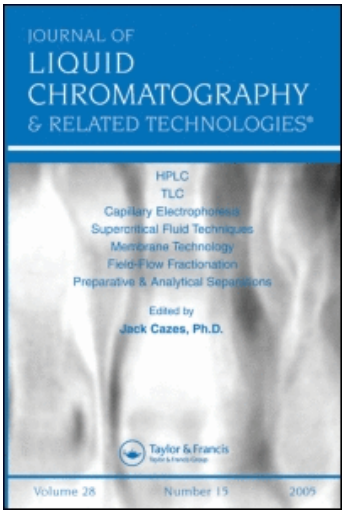

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ON-LINE CD DETECTION IN CHIRAL SEPARATION OF SPIRO-λ⁴-SULFANES

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ON-LINE CD DETECTION IN CHIRAL SEPARATION OF SPIRO-λ^4-SULFANES

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ABSTRACT

Enantiomers of chiral spiro-λ^4-sulfanes with equatorial diaryl and axial bis(acyloxy), (alkoxy)-(acyloxy) or (acylamino)-(acyloxy) S-substituents were separated on a Kromasil-based chiral sorbent, namely on O,O´-bis(3,5-dimethylbenzoyl)-N,N´-diallyl-L-tartardiamide silica CSP, by using n-hexane (or n-heptane) – dioxane (or 2-propanol) isocratically mixed mobile phases. Direct chiral separation was monitored by a home-made HPLC-CD system consisting of a circular dichroism (CD) spectrophotometer (Jobin-Yvon Model III Dicrograph) and a high performance liquid chromatograph. The system was used in conjunction with HPLC-UV to study the chemical and stereochemical purity of the samples. By the stopped-flow technique CD spectra were measured in the 350-230 nm spectral range. Monitoring at a selected wavelength enabled high-sensitivity detection. Racemic spiro-λ^4-sulfanes were also separated into pure enantiomers on preparative scale. Regardless of the structural type of diaryl-spiro-λ^4-sulfanes, the first-eluted enantiomer was always found to show a CD spectrum marked by an intense positive band near 240 nm and a negative one at ≈210 nm (positive couplet) that allows prediction of absolute configuration.

INTRODUCTION

Recently, there is an increased interest in developing methods which can be used to study chiroptical properties and determine absolute configurations, to resolute racemates and to detect and quantitate stereochemical purity of optically active compounds.

Apparently, high performance liquid chromatography (HPLC) is the method of choice to separate diastereomers or, by using columns packed with chiral stationary phase, to separate enantiomers of chiral molecules.[1,2] In the case of enantiomer separation the use of chiral monochromatic (e.g. polarimetric) detectors has the advantage of establishing a correlation between the elution order (R_F) of enantiomers and the optical activity at a given wavelength.[3-5] The most efficient experimental approach is the application of a spectropolarimeter or dichrograph as chiral detector (HPLC-ORD or HPLC-CD system).[6,7] Monitoring at selected wavelength values enables one to detect and quantitate both enantiomeric and diastereomeric impurities and to improve detection level. However, such a device can also be used in the stopped-flow mode for recording the full-scale circular dichroism spectrum during chromatographic separation.[8,9]

As a part of our systematic efforts to develop new methods for determining the stereochemical purity of chiral compounds, we coupled an HPLC system with a CD spectrophotometer (Jobin-Yvon Model III Dichrograph). The combination of UV and CD detection opened a simple and inexpensive route for optimizing the conditions of separation and test the column filled with chiral stationary phase.

In this paper we report the direct chiral chromatographic resolution and chiroptical characterization of a series of racemic spiro-λ^4-sulfanes with O-acyl (**1a-e**),[10, 11] O-alkyl (**2**),[12] and N-acyl (**3a-e**, **4** and **5**)[13, 14] type axial ligands, as well as those of sulfoxide **6**[10] (the precursor of **1c**) and sulfoxide-lactone **7**[12] (a monocyclic isomer of **2**, Figure 1).

Starting from *o,o'*-disubstituted diaryl sulfoxides, all these compounds were synthesized earlier by Kapovits et al.[10] who also determined their geometry (except for **1b-e** and **3b-e**) by X-ray diffraction. Spiro-compounds **1-5** have trigonal bipyramidal structure. The hypervalent axial S–O bonds in bis(acyloxy) species (type **1**) are equivalent, whereas the bonding systems of alkoxy-acyloxy (type **2**) and acylamino-acyloxy compounds (type **3-5**) practically correspond to an alkoxysulfonium- and acylaminosulfonium-carboxylate zwitterionic structure, respectively, which is stabilized by an axial sulfur-oxygen close contact.

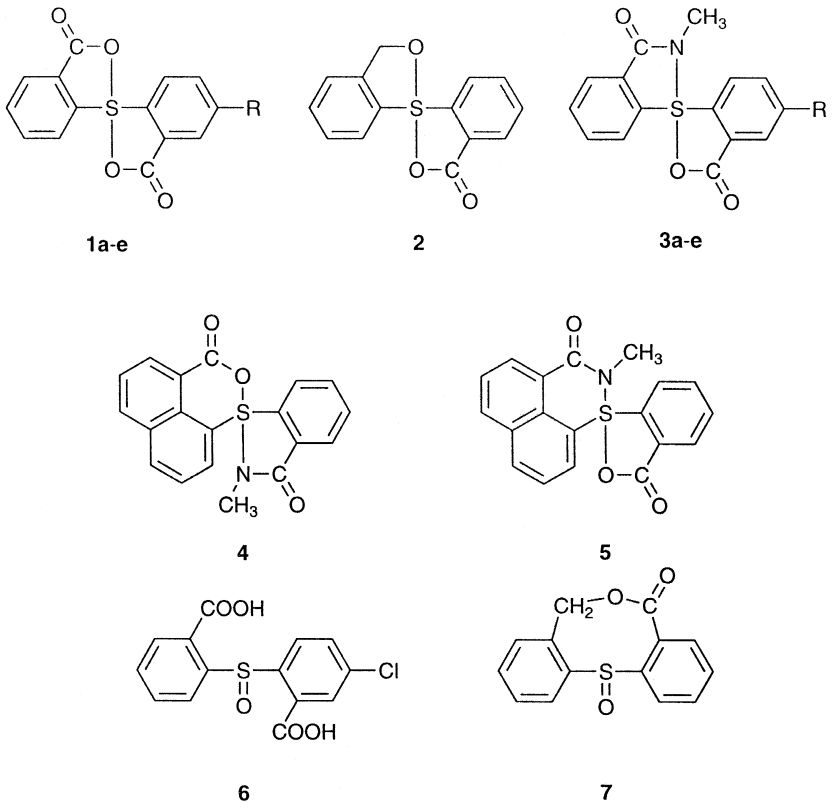

Figure 1. Model compounds; R = H (**a**), NO_2 (**b**), Cl (**c**), OMe (**d**), Me (**e**).

The spiro-λ⁴-sulfanes having a central four-coordinated stereogene spiro-sulfur atom of (ab)S(ab) or (a'b)S(ab) type are of particular interest because they exhibit chirality due to a special type of molecular dissymmetry not investigated so far in detail.

By using the method of chiral chromatographic separation, Allenmark et al.[15,16] succeeded in separating the first known bis(acyloxy)spiro-λ⁴-sulfane **1a**[10] and its analogue with two naphthalene rings (see compound **4** in ref. 17) into optically active components. To obtain enantiomers a kinetic resolution procedure was applied for racemic bis(alkoxy)spiro-λ⁴-sulfanes (see compounds **2a-b** in ref. 18). In another approach prochiral sulfoxide diols were dehydrated under asymmetric conditions to yield the same bis(alkoxy)spiro-λ⁴-sulfanes with a rather low enantiomeric excess (below 5%).[19] In all of the above cases, however, the correlation between chiroptical properties and absolute

configuration was not established. Recently, Szabó et al. dehydrated stereospecifically an optically active sulfoxide of known absolute configuration[20] into the optically active (alkoxy)(acyloxy)-spiro-λ^4-sulfane (+)-**2** and determined its absolute configuration by X-ray diffraction.[21] This first provided a means of correlating the CD behaviour of a spiro-λ^4-sulfane with its absolute configuration. The possibility of establishing the configuration of related spiro-λ^4-sulfanes **1** and **3** prompted us to separate and characterize the enantiomers of 12 racemic spiro-λ^4-sulfanes on a column packed with chiral stationary phase by using HPLC-CD detection.

Materials

5-X-1,1´-spirobi(3*H*-2,1-benzoxathiol)-3,3´-dione (**1a-e**, X = H, NO_2, Cl, OMe and Me, respectively), 1,1´-spirobi(3*H*-2,1-benzoxathiol)-3-one (**2**), spiro(5-X- 3*H*-2,1-benzoxathiol-3´-one-1,1´-3*H*-2,1-benzazathiol-2-methyl-3-one) (**3a-e**, X = H, NO_2, Cl, OMe and Me, respectively), spiro[3*H*-2,1-benzazathiol-2´-methyl-3´-one-1,1´- naphtho-(1,8-*d,e*)-3*H*-2,1-oxathiin-3-one] (**4**), spiro[3H-2,1-benzoxathiol-3´-one-1,1´-naphtho-(1,8-*d,e*)-3*H*-1,2-thiazin-2-methyl-3-one] (**5**), 5-chloro-2,2´-sulfinyldibenzoic acid (**6**) and 5*H*,7*H*-dibenzo[*c,f*]-1,5-oxathiocin-5-one 12-oxide (**7**) were synthesized according to the methods given in the literature. (ref. 10 for **1a-d** and **6**; ref. 12 for **2** and **7**; ref. 13 for **3a**, **4** and **5**; ref. 14 for **3b-e**; ref. 11 for **1e**). The formulae of compounds investigated are shown in Fig. 1. The solvents n-hexane, n-heptane, 2-propanol, dioxane, dichloromethane and acetonitrile were all of HPLC grade from Merck (Germany).

EXPERIMENTAL

Apparatus

Separations were achieved on a Knauer system consisting of two pumps Model 64 with analytical pump head, a gradient programmer Model 50B, an injection valve with 20 μL sample loop and a UV spectrophotometer with analytical flow cell (Knauer GmbH, Germany). The chromatographic data were collected and processed with CHROMAPEX software (Data-Apex Ltd., Czech Republic).

The Knauer system was also applied for semipreparative HPLC with preparative pumpheads, flow cell and injector (1-10 mL loop). The CD spectra were measured in acetonitrile on a Jobin-Yvon Model VI Dichrograph (France) at room temperature in 0.02, 0.1, and 0.2 cm cells, at concentrations of 0.2-1

$mM \cdot dm^{-3}$. The on-line HPLC-CD measurements were performed on a home-made HPLC-CD system consisting of a Liquochrom (Labor MIM, Hungary) or Knauer chromatograph and a Jobin Yvon Model III Dichrograph by using a flow cell of 20 μL (Hellma Co., Germany). The software handling of CD, HPLC-CD, and HPLC-UV, elaborated and developed by Dr. Ö. Farkas will be published elsewhere. IR spectra were taken on a Specord IR 75 (Zeiss, Jena) spectrophotometer. NMR spectra were recorded on a Bruker WP 80SY instrument.

HPLC Conditions

The column packing material was a Kromasil-based chiral sorbent, O,O´-bis(3,5-dimethylbenzoyl)-N,N´-diallyl-L-tartardiamide-Kromasil-silica CSP[22, 23], 5 μm, (250x4.6 mm), No 2536, developed by Allenmark et al. and available from EKA Nobel AB (Sweden). The mixtures of n-hexane (or n-heptane) and 2-propanol (or dioxane) were used as mobile phase systems.

The column effluents were monitored by UV at 254 nm and by CD at 242 nm. The chromatograph was operated isocratically between 0.8 and 1.5 $mL \cdot min^{-1}$. The same eluent systems were used for semipreparative separations with a 250x8 mm Knauer column own-packed with the chiral sorbent above (particle size 10 μm, methanol–acetone slurry packing at 375 bars by Haskel-pump).

The sensitivity of the spiro-λ⁴-sulfanes towards hydrolysis required the chromatography to be carried out under strictly anhydrous conditions. We used completely dry solvents as mobile phases and for dissolution of samples. The anhydrous solvents were stored on sicc. Na_2SO_4.

Because the solubility of racemates is rather poor in apolar solvents, samples were dissolved in a small amount of an effective solvent (dioxane, dichloromethane or dimethylformamide) then diluted with the eluents. The starting concentration was usually 0.5-1.0 mg/mL and the solutions were diluted 20-50 times according to sensitivity requirements [AUFS (UV) 0.04-0.16]. By the same reason the separated enantiomers crystallized very easily from the pooled fractions of the eluents. The enantiomeric purity of the isomers was checked on an analytical column with the same packing.

RESULTS AND DISCUSSION

The direct chromatographic resolutions of spiro-λ⁴-sulfanes **1a-e**, **2**, **3a-e**, **4** and **5**, as well as that of sulfoxide **6**, and sulfoxide-lactone **7** were performed on

Table 1

Separation of Racemic Spiro-λ^4-Sulfanes 1-5, Sulfoxide 6, and Sulfoxide-Lactone 7[a]

λ^4-Sulfane	k_1'	k_2'	α	R_s	Eluent[b] (v/v)
	5.51	8.37	1.52	7.78	Hx-D 80:20
1b	3.17	5.05	1.59	7.25	Hp-D 70:30
1a	3.80	7.48	1.97	12.38	Hx-D 80:20
	4.14	8.14	1.96	12.32	Hx-D-P 84:8:8
1d	5.45	10.26	1.88	12.08	Hx-D 80:20
1e	4.07	6.60	1.62	8.93	Hx-D 80:20
2	5.34	6.32	1.18	2.07	Hx-D 70:30
	10.00	11.00	1.10	1.28	Hx-Pr 90:10
3a	5.89	6.43	1.09	1.35	Hx-D-Pr 80:10:10
3b	22.65	24.94	1.10	1.25	Hp-D 70:30
3c	9.76	12.08	1.24	3.50	Hp-D 70:30
3d	8.89	10.34	1.16	2.30	Hp-D 70:30
3e	8.31	9.43	1.13	1.93	Hp-D 70:30
4	3.22	6.06	1.88	9.81	Hx-D 80:20
5	3.13	5.70	1.82	8.75	Hx-D 80:20
6	4.10	---	---	---	Hx-P 90:10
7	4.27	5.00	1.17	1.37	Hx

[a] In n-hexane-dioxane (Hx-D) and n-heptane-di9xane (Hp-D) systems used the first eluted enantiomer always had a positive $\Delta\varepsilon$ value at 242 nm and a CD spectrum marked by a positive band at =240nm.

[b] Solvents used for elution: Hx = n-hexane; Hp = n-heptane; D = dioxane; P = 2-propanol.

the chiral sorbent (see Experimental). Data on chromatographic separations, including capacity factors (k'), separation factors (α) and resolution (R_S) values obtained are summarized in Table 1. Fig. 2a shows a typical chromatographic pattern for racemic **1c**.

Under isocratic conditions, optimum analysis time and effective resolutions were achieved (except for **6**) with the optimization of the eluent composition, as shown in Table 1. In some cases (e.g. for **1c** and **1d**) more than 10 minutes difference in retention time was measured for the enantiomers. The theoretical plate numbers of columns were generally between 5,000 and 10,000. Baseline separations required to perform quantitative analysis of stereochemical purity were obtained without difficulty (α = 1.2-1.9; R_S = 1.9-12.3).

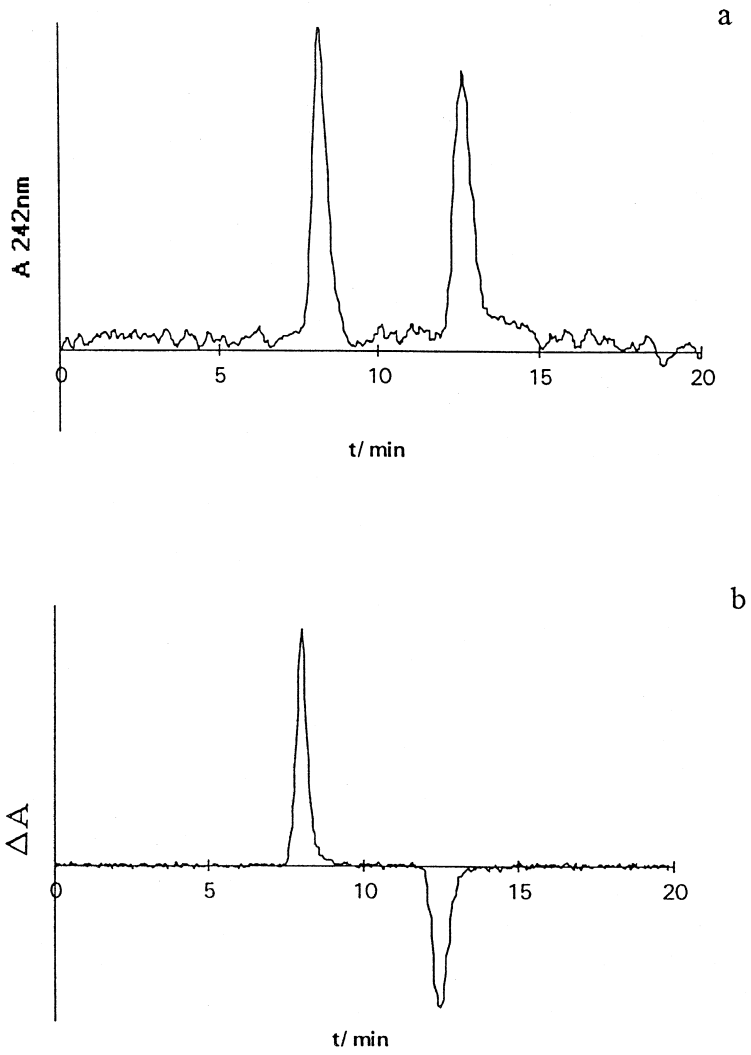

Figure 2. Chromatographic patterns for racemic **1c**. Column: Kromasil-CSP, 5μm (250 x 4.6 mm). Eluent: 80:20 (v/v) n-hexane–dioxane. Flow rate: 1.2 mL·min^{-1}. Detection: (a) UV at 242 nm, (b) CD at 242 nm.

A 80:20 hexane-dioxane mixture was used generally for the separation of bis(acyloxy)spiro-λ^4-sulfane enantiomers (type **1**). Here the parent compound **1a** has a greater retention time than its substituted derivatives **1c-e**. Because the (acylamino)(acyloxy)spiro-λ^4-sulfanes (type **3**) always showed higher retention than the corresponding bis(acyloxy) derivatives, these compounds were

separated with a more polar eluent (usually with a 70:30 heptane-dioxane mixture). In this series the nitro derivative **3b** showed the greatest retention, and the measured values also markedly exceeded those obtained for the bis(acyloxy) analogue **1b** in the same solvent. The comparison of data on substituted **1b-e** and **3b-e** derivatives indicates that in both series the decrease of α and R_S values follows the substituent order Cl > OCH_3 > CH_3 > NO_2, meaning that the separation of nitro-derivatives takes place with the lowest efficiency. On the other hand, this is why the chloro derivative **1c** was chosen to investigate the separation of spiro-λ^4-sulfanes in various solvents and to illustrate their chromatographic behaviour. It is remarkable that the unsubstituted parent compound **3a** (with two benzene rings) and its analogues **4** and **5** (with a benzene and a naphthalene ring) could be well separated only by eluent mixtures containing the apolar n-hexane component in a higher (80%) concentration, and the former compound showed the greater retention.

From the (alkyloxy)(acyloxy)spiro-λ^4-sulfanes only the unsubstituted parent compound **2** was prepared in enantiomeric forms of known absolute configuration by stereospecific synthesis. The racemic form of **2** was well separated by using a solvent mixture n-hexane–dioxane (70:30).

The chromatographic patterns of crude spiro-λ^4-sulfanes clearly show that the precursor sulfoxides were always eluted before the corresponding spiro-λ^4-sulfanes, but in many cases without enantiomeric separation (see e.g. the pure racemic form of sulfoxide **6**, the precursor of **1c**, in Table 1). Sulfoxide impurities were not found in the separated spiro-λ^4-sulfane enantiomers, which excludes the possibility of hydrolytic decomposition of spiro-λ^4-sulfanes during the chromatographic process.

It may be assumed that the good chiral separation of spiro-λ^4-sulfanes having two equatorial S-aryl substituents can be attributed to their butterfly-like (see ref. 1) molecular shape. The role of the rigid spiroring structure is obviously very important, because the sulfoxide lactone **7** (the monocyclic isomer of **2**) with eight-membered ring exhibits only very poor resolution (see Table 1), and the sulfoxide **6** (the precursor of **1c**) with two "free-rotating" aryl groups can not be separated at all under similar conditions. The greater retention of (acylamino)(acyloxy)spiro-λ^4-sulfane as compared to that of bis(acyloxy) analogues (see e.g. **3b** and **1b** in Table 1) may be ascribed to the more polar (zwitterionic) structure of the former compounds, which presumably promotes the interaction with the chiral sorbent. The substitution of one of the acyl C=O groups for CH_2 groups (**1a**→**2**) decreases the interaction with the chiral sorbent simultaneously with decreasing α, but increasing k' due to higher asymmetry. (Note that in the (acyloxy)(alkoxy)spiro-λ^4-sulfanes **2** the C_2 symmetry of the parent diacyloxy compound **1a** is lost.)

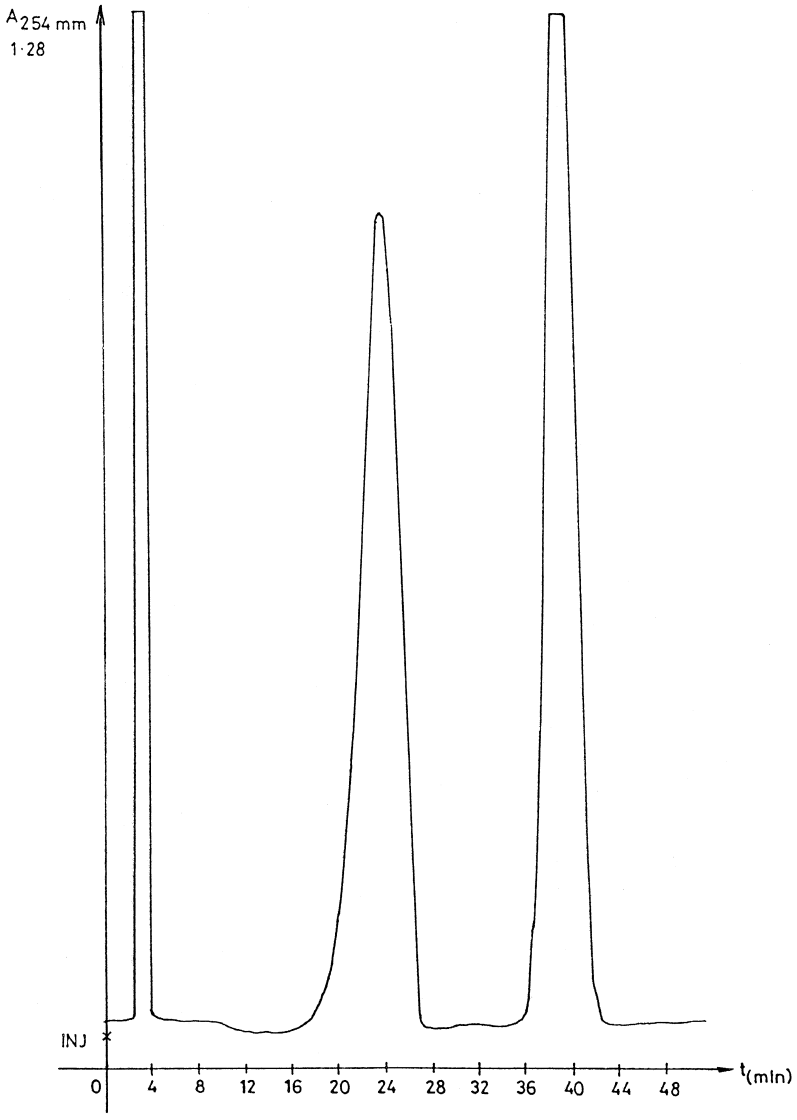

Figure 3. Semipreparative chromatogram showing the behaviour of **1c** on the chiral column described in Experimental. Mobile phase: 90:10 (v/v) n-hexane–2-propanol. Flow rate: 4 mL·min^{-1}, from 30. min 6 mL·min^{-1}. Quantity: 60 mg (196 μmol)/1 mL solvent mixture.

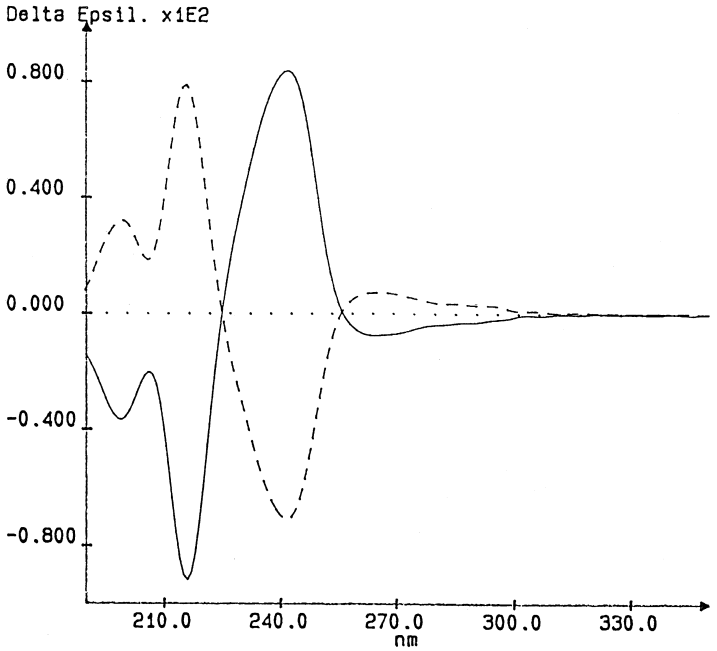

Figure 4. CD-spectra recorded in acetonitrile for the enantiomers of **1c**. First eluted enantiomer (—): $\Delta\varepsilon$ = –91.94 (216 nm), +83.93 (242 nm), –7.37 (266 nm); Second eluted enantiomer (---): $\Delta\varepsilon$ =79.90 (216 nm), –70.35 (242 nm), +7.93 (266 nm).

The good results in separating spiro-λ^4-sulfane enantiomers drew our attention to scale-up the separation from analytical to semipreparative or preparative scale. As shown in Figure 3, the separations were found to be excellent with packing material of 10 μm particle size. Thus a semipreparative column was packed for production of pure enantiomers which could not be obtained by other separation methods.

The elution order of enantiomers was established by both off-line and on-line CD detection. At first we made repeated injections and collected the respective peaks eluted from the column. Larger amounts were obtained by fraction collection from the semipreparative column. A typical CD spectrum for an isolated enantiomer of **1c** is shown in Figure 4.

The HPLC-CD system provided a means of directly establishing a correlation between elution order and optical activity by on-line chiral detection at a selected wavelength (242 nm, see Figure 2b).

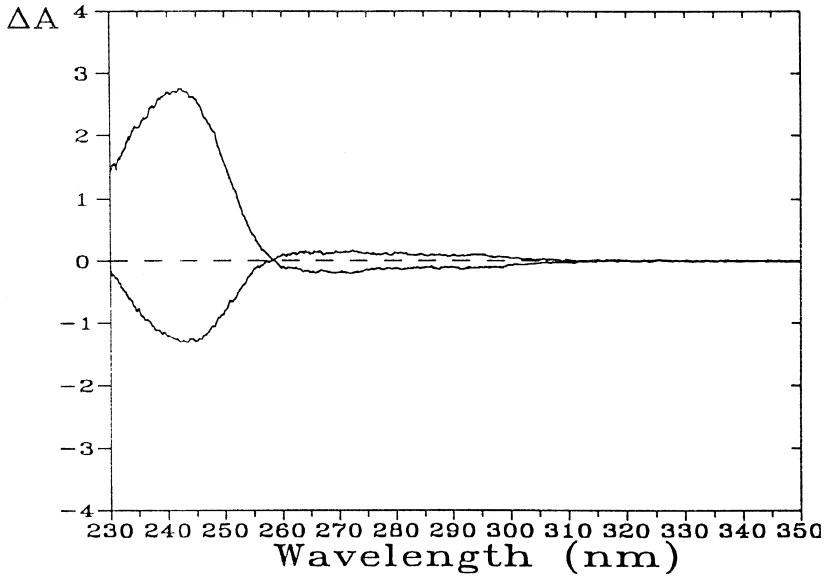

Figure 5. Stopped-flow CD spectra recorded during the separation of racemic **1c** on the chiral column described in Experimental. Mobile phase: 80:20 (v/v) n-hexane–dioxane. Flow rate: 1.2 mL·min^{-1}. Quantity: 3.5 mg (11.4 μmol)/1mL solvent mixture. Sensitivity: 5x10^{-6}. Stop points: at 580 sec for the first eluted enantiomer (—); at 920 sec for the second eluted enantiomer (---).

The enantiomer having a positive CD value at 242 nm was consistently the first eluted by the optimized mobile phase system used. By using stopped-flow technique, full CD spectra of the enantiomers could also be obtained on-line. The CD spectra of the enantiomers are in an almost complete mirror image relationship. More importantly regardless of the structural type of diaryl-spiro-λ^4-sulfanes, the first-eluted enantiomer was always found to show a CD spectrum marked by an intense positive band near 240 nm and a negative one at ≈210 nm (positive couplet, see later, Figure 5).

The dual UV-CD detection helped us to identify all components (enantiomeric spiro-λ^4-sulfanes, sulfoxide impurities, etc.) in the samples. It was possible to check, directly, the enantiomeric relationships and the full CD spectra of the separated enantiomers.

To obtain samples for X-ray crystallographic determination of absolute configurations a scaled-up separation has been developed on the same chiral sorbent (10 μm), but in a semipreparative HPLC column (250 x 8 mm) with higher flow rate (4-8 mL·min^{-1}). The purity of the pooled fractions was checked

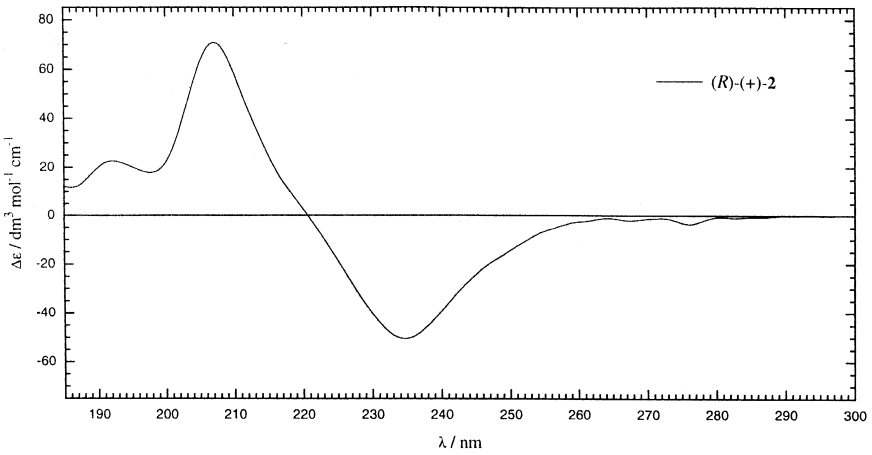

Figure 6. CD spectrum recorded in acetonitrile for spiro-λ^4-sulfane *R*-(+)-**2**.

by the analytical HPLC method. The optical purity values were greater than 99.8%. The solvents were slowly evaporated, the crystallization started directly very soon. The pure enantiomers were collected, washed, and dried. Thus, the possibility is given now for the determination of absolute configuration of various spiro-λ^4-sulfanes.

The HPLC-CD system described in Experimental made it possible to find a general correlation between chromatographic parameters and optical activity of spiro-λ^4-sulfanes **1**-**3**. As mentioned earlier, the absolute configuration of one of the enantiomers of the diaryl(acyloxy)(alkoxy)spiro-λ^4-sulfane **2** has been reported recently.[21] According to the nomenclature introduced by Martin et al,[24] the absolute configuration for the enantiomer of **2** which has a positive rotation at 546 nm ($[\alpha]^{25}_{546}$ = 31.2; c = 0.5, DMF) is to be assigned as *R*. This enantiomer shows a CD spectrum marked by a negative first and a positive second band (negative exciton couplet, Figure 6).[25]

By using the same eluent system as for the separation of spiro-λ^4-sulfanes of type **1** and **3**, the peak of *R*-(+)-**2** appeared with a longer retention time than its enantiomer. We mentioned above that the CD spectra of the first eluted enantiomer of all the other known representatives of types **1** and **3** spiro-λ^4-sulfanes have a positive first and negative second band in the ^1L_a region (positive couplet). The CD spectra of spiro-λ^4-sulfanes **1**-**3** are governed by the optical activity of the aromatic chromophores.

The similar band positions and the opposite positive sign of the exciton couplet in the ^1L_a region strongly suggest an *S* absolute configuration for the enantiomers which are first eluted by the mobile phase used for the separation. (The chiroptical properties of spiro-λ^4-sulfanes **1**-**3** will be discussed in detail elsewhere.)

The application of the HPLC-CD system for monitoring on-line both the separation and the CD spectra opened a new and simple route for assigning or at least predicting the absolute configuration of spiro-λ^4-sulfanes **1**-**3** having a trigonal bipyramidal chiral structure. Notably, the comparison of the chromatographic and CD spectroscopic behaviour of the enantiomers described in this paper also allowed us to predict firstly the absolute configuration of the enantiomers of the C_2 symmetric molecule **1a** which has an achiral sulfoxide precursor.

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11. Compound 1e was prepared by the dehydration of 5-methyl-2,2´-sulfinyl-dibenzoic acid with Ac_2O by the analogy with other spiro-λ^4-sulfanes (cf. ref. 10). Yield 77%; mp 273-278 °C; IR (KBr): 1735vs (C=O) cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ 2.37 (s, Me), 7.2-8.2 (m, ArH).

12. Racemic spiro-λ^4-sulfane **2** and sulfoxide-lactone **7** were obtained by the method given for the preparation of the enantiomers of **2** and **7** in ref. 21. Spectroscopic data (IR and NMR) were identical with those of the enantiomers.

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