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Enantioselective Liquid Chromatographic Retention of a Series of Sulfoxides and *N*-Substituted Sulfoximines on Chiral Stationary Phases

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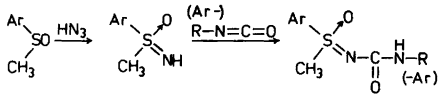
With the use of stationary phases comprised of (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine bound to aminopropyl silica, either covalently *via* an amide bond (CSP 1) or ionically (CSP 2), the liquid chromatographic behaviour of a series of methoxycarbonyl substituted sulfoxides as well as *N*-aryl- and -alkylcarbamyl *S*-methyl *S*-phenyl sulfoximines was studied. Generally, the sulfoximine derivatives were better resolved on columns containing CSP 1, whereas the CSP 2 columns were most suitable for the sulfoxides. The substituted sulfoximines, with one exception, were all shown to be resolvable, giving separation factors $\alpha = 1.10-1.13$; the *R* enantiomer being the first eluted. This contrasts with the behaviour of the parent compound, methyl phenyl sulfoxide as well as other alkyl phenyl sulfoxides where on CSP 2, with no known exception, the *S*-form always is the first eluted enantiomer.

Chiral stationary phases based on (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine have been shown to be highly efficient for the direct liquid chromatographic separation of enantiomers of a wide variety of compounds.[1–5] In this paper the resolution of a type of compounds not earlier investigated, *N*-substituted sulfoximines, is described together with a series of sulfoxides with a methyl or diphenylmethyl ester group.



Scheme 1.

RESULTS AND DISCUSSION

The sulfoximines were synthesized according to the route given below. A series of carboxylic substituted sulfoxides served as precursors for the esters which were obtained *via* reactions with diazomethane or diphenyldiazomethane. The compounds investigated, the types of stationary and mobile phases used and a summary of retention data are shown in Table 1.

A quantitative measure of the degree of chiral recognition exerted by the stationary phase is given by the enantiomeric separation factor, α, which is defined as the ratio of the two capacity factors,[6] k', obtained for the last and first eluted enantiomer, respectively.

The structures of the chiral stationary phases are given in Fig. 1.

It is evident that the methyl aryl sulfoxides investigated, all conform within the chiral recognition model proposed earlier,[5] the *R* enantiomer being the one last eluted (Fig. 2). The relatively high α-value obtained for the non-aromatic methyl 2-ethylsulfinylcyclopentene-1-carboxylate, however, is noteworthy in view of its reduced ability to act as a π-donor. Unfortunate-

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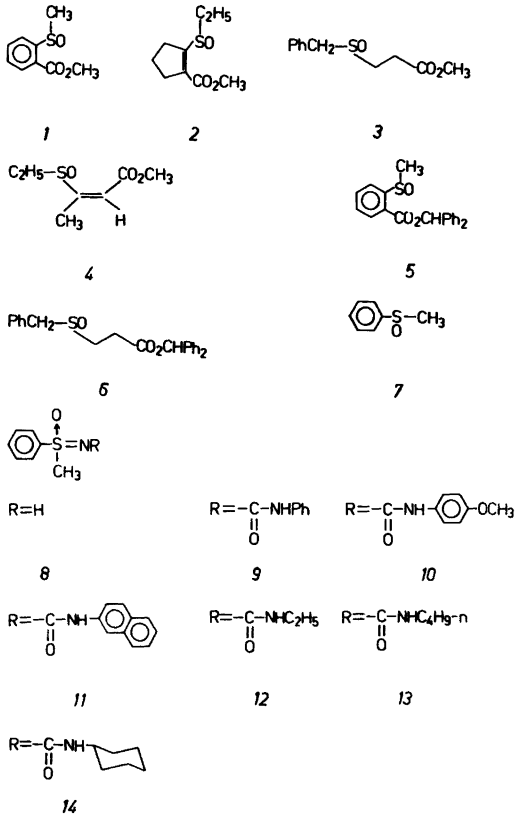
Table 1. Chemical structures and chromatographic retention data of the various compounds investigated.

No.	M.p. °C	*k'* s	*α*	First enantiomer eluted
A. Sulfoxides. Column: CSP 2, mobile phase: 5 % 2-propanol in hexane.				
1	65	15.8, 17.3	1.10	*S*-(−)
2	[a]	8.9, 9.7	1.09	(+)
3	72–75	18.3	(1.0)	–
4	[a]	6.4	(1.0)	–
5	127–9	21.2, 21.9	1.03	*S*-(−)
6	116–9	[b]	(1.0)	–
7	[a]	4.7, 4.9 [c]	1.05	*S*-(−)
B. Sulfoximines. Column: CSP 1, mobile phase: 20 % 2-propanol in hexane.				
8	[a]	5.38	(1.0)	–
9	125–8	12.38, 13.97	1.13	R
10	[b]	24.25, 27.25	1.12	R
11	[b]	27.38	(1.0)	–
12	[b]	8.25, 9.03	1.10	R
13	[b]	4.88, 5.50	1.13	R
14	[b]	4.50, 5.03	1.11	R

[a] Liquid at room temperature. [b] Not determined. [c] 10 % 2-propanol in hexane.



ly, the absolute configurations of the antipodes are not yet known for this compound, so whether the elution order with respect to the configuration at sulfur is the same or not cannot be deduced.

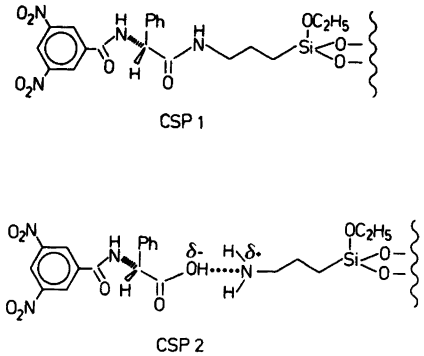


Fig. 1. Structural representation of the chiral stationary phases used; (a) CSP 1, (b) CSP 2.

In the case of the substituted sulfoximines, all compounds that resolved showed the same elution order, *R* before *S*, despite the very large variation in the *k'*-value with the nature of the *N*-substituent. Considering the rules of the Cahn-Ingold-Prelog nomenclature system, however, these results mean that the elution order is reversed when the lone-pair in methyl phenyl sulfoxide is replaced by the RN-group. This, in turn, implies that the sulfoximines adopt another orientation with respect to the stationary phase than the sulfoxides. The limited data obtained so far, however, preclude any suggestion of a chiral recognition model for this case. Fig. 3 shows a chromatogram of one of the compounds in the series of substituted sulfoximines corresponding to an *α*-value of 1.13.

EXPERIMENTAL

Chromatography. The liquid chromatography experiments were performed isocratically with

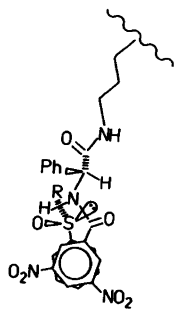


Fig. 2. Chiral recognition model showing the preferred orientation between CSP 1 and the most retained enantiomer (*R*) of an alkyl aryl sulfoxide.

the use of an Altex mod. 100 or 110 A solvent pump, a Beckman 210 injector equipped with a 20-μl loop, and an Altex mod. 152 dual wavelength (254 and 280 nm) or Beckman mod. 165 variable wavelength detector. The analytical columns used (4.6×250 mm) were packed with γ-aminopropylsilica (5 μm) to which (*R*)-*N*-(3,5-dinitrobenzoyl)-phenylglycine is anchored covalently (CSP 1) or ionically (CSP 2). The columns are commercially available from Regis Chem. Co. (CSP 1) and Baker Chem. Co. (CSP 2), respectively. Hexane containing 5–20 % of 2-propanol was used as the mobile phase for all chromatographic runs.

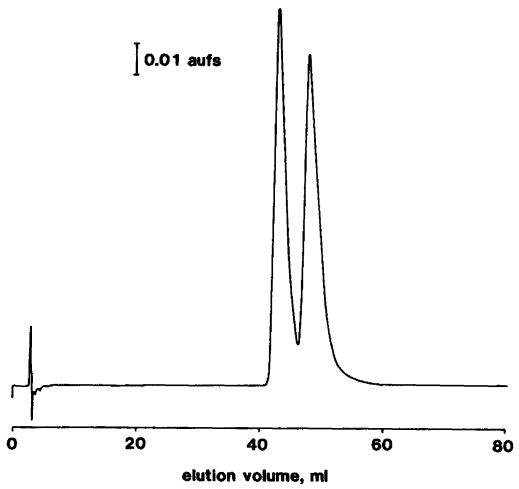


Fig. 3. Illustration of the enantiomeric separation obtained on chromatography of (±)-*N*-phenylcarbamyl *S*-methyl *S*-phenyl sulfoximine (*9*). Conditions: CSP 1-column, hexane −20 % 2-propanol, 2.0 ml/min.

Elution orders were determined by chromatography of samples enriched in one enantiomer of known absolute configuration or sign of optical rotation or by the use of a polarimetric detector. In the latter case the eluate was passed *via* a quartz cell of 200 mm pathlength and the optical rotation registered by means of a Rudolph Auto Pol III polarimeter interfaced with the potentiometric recorder. All compounds were injected as solutions in methylene chloride.

Esterification of the carboxylic substituted sulfoxides. A. Methyl esters. Diazomethane was generated from *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide and distilled.[7] The sulfoxide was dissolved in a small amount of methanol, the solution cooled in ice-water and the diazomethane added until a persistent yellow colour remained. Evaporation of the ether and methanol yielded a product which had the expected structure according to ^{1}H NMR. ^{1}H NMR ($CDCl_3$) of compound Nos. (Table 1): *1*: δ 8.28 (1H,d*, *J* 7.1 Hz), 8.06 (1H,d*, *J* 7.1 Hz), 7.83 (1H,t*, *J* 7.1 Hz), 7.56 (1H,t*, *J* 7.1 Hz), 3.95 (3H,s), 2.85 (3H,s); *2*: δ 3.77 (3H,s), 2.96 (2H,q, *J* 7.5 Hz), 3.1–2.6 (4H,m), 2.08 (2H,m), 1.39 (3H,t, *J* 7.5 Hz); *3*: δ 7.34 (5H,bs), 4.01 (2H,q(AB), *J* −12.4 Hz), 3.70 (3H,s), 2.82(4H,m); *4*: δ 6.22 (1H,m), 3.74 (3H,s), 2.94 (2H,q, *J* 7.5 Hz), 2.21 (3H,m), 1.41 (3H,t, *J* 7.5 Hz). The asterisk denotes further splitting due to m-coupling.

B. Diphenylmethyl esters. Diphenyldiazomethane was prepared from benzophenone hydrazone and mercuric oxide.[8] The red crystals obtained after evaporation of the solvent (light petroleum) were dissolved in ethyl ether. The sulfoxide was dissolved in a small amount of dioxane (purified by filtration through a short column of active alumina). To this solution the diphenyldiazomethane was added in portions and the reaction mixture kept on a water-bath at 70 °C until the red colour obtained after each addition no longer disappeared. Evaporation of the solvent yielded a product which was digerated with ether which in some cases induced crystallization of the product. ^{1}H NMR ($CDCl_3$) of compound Nos. (Table 1): *5*: δ 8.31 (1H,d*, *J* 7.1 Hz), 8.26 (1H,d*, *J* 7.1 Hz), 7.83 (1H,t*, *J* 7.1 Hz), 7.58 (1H,t*, *J* 7.1 Hz), 7.1–7.5 (10H,m), 7.10 (1H,s), 2.72 (3H,s); *6*: δ 7.1–7.5 (15H,m), 6.86(1H,s), 3.96(2H,q(AB), *J* −12.4 Hz), 2.88 (4H,m). The asterisk denotes further splitting due to m-coupling.

Preparation of the N-*substituted sulfoximines.* A. Derivatives of *S*-methyl *S*-phenyl sulfoximine. The unsubstituted sulfoximine was prepared from methyl phenyl sulfoxide and hydrozoic acid according to Johnson *et al.*[9] *N*-Alkyl- or

-arylcarbamyl sulfoximines were obtained *via* reactions with the corresponding alkyl or aryl isocyanate according to the following general procedure: To the sulfoximine (500 μmol), dissolved in ether in a 5 ml screw-cap glass vial containing a small magnetic stir bar, was added an equimolar amount of the isocyanate. The vial was capped and stirred for 0.25–2 h at room temperature or at *ca.* 40 °C, depending upon the isocyanate used. With the aryl isocyanates an immediate reaction occurred with concomitant precipitation of the *N*-arylcarbamyl derivative. After completion of the reaction and cooling, 4 % aqueous sulfuric acid (1 ml) was added to the vial and stirring continued for 1 min. The lower phase (containing extracted unreacted sulfoximine) was removed with a Pasteur-pipette, another ml of acid added and the procedure repeated. The remaining ether solution was dried with a small amount of magnesium sulfate, filtered and evaporated in an air stream. The purity of the product was readily ascertained by HPLC. In the cases where a crystalline material was obtained, this was characterized by its m.p. and ^{1}H NMR spectrum. Compound Nos. (Table 1): *9*: M.p. 125–128 °C (lit.[9] m.p. 129–130 °C). *10–14*: These compounds were only characterized by their retention properties on HPLC. As derivatives of the parent sulfoximine *8*, their structural identities, however, were evident from the resolution pattern obtained from HPLC of these derivatives obtained by synthesis from optically enriched *8*.

Preparative resolutions. The optically active forms of 2-methylsulfinylbenzoic acid were obtained by resolution of the racemic compound with brucine in ethanol as described elsewhere.[10] Esterification of the enantiomers of the acid caused no racemization of the material.

Racemic *S*-methyl *S*-phenyl sulfoximine was resolved partially with (+)-10-camphorsulfonic acid in acetone according to Johnson *et al.*[11]

NMR-spectra. The ^{1}H NMR-spectra were recorded with a JEOL mod. FX-100 Fourier transform NMR-spectrometer.

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