Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 1, pp. 27-30, 1995

0957-4166/95 $9.50+0.00

0957-4166(94)00343-2

Chromatographic Resolution of the Interconverting Stereoisomers of Hindered Sulfinyl and Sulfonyl Naphthalene Derivatives

Claudio Villani[#] and William H. Pirkle*

School of Chemical Sciences, University of Illinois, Urbana, IL 61801 (USA)

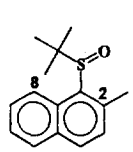
Abstract:: 1-Naphthyl sulfoxides and sulfones having a β-methyl group on the aromatic ring show hindered rotation around the C_{ar}-S bond, giving rise to conformational diastereoisomers and enantiomers, respectively. Low temperature HPLC separation of the interconverting stereoisomers on a recently developed chiral stationary phase is reported; a model to account for the observed sense of chiral recognition is also presented.

INTRODUCTION

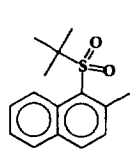
The chromatographic resolution of interconverting enantiomers on GC and HPLC chiral stationary phases has recently received considerable attention as an additional approach to the investigation of stereolabile compounds.[1,2] Dynamic chiral HPLC, in the form of variable temperature and/or variable flow chromatography, has been successfully used to obtained kinetic data for the enantiomerization of triaryl methane derivatives[2] and spirobichromenes.[3]

Sulfoxide **1** has been shown to exist in two conformations, either having the oxygen atom close to the 2-methyl group (*E* rotamer) or close to H-8 of the aromatic ring (*Z* rotamer); in each case the bulky t-butyl group is nearly perpendicular to the naphthalene plain. The *Z*-rotamer is the more stable in solution and in the solid state.[4] Although the $E \rightleftharpoons Z$ isomerization is fast at room temperature on the HPLC time scale, the expected four stereoisomers (due to the sulfur stereogenic center and to the hindered rotation around the C_{ar}-S bond) can be separated on a π-acidic chiral stationary phase at –35°C. We now report on the low temperature HPLC investigations of sulfoxide **1** and the related sulfone **2** on a new chiral phase[5,6] (scheme 1) which affords appreciable levels of enantioselectivity toward a broad range of analytes containing aromatic substituents. This phase has been successfully employed in the resolution of the long lived (at room temperature) atropisomers of N,N-disubstituted-2-methyl-1-naphthylcarboxamides, **3**,[7] which show some structural resemblance to the sulfur-containing compounds **1** and **2**.

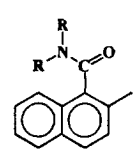
Scheme 1



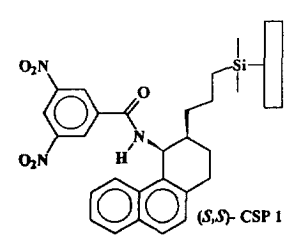
1



2



3



(*S*,*S*)- CSP 1

#) Present address: Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università "La Sapienza", P.le A. Moro 5, 00185 Roma.

EXPERIMENTAL

Racemic **1** and the individual enantiomers were available from previous work.[4] Sulfone **2** was obtained by 3-chloroperbenzoic acid oxidation of **1** in $CHCl_3$ at 25°C.[8] A commercially available (*S,S*) Whelk O-1 column (250*4.6 mm ID) was used (Regis Chemical Company, Morton Groove, IL, USA). Low temperature chromatography was performed placing the column in a Dry-Ice/2-propanol cooling bath, a 1 m long connecting capillary being wrapped around the cooled column to ensure thermal equilibration of the mobile phase.

RESULTS AND DISCUSSION

Variable temperature chromatograms of sulfoxide **1** on the (*S,S*) CSP are shown in fig. 1. At room temperature only two peaks are observed, the second showing a pronounced exchange-broadening. Progressive decoalescence of the peaks is observed as the temperature is progressively reduced to –30°C and the slow-exchange situation (interconversion rate lower than the separation rate) is reached at –40°C. Under these conditions, the elution order of the four stereoisomers is (*E,R*); (*E,S*); (*Z,S*); (*Z,R*). It is interesting to note that for (*R*)-**1**, conformational changes produce larger variations in retention times than its configurational changes. The opposite is observed for (*S*)-**1**.

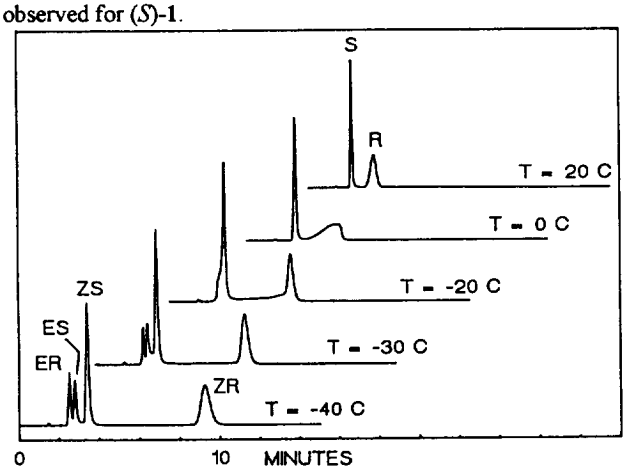


Figure 1: Variable temperature chromatography of racemic **1** on (*S,S*)-CSP 1. Eluent: dichloromethane/methanol 98/2; flow rate 2.0 ml/min; UV detection at 300 nm. At –40°C, the following chromatographic parameters are obtained:[9] $K'_{(E,R)} = 0.73$; $K'_{(E,S)} = 0.91$; $K'_{(Z,S)} = 1.32$; $K'_{(Z,R)} = 5.36$; $\alpha_{(E)} = 1.25$; $\alpha_{(Z)} = 4.06$.

A large body of chromatographic and spectroscopic data indicates that aromatic sulfoxides form molecular complexes with dinitrobenzoylated amines or aminoacid derivatives through hydrogen bond and face-to-face π–π interactions.[10,11] CSP 1 was designed specifically to utilize, in addition to the above mentioned interactions, a face-to-edge attractive interaction between the naphthyl ring of the CSP and the aromatic portion of the analytes. Face-to-edge aromatic interactions, favoring T-shaped geometries both in the solid state and in solution, are often explained as a combination of electrostatic and van der Waals interactions;[12a,b] and have been suggested to play an important role in the chromatographic separation of enantiomers on chiral stationary phases.[12c] Inspection of molecular models[13] reveals that only the (*Z,R*)

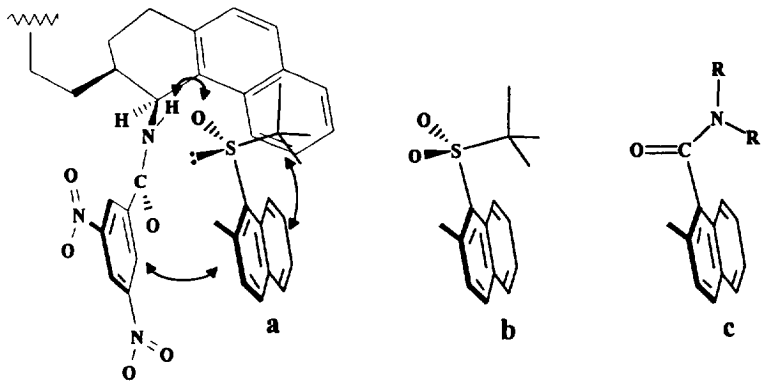


Figure 2: Proposed mode of interaction between (*S,S*)-CSP 1 and the more retained isomers of **1** (a), **2** (b) and **3** (c)

isomer of **1** can simultaneously establish these three interactions (fig. 2a) whereas at least one of the three is prevented by either the bulky *t*-butyl group or by unfavourable geometries for the remaining isomers of **1**. These appear in the low temperature chromatogram clustered around 2-4 minutes, well separated from (*Z,R*)-**1**.

Oxidation of **1** gives the corresponding sulfone **2** whose sulfur atom is no longer a stereogenic center. Thus only two peaks, corresponding to the conformational enantiomers, are observed in the low temperature chromatography on CSP 1 (fig. 3). The useful temperature range is considerably shifted to lower temperatures with peak coalescence observed at –60°C and complete decoalescence at –80°C, indicating a lower barrier to $C_{Ar\text{-}S}$ bond rotation in **2** compared to **1**. Molecular mechanics[14] calculations carried out on **2** give a low energy conformation with the *t*-butyl group almost perpendicular to the naphthyl ring, corresponding to the low energy conformations found for the *E* and *Z* isomers of **1**.[4] On the basis of these observations, (assuming a similar recognition mechanism for **1** and **2**) the most retained enantiomer of the sulfone derivative should be

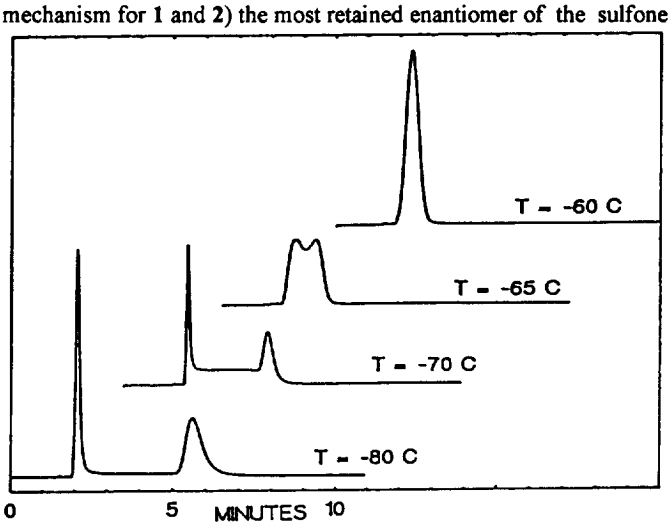


Figure 3: Variable temperature chromatography of **2** on (*S,S*)-CSP 1. Eluent: dichloromethane/methanol 98/2; flow rate 2.0 ml/min; UV detection at 300 nm. At –80°C the following chromatographic data are obtained: $K'_1 = 0.54$; $\alpha = 5.79$

the one depicted in fig. 2b (i.e. the one formally derived from the (*Z,R*) sulfoxide). The proposed recognition model is consistent with that reported for the separation of hindered naphthyl carboxamide atropisomers **3** (fig 2c) on the same CSP.[7]

The use of chiral HPLC columns operating at cryogenic temperatures represents an additional tool for the investigation of stereolabile compounds featuring very low interconversion barriers. Brush-type stationary phases based on low-molecular weight selectors have a distinct advantage as they can show high chromatographic efficiency even at low temperatures.

Acknowledgements. This work has been supported by the National Science Foundation and by EM Science, a Division of EM Merck.

REFERENCES AND NOTES

1. Jung, M.; Schurig, V. *J. Amer. Chem. Soc.* **1992**, *114*, 529.
2. Veciana, J.; Crespo, M.I. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 74.
3. Stephan, B.; Zinner, H.; Kastner, F.; Mannschreck, A. *Chimia* **1990**, *44*, 336.
4. Casarini, D.; Foresti, E.; Gasparrini, F.; Lunazzi, L.; Macciantelli, D.; Misiti, D.; Villani, C *J. Org. Chem.* **1993**, *58*, 5674.
5. Pirkle, W.H.; Welch, C.J.; Lamm, B. *J. Org. Chem.* **1992**, *57*, 3854.
6. Pirkle, W.H.; Welch, C.J. *J. Liq. Chromatogr.* **1992**, *15*, 1947.
7. Pirkle, W.H.; Welch, C.J. and Zych, A. J. *J. Chromatogr.* **1993**, *648*, 101.
8. IR (KBr) 1285, 1115 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.39 (s, 9H), 2.97 (s, 3H), 7.39 (d, J = 8.6 Hz, 1H), 7.45-7.65 (m, 3H), 7.82 (m, 1H), 7.95 (d, J = 8.6 Hz, 1H), 9.28 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 23.75, 24.73, 63.50, 125.52, 126.55, 127.42, 128.33, 128.43, 130.86, 132.35, 132.88, 134.23, 143.25
9. K': capacity factor, defined as $(V - V_0)/V_0$ where V and V_0 denote the retention volume and the void volume, respectively. α: enantioselectivity factor, defined as the ratio of the capacity factors of the two enantiomers; the subscripts refer to the *E* and *Z* diastereomers.
10. Pirkle, W.H.; Finn J.M.; Hamper, B.C.; Schreiner, J.; Pribish, J.R. In *Asymmetric Reactions and Processes in Chemistry*; ACS Symposium Series: Washington, 1982, p. 254.
11. Charpin, P.; Dunach. E,; Kagan. H.B. and Theobald, F.R. *Tetrahedron Lett.* **1986**, *27*, 2989.
12. a. Burley, S.K.; Petsko, G.A. *Science* **1985**, *229*, 23; b. Jorgensen, W.L.; Severance, D.L. *J. Amer. Chem. Soc.* **1990**, *112*, 4768; c. Pirkle, W.H.; Welch, C.J.; Hyun, M.H. *J. Chromatogr.* **1992**, *607*, 126.
13. A complete conformational search using the BAKMDL software (Steliou, K., BAKMDL-MM2, version K.S.2.94; Boston University, USA) was carried out on a model compound of CSP 1, having a methyl group in place of the alkyl chain connecting the chiral selector to the silica surface: the more stable conformation, depicted in fig. 2, corresponds to the solid-state structure found by X-ray analysis of the same model .[15]
14. We used the MMX force field (PC Model, Version 4.0, Serena Software, Bloomington, IN) and the built-in dihedral driver option; the Ar-^{t}Bu dihedral angle was varied in 5° steps in a first scan and in 1° steps in the proximity of 90°.
15. Welch, C.J. Ph. D. Thesis, University of Illinois; Urbana, IL, 1992; *Chirality*, in press.

(*Received in USA* 26 *August* 1994)