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Behaviour of allyl aryl sulfoxides in high-performance liquid chromatography on a chiral stationary phase

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Abstract

Several racemic allyl aryl sulfoxides were resolved by HPLC on a brush-type chiral stationary phase based on the 3,5-dinitrobenzoyl derivative of (*R*,*R*)-1,2-diaminocyclohexane. Peak deformations due to exchange phenomena (on-column enantiomerization) were observed at high column temperatures and low eluent flow-rates; under these conditions the extent of interconversion during chromatography was dependent on the kind of substitution of the aromatic ring of the analytes. Kinetic data for the racemization process in solution were also obtained after preparative HPLC separation of the individual enantiomers.

1. Introduction

Thermal racemization of allylic sulfoxides was extensively investigated by Mislow and co-workers [1,2], who showed that the $R \rightleftharpoons S$ interconversion is due to a [2,3]-sigmatropic process involving an achiral sulfenate ester as intermediate (Fig. 1); polar solvents and electron-releasing groups on the aromatic ring of allyl aryl sulfoxides were found to decrease the racemization rates and the amount of sulfenate present at equilibrium.

The values of the activation parameters (e.g., $\Delta H^{\#} = 22.5$ kcal/mol and $\Delta S^{\#} = -6.2$ cal/mol·K for allyl phenyl sulfoxide in benzene) [2] indicate that the interconversion can be conveniently investigated by HPLC on a chiral stationary phase under conditions of slow exchange (room temperature) and fast exchange ($T >$ 70°C).

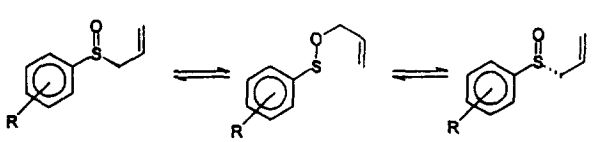

Fig. 1. $R \rightleftharpoons S$ interconversion of allylic sulfoxides.

A totally synthetic chiral sorbent [(*R*,*R*)-DACH-DNB chiral stationary phase (CSP)] [3] containing the 3,5-dinitrobenzoyl derivative of (*R*,*R*)-1,2-diaminocyclohexane has been successfully used [4,5] for the resolution of a broad range of alkyl aryl sulfoxides on the analytical and preparative scales and for the low-temperature investigation of hindered naphthyl sulfoxides undergoing fast *E*–*Z* isomerization [6]. In this work, the application range of the above CSP was extended to the analysis of interconverting allyl sulfoxides (Fig. 2).

2. Experimental

The synthesis of the CSP and the HPLC

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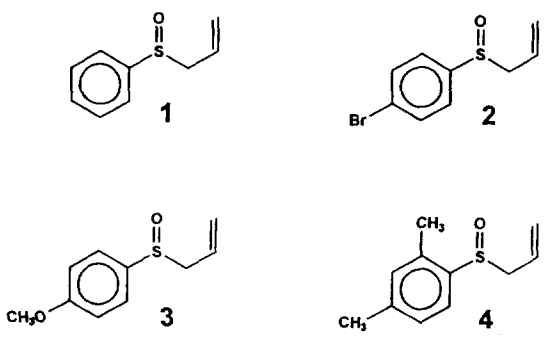

Fig. 2. Structures of the allyl sulfoxides studied.

apparatus have been described elsewhere [3]. Allyl phenyl sulfoxide (**1**) is commercially available (Fluka, Buchs, Switzerland); sulfoxides **2–4** were obtained by alkylation of the appropriate thiophenol with allyl bromide under phase-transfer conditions followed by 3-chloroperbenzoic acid oxidation in $CHCl_3$ at −20°C and column chromatography on silica gel ($CHCl_3$–AcOEt); satisfactory analytical values for C, H and S and spectral data (IR and ^1H NMR) were obtained.

The individual enantiomers of compounds **1–4** were obtained by semi-preparative HPLC on (*R*,*R*)-DACH-DNB CSP (column dimensions 250 × 10 mm I.D.) on a 10–20-mg scale using the same eluents listed in Table 1 at a flow-rate of 7.0 ml/min; in all instances the enantiomeric excess of the collected fractions was >98% with recoveries of 95% and 80% for the first- and second-eluted enantiomers, respectively.

Out-of-column racemization kinetics were conducted on 1–2 mg of enantiomerically pure sulfoxides dissolved in 1 ml of solvent at three temperatures (50, 60 and 70°C); the enantiomeric excess was monitored as a function of time by HPLC on the analytical chiral column kept at 15°C.

3. Results and discussion

Chromatographic data collected under standard conditions are given in Table 1; dioxane–methanol proved to be the best combination of polar modifiers in terms of selectivity and peak shapes, permitting fast and complete separations of all the analytes. As expected on the basis of previous investigations on closely related compounds, both retention and selectivity are raised by electron-donating substituents on the aromatic moiety of the analytes as a result of increased interaction with the π-acidic aromatic groups of the CSP [4,5]. The elution order of the enantiomers (established by a combination of polarimetric and circular dichroism measurements and comparison with literature data [1,2]) is also consistent with previous findings [5], the sulfoxides with *R* configuration being the first eluted on the (*R*,*R*)-CSP. Under standard chromatographic conditions no detectable interconversion occurs during the analysis as judged by the absence of any reaction zone (plateau) between the resolved peaks (Fig. 3); this result was expected on the basis of the known barriers of activation for the racemization of **1** and **3**: at room temperature the overall chromatographic process occurs at a higher rate relative to the interconversion process. The two rates become

Table 1
Chromatographic data

Compound	k'_1	α
1	8.11	1.36
2	4.19	1.24
3	14.86	1.47
4	10.54	1.65

CSP, (*R*,*R*)-DACH-DNB-LiChrosorb Si100, 5-μm (250 × 4 mm I.D.); eluent, *n*-hexane–dioxane–methanol (70 : 30 : 1); flow-rate, 2.0 ml/min; temperature, 25°C; UV detection at 254 nm. k'_1 = Retention factor; α = separation factor.

Table 2
Chromatographic data with different eluents

Compound	Eluent	k'_1	α
1	A	4.64	1.21
2	A	3.02	1.14
3	B	3.03	1.14
4	B	2.09	1.26

Eluent A, *n*-hexane–dioxane–methanol (70 : 30 : 1); eluent B, *n*-hexane–dioxane–methanol (60 : 20 : 5); flow-rate, 0.5 ml/min; temperature, 85°C; other conditions as in Table 1. k'_1 = Retention factor; α = separation factor.

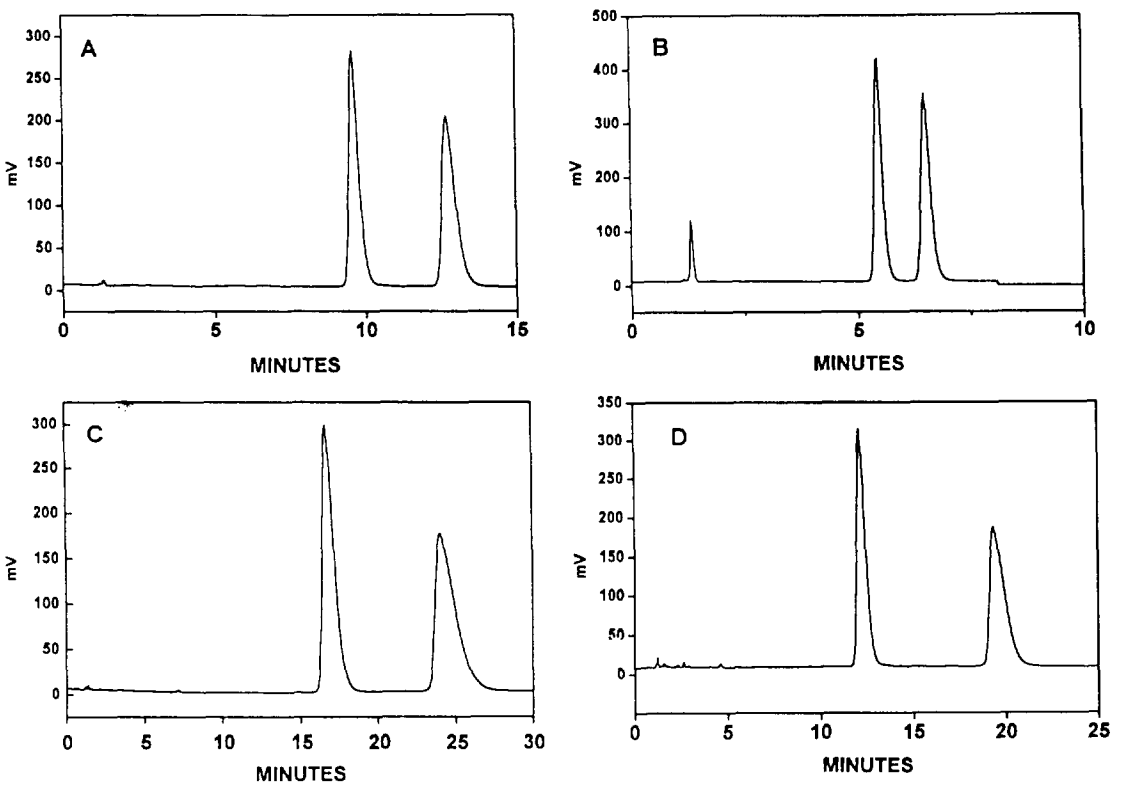

Fig. 3. Resolution of racemic allylic sulfoxides on (*R*,*R*)-DACH-DNB CSP. Chromatograms A, B, C and D for compounds **1**, **2**, **3** and **4**, respectively. Chromatographic conditions as in Table 1.

Table 3
Kinetic data for the out-of-column racemization of compounds **1–4**

R-Enantiomer of compound	T(°C)	$K_{rac} \times 10^4$ (s^{-1})	Solvent	$\Delta G^{\#}$ (kcal/mol)	$\Delta H^{\#}$ (kcal/mol)	$\Delta S^{\#}$ (cal/mol · K)
1	50	1.74	A	24.08		
	60	5.59	A	24.07	21.77	−7.1
	70	13.3	A	24.22		
2	50	3.31	A	23.67		
	60	8.69	A	23.78	20.69	−9.2
	70	23.0	A	23.85		
3	50	0.73	B	24.64		
	60	2.30	B	24.66	22.80	−5.7
	70	6.10	B	24.75		
4	50	3.84	B	23.57		
	60	11.0	B	23.62	22.57	−3.1
	70	31.7	B	24.63		

Solvent A, *n*-heptane–dioxane–methanol (70 : 30 : 1); solvent B, *n*-heptane–dioxane–methanol (60 : 20 : 5). 1 cal = 4.184 J.

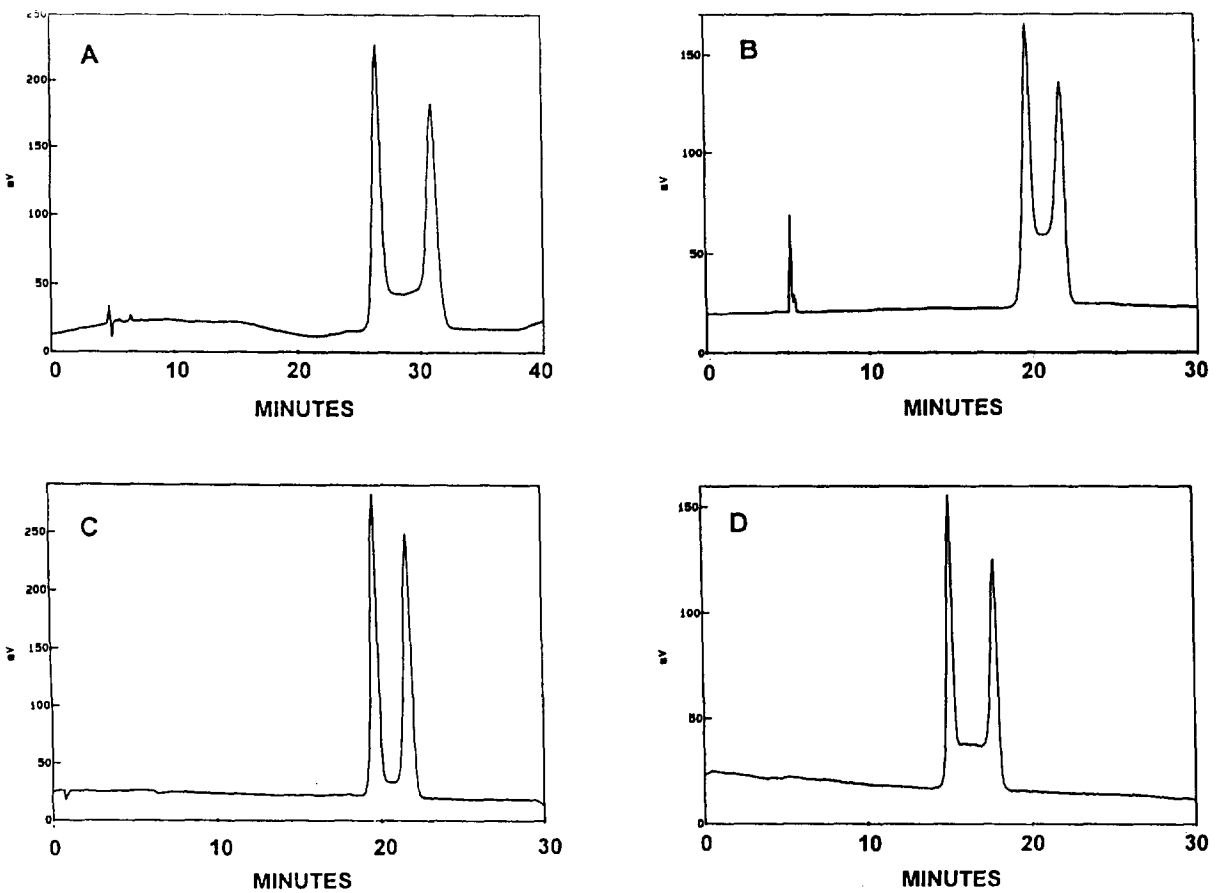

Fig. 4. On-column enantiomerization of racemic allylic sulfoxides on (*R,R*)-DACH-DNB CSP. Chromatograms A, B, C and D for compounds **1**, **2**, **3** and **4**, respectively. Chromatographic conditions as in Table 2.

commensurable as the column temperature is raised to 85°C (increase in the interconversion rate) and the eluent flow-rate is lowered to 0.5 ml/min (decrease in the separation rate) and the typical dynamic patterns due to on-column exchange phenomena are clearly observed in Fig. 4.

At 85°C the enantioselectivity of the CSP is still large enough to permit almost complete resolution of the analytes (Table 2); two different mobile phases were used for these resolutions in order to obtain reasonable analysis times for the more strongly retained sulfoxides **3** and **4**. The extent of interconversion between two enantiomeric species during their passage through the chiral column is, to a first approximation, related to the area of the "reaction zone" observed between the two peaks: it is clear that on-column interconversion is less pronounced for sulfoxide **3**, which shows a small plateau region (Fig. 4C) in comparison with the remaining compounds.

Inspection of the data obtained for the out-of-column racemization processes (Table 3) reveals qualitative agreement with the high-temperature chromatographic analysis: again, sulfoxide **3** is found to have the highest barrier to racemization under our experimental conditions. Although two different solvents were used for compounds **1–2** and **3–4**, the solvent effect on the reaction rate is not expected to obscure their relative stereochemical stabilities; larger solvent effects have been observed on passing from non-polar

solvents (e.g., methylcyclohexane or benzene) to polar solvents (ethanol, 2,2,3,3-tetrafluoro-1-propanol) [1,2].

Extrapolation of the data of Table 3 to 85°C reveals that the interconversion is very fast at this temperature, the complete loss of optical activity occurring in a few minutes in solution (i.e., in the absence of the chiral solid support).

On the other hand, interconversion during chromatography takes place both in solution and on the silica surface, and the two rate constants may in principle be different [7,8]; in the present case, a retarding effect of the chiral stationary phase on the interconversion process is observed, the two enantiomeric peaks being still recognizable even after long residence times in the chiral column.

4. Conclusions

The application range of DACH-DNB CSP has been extended to the investigation of interconverting enantiomeric species featuring relatively high activation barriers. The above CSP is particularly suited for the study of on-column isomerizations even at unusually high temperatures in view of its thermal stability, and may be a valid alternative to polarimetric measurements for the investigation of the same processes in solution.

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