Notes

Determination of the Enantiomerization Barrier of Arylnaphthalene Lignans by Cryogenic Subcritical Fluid Chromatography and Computer Simulation

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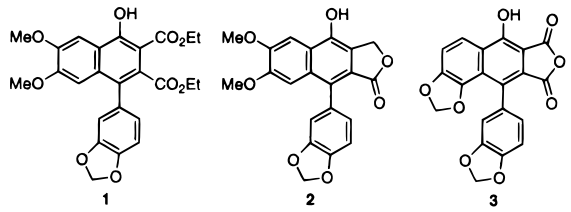
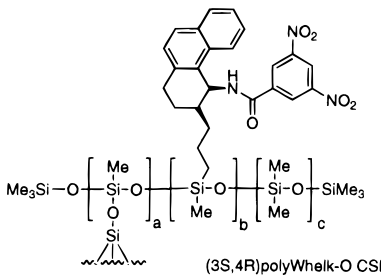
Recently, some of us reported on the hindered rotation about the chiral axis in arylnaphthalene lignans and analogs.[1] The rotational energy barrier of several atropisomers, i.e. the barrier to enantiomerization, was determined by dynamic nuclear magnetic resonance (DNMR) and molecular orbital calculations.

In addition to polarimetry and DNMR, chromatographic techniques, such as dynamic high performance liquid chromatography (DHPLC)[2−4] and dynamic gas chromatography (DGC),[5−10] have been established as useful tools for the investigation of dynamic processes. In the chromatographic separation of interconverting enantiomers on chiral stationary phases (CSPs), a series of temperature-dependent plateaus and peaks can be observed. Such coalescence phenomena result from a combination of on-column enantiomerization and enantioseparation equilibria. Computer simulation of the elution profiles allows one to determine rate constants and energy barriers for the interconversion process.

The brush-type CSP Whelk-O 1 and its polysiloxane-based analog, the polyWhelk-O, have been used to separate the stereoisomers of numerous compounds of different classes using either HPLC or supercritical fluid chromatography (SFC).[11−15] In addition, the Whelk-O 1 has been used to separate the enantiomers of a number of atropisomers,[13,16] including a series of rapidly interconverting sulfinyl and sulfonyl naphthalenes which can be resolved at cryogenic temperatures in the HPLC mode.[17,18] Both of these CSPs often provide high chromatographic efficiency even at low temperatures. Thus, they can be used for the separation of stereolabile compounds and the determination of interconversion barriers.

Owing to their low conformational stability, the enantioseparation of arylnaphthalenes **1** to **5** requires cryogenic temperatures. We report the enantioseparation of these atropisomers by subcritical fluid chromatography (SubFC) on the polyWhelk-O using temperatures as low as −50 °C. The rotational energy barriers of compounds **1**, **2**, and **4** were determined by dynamic SubFC (DSubFC) and computer simulation using methods employed previously for DGC and DHPLC studies.





Experimental Section

The arylnaphthalene lignans were prepared according to previously reported methods.[1] All enantiomers were separated on a commercially available (3*S*,4*R*)polyWhelk-O column (250 mm × 4.6 mm) using a Hewlett Packard 1050 supercritical fluid chromatograph equipped with an HP 1050 diode-array detector. Samples were dissolved in methanol and ethyl acetate, respec-

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(1) Charlton, J. L.; Oleschuk, C. J.; Chee, G.-L. *J. Org. Chem.* **1996**, *61*, 3452.
(2) Stephan, B.; Zinner, H.; Kastner, F.; Mannschreck, A. *Chimia* **1990**, *44*, 336.
(3) Veciana, J.; Crespo, M. I. *Angew. Chem.* **1991**, *103*, 85. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 74.
(4) Cabrera, K.; Jung, M.; Fluck, M.; Schurig, V. *J. Chromatogr. A* **1996**, *731*, 315.
(5) Jung, M.; Schurig, V. *J. Am. Chem. Soc.* **1992**, *114*, 529.
(6) Bürkle, W.; Karfunkel, H.; Schurig, V. *J. Chromatogr.* **1984**, *288*, 1.
(7) Schurig, V.; Jung, M.; Schleimer, M.; Klärner, F.-G. *Chem. Ber.* **1992**, *125*, 1301.
(8) Wolf, C.; König, W. A.; Roussel, C. *Liebigs Ann.* **1995**, 781.
(9) Wolf, C.; Hochmuth, D. H.; König, W. A.; Roussel, C. *Liebigs Ann.* **1996**, 357.
(10) Hochmuth, D. H.; König, W. A. *Liebigs Ann.* **1996**, 947.
(11) Pirkle, W. H.; Welch, C. J.; Lamm, Bo *J. Org. Chem.* **1992**, *57*, 3854.
(12) Villani, C.; Pirkle, W. H. *J. Chromatogr. A* **1995**, *693*, 63.
(13) Pirkle, W. H.; Welch, C. J. *Tetrahedron Asym.* **1994**, *5*, 777.
(14) Terfloth, G. J.; Pirkle, W. H.; Lynam, K. G.; Nicolas, E. C. *J. Chromatogr. A* **1995**, *705*, 185.
(15) Pirkle, W. H.; Brice, L. J.; Terfloth, G. J. *J. Chromatogr. A* **1996**, *753*, 109.
(16) Pirkle, W. H.; Welch, C. J.; Zych, A. J. *J. Chromatogr.* **1993**, *648*, 101.
(17) Villani, C.; Pirkle, W. H. *Tetrahedron Asym.* **1995**, *6*, 27.
(18) Casarini, D.; Lunazzi, L.; Alcaro, S.; Gasparrini, F.; Villani, C. *J. Org. Chem.* **1995**, *60*, 5515.

S0022-3263(96)02370-5 CCC: $14.00

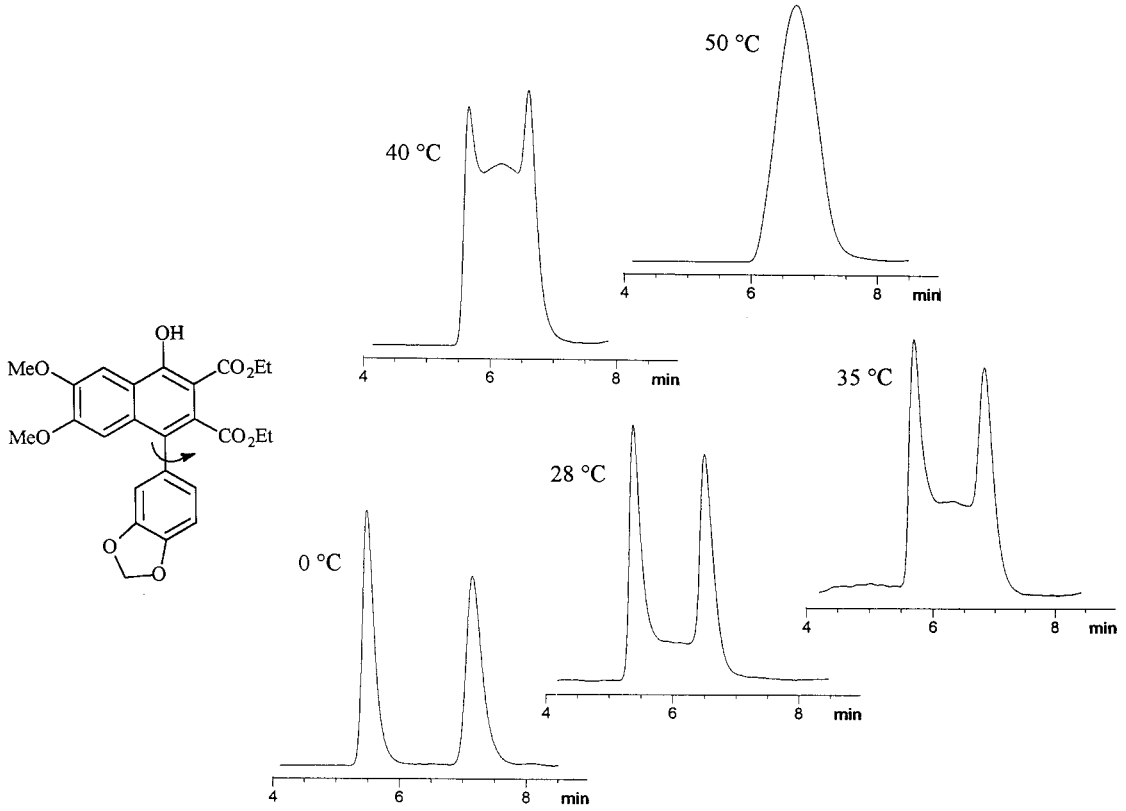

Figure 1. SubFC and SFC separations of the enantiomers of **1** on the polyWhelk-O at various temperatures. Operating conditions: mobile phase, carbon dioxide containing 5% methanol; flow rate, 2 mL/min; back pressure, 200 bar; UV detection at 254 nm.

tively, in a concentration of 1.0 mg/mL. The mobile phase consisted of carbon dioxide modified with different amounts of methanol and acetonitrile of HPLC grade. The flow rate was 2.0 mL/min and a back pressure of 200 bar was employed. Cryogenic SubFC was performed by placing the column in a dry ice/2-propanol bath. The temperature was measured with a calibrated thermocouple and held constant through the run. Before each run, the column was allowed to equilibrate at the chosen temperature for 10 min.

The energy barriers were determined by computer simulation of the elution profiles using the program package Mimesis 1.1[19] based on the program SIMUL.[20]

Results and Discussion

Among the investigated arylnaphthalenes, only **1** has sufficient conformational stability, i.e. a sufficiently high rotational energy barrier, to be resolved into enantiomers on the polyWhelk-O by SubFC at 0 °C. As the temperature of the column is progressively increased, elution profiles with temperature-dependent plateaus are obtained. As a consequence of rapid interconversion of the enantiomers relative to the chromatographic time scale, peak coalescence is observed at 50 °C (Figure 1).

Computer simulation of the elution profiles obtained at 28.0 °C and 35.0 °C, respectively, provides the rate of enantiomerization and thus the rotational energy barrier of **1**. A comparison of an experimentally obtained chromatogram and its corresponding simulation is shown in Figure 2. Similar elution profiles were observed for **2** and **4** at −21.0 °C and −24.0 °C, respectively. The chromatographic data required for the computer simulation are easily calculated from the chromatogram.[21] The unknown rate constant[22] remains as the only variable parameter and is determined using a trial-and-error algorithm until the calculated and observed elution profiles are superimposable.

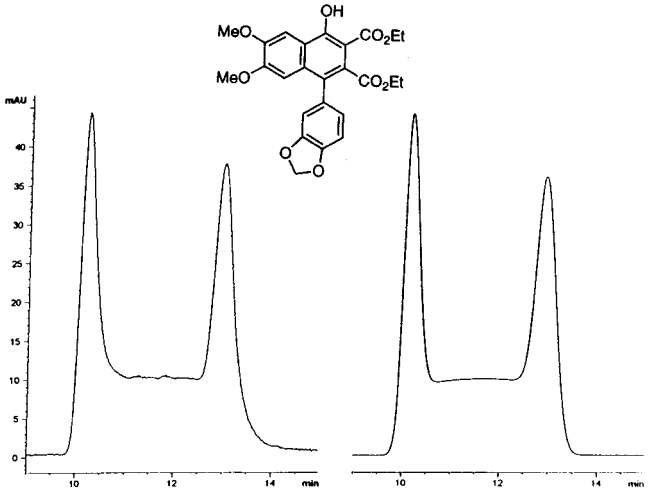

Figure 2. Experimentally obtained (left side) and simulated (right side) elution profiles of **1**. Operating conditions: mobile phase, carbon dioxide containing 2% methanol; temperature, 28.0 C; flow rate, 2 mL/min; back pressure, 200 bar; UV detection at 254 nm.

(19) Hochmuth, D. H., program package Mimesis 1.1, University of Hamburg, 1995; optimized version for a PowerChallenge SC900 parallel computer.

(20) Jung, M. *QCPE Bull.* **1992**, *12(3)*, 52.

(21) Required input data for the computer simulation: Void volume, retention times, number of theoretical plates.

(22) On elution, each enantiomer has spent the same amount of time in the mobile phase but differing amounts of time adsorbed. Enantiomerization rates in the mobile phase are the same for each enantiomer but may be different than those while adsorbed in the CSP. The simulation program affords an "averaged" value for the rate constant and not any of the three individual values.

Table 1. Rotational Energy Barriers $\Delta G^{\ddagger}$ of Compounds 1, 2, and 4 Determined by DSubFC on the polyWhelk-O and Computer Simulation

entry	conditions[a]	temp (°C)	$\Delta G^{\ddagger}$ [b] (kJ/mol)
1	15% MeOH, 0.8 mL/min	28.0	91.2 ± 0.2
1	2% MeOH, 2.0 mL/min	28.0	91.2 ± 0.2
1	1% MeOH, 3.0 mL/min	28.0	91.1 ± 0.2
1	5% MeOH, 2.0 mL/min	28.0	91.1 ± 0.2
1	5% MeOH, 2.0 mL/min	35.0	91.8 ± 0.2
2	15% MeOH, 2.0 mL/min	−21.0	77.7 ± 0.2
4	5% MeOH, 2.0 mL/min	−24.0	75.0 ± 0.2
4	8% acetonitrile, 2.0 mL/min	−25.0	75.0 ± 0.2

[a] Modifier content in carbon dioxide and flow rate of the mobile phase. [b] Average value of the enantiomerization process in the mobile and in the stationary phase.

The results of the computer simulations are summarized in Table 1. Using the chromatographic results, the rotational energy barrier of **1** was determined as 91.2 ± 0.2 kJ/mol (28.0 °C) and 91.8 ± 0.2 kJ/mol (35.0 °C). As was reported for similar arylnaphthalenes, substitution of the ester groups in position 2 and 3 for 2,3-lactone or 2,3-anhydride rings significantly reduces the energy barrier to rotation.[1] The energy barrier of **2** was determined as 77.7 ± 0.2 kJ/mol (−21.0 °C) and as 75.0 ± 0.2 kJ/mol (−24.5 °C) for **4**. The slight variation of the calculated values mainly results from limited precision of temperature measurements. We determined the energy barriers of **1** and **4** using different amounts of methanol or acetonitrile as the mobile phase (Table 1). It is interesting to note that there is no perceptable influence on the rotational energy barrier by the nature and the concentration of the modifier.

Because of their low conformational stability, resolution of the enantiomers of atropisomers **2**, **3**, and **4** on the polyWhelk-O requires cryogenic temperatures, i.e. −29.5 °C, −47.5 °C, and −42.0 °C. As a consequence of favorable mass transfer kinetics, this CSP provides selectivity *and* relatively high chromatographic efficiency even at low temperatures. We were not able to separate the rotamers of **5** even at −50.0 °C. This might result either from insufficient conformational stability of the enantiomers or from insufficient chiral recognition on the column.

Used in conjunction with broadly applicable and efficient CSPs, such as the Whelk-O 1 and polyWhelk-O, cryogenic SubFC and computer simulation is complementary to the well-established DNMR method for investigation of stereolabile compounds.

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