M.A. Medina, M. Martin-Lomas, J. Ruano, G. Solladie, J. Org. Chem. 63 (1998) 8918.
[13] C. Pesenti, P. Bravo, E. Corradi, M. Frigerio, S. Meille, W. Panzeri, F. Viani, M. Zanda, J. Org. Chem., 1997.
[14] Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi, Y. Takemoto, J. Org. Chem. 66 (2001) 81.
[15] Y. Yamanoi, T. Imamoto, J. Org. Chem. 62 (1997) 8560.
[16] B. Delouvrie, L. Fensterbank, E. Lacote, M. Malacria, J. Am. Chem. Soc. 121 (1999) 11395.
[17] N. Khiar, I. Fernandez, F. Alcudia, Tetrahedron Lett. 34 (1993) 123.
[18] K. Hiroi, Y. Suzuki, Tetrahedron Lett. 39 (1998) 6499.
[19] R. Tokunoh, M. Sodeoka, K. Aoe, M. Shibasaki, Tetrahedron Lett. 36 (1995) 8035.
[20] F. Furia, G. Licini, G. Modena, R. Motterle, W. Nugent, J. Org. Chem. 61 (1996) 5175.
[21] G. Farina, F. Montanari, A. Negrini, Gazz. Chim. Ital. 89 (1959) 1548.
[22] S.A. Matlin, M.E. Tiritan, Q.B. Cass, D.B. Boyd, Chirality 8 (1996) 147.
[23] C.R. Mitchell, M.J. Desai, R.D. McCulla, W.S. Jenks, D.W. Armstrong, Chromatographia (2002) submitted.
[24] A. Berthod, L.S. Xiao, R.D. McCulla, W.S. Jenks, D.W. Armstrong, J. Chromatogr. A (2002) submitted.
[25] E. Bayer, E. Küsters, G.J. Nicholson, H. Frank, J. Chromatogr. 320 (1985) 393.
[26] E. Küsters, G. Gerber, Chromatographia 44 (1997) 91.
[27] P. Charlesworth, W. Lee, W.S. Jenks, J. Phys. Chem. 100 (1996) 10152.
[28] W.S. Jenks, W. Lee, D. Shutters, J. Phys. Chem. 98 (1994) 2282.
[29] J.W. Cubbage, Y. Guo, W.S. Jenks, 2001, manuscript in preparation.

[30] J.W. Cubbage, Computational and experimental evidence on reaction mechanisms of oxidized sulfur-containing compounds in ground and excited states; Iowa State University, Ames, IA, 2001, p. 335.
[31] W. Lee, W.S. Jenks, J. Org. Chem. 66 (2001) 474.
[32] A.R. Hajipour, S.E. Mallakpour, A. Afrousheh, Tetrahedron 55 (1999) 2311.
[33] J.M. Klunder, K.B. Sharpless, J. Org. Chem. 52 (1987) 2598.
[34] M.A.M. Capozzi, C. Cardellicchio, F. Naso, P. Tortorella, J. Org. Chem. 65 (2000) 2843.
[35] D. Landini, G. Modena, G. Scorrano, F. Taddei, J. Am. Chem. Soc. 91 (1969) 6703.
[36] L. Bohe, M. Lusinchi, S. Lusinchi, Tetrahedron 55 (1999) 155.
[37] R.C. Gadwood, I.M. Mallick, A.J. DeWinter, J. Org. Chem. 52 (1987) 774.
[38] M. Hirano, S. Yakabe, S. Itoh, J.H. Clark, T. Morimotoa, Synthesis (1997) 1161.
[39] M.D. Refvik, R.D.J. Froese, J.D. Goddared, H.H. Pham, M.F. Pippert, A.L. Schwan, J. Am. Chem. Soc. 117 (1995) 184.
[40] K. Mislow, M. Green, P. Laur, J. Melillo, T. Simmons, A. Ternay, J. Am. Chem. Soc. 87 (1965) 1958.
[41] S.M. Han, Y.I. Han, D.W. Armstrong, J. Chromatogr. 441 (1988) 376.
[42] D.W. Armstrong, W. Li, C.-D. Chang, J. Pitha, Anal. Chem. 62 (1990) 914.