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Enantiomerization of an inherently chiral resorcarene derivative: determination of the interconversion barrier by computer simulation of the dynamic HPLC experiment

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Abstract—The inherently chiral tetrabenzoxazine resorcarene derivative **1** shows characteristic plateau-formation during enantioselective HPLC separation on the chiral stationary phase Chiralpak AD. By computer assisted peak form analysis of the elution profiles, obtained from temperature dependent dynamic HPLC (DHPLC) experiments, with ChromWin, the enantiomerization barrier $\Delta G^{\#}(298\ \mathrm{K}) = 92 \pm 2$ kJ mol^{-1} and the activation parameters $\Delta H^{\#} = 53.0 \pm 1.8$ kJ mol^{-1} and $\Delta S^{\#} = -131 \pm 14$ J (K mol)$^{-1}$ were determined.

Resorcarenes are macrocyclic compounds, which are easily synthesized in a one-step procedure by acid catalyzed condensation of resorcinol with various aldehydes.[1] Of the four possible diastereomers often the rccc isomer is formed as the only product. Its conversion with primary amines and formaldehyde in excess leads to tetrabenzoxazine derivatives.[2] This reaction is regioselective and furnishes exclusively the chiral C_4-symmetric derivative, e.g. **1**, which is stabilized by four intramolecular O-H···O hydrogen bonds (cf. Fig. 1).

The enantiomerization of tetrabenzoxazine resorcarene derivatives, which involves a consecutive rearrangement at all four resorcinol moieties, is feasible by a degenerated cleavage of the oxazine ring via an iminium intermediate and ring closure with the opposite OH-group of the resorcinol unit.[2b,3] This reaction pathway can be catalyzed by traces of water and acids, because of the very labile hemiaminal group in the oxazine ring and has been proven by exchange of the methylene group for a methylene-d_2 group in presence of CD_2O. It should be noted that, in contrast to CH_2-bridged calix[4]arenes with C_4-symmetry,[4] a cone-to-cone ring inversion does not lead to the enantiomer. The product would be the diastereomeric cone conformer with an equatorial orientation of the residues R (here CH_3), but the same configuration of the CHR-bridges (*C*-atoms 2, 8, 14, 20) which, however, was never observed (Scheme 1).

Recently, some of us separated the enantiomers of **1**[5] by HPLC using the chiral stationary phase (CSP) Chiralpak AD.[6] The elution profiles show distinct plateau formation, caused by enantiomerization. Herein, we present the results obtained by evaluation of the dynamic HPLC experiments of **1**.

Dynamic chromatography and electrophoresis, i.e. DGC,[7] DSFC,[8] DHPLC,[9] DCE, DCEC and DMEKC,[10] are well established and powerful tools for the investigation of dynamic processes, i.e. enantiomerization,[11] epimerization[12] and diastereomerization,[13] occurring during the separation of stereolabile compounds. The prerequisite of dynamic chromatography is the quantitative on-column separation of the stereoisomers on a stereoselective stationary phase. As already mentioned, the elution profile of interconverting enantiomers in an enantioselective dynamic chromatographic experiment is characterized by plateau formation between the first enantiomer (eluted with peak tailing) and the second enantiomer (eluted with peak fronting). To yield the rate constants of the forward and backward reaction and the enantiomerization barrier from the elution profiles, a fast and efficient

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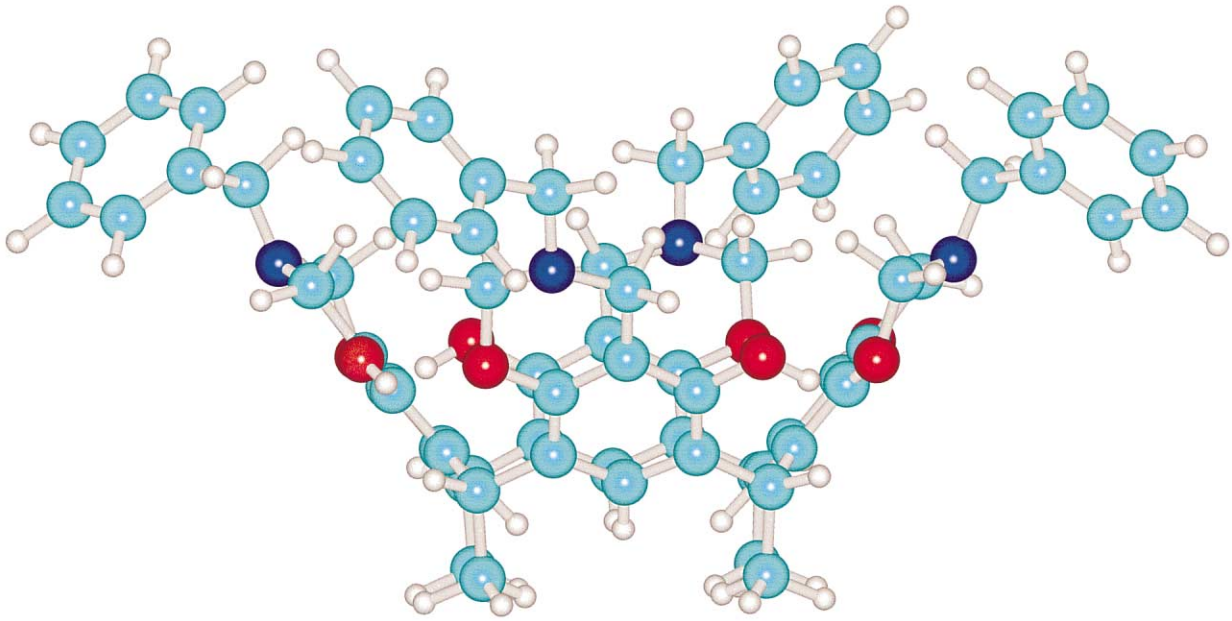
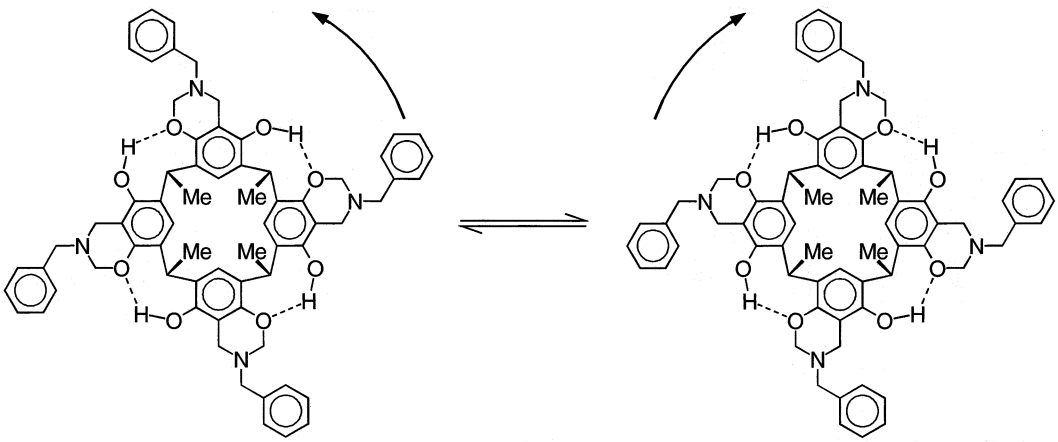


Figure 1. PM3-optimized structure of (2*R*,8*R*,14*R*,20*R*)-1. The structure is stabilized by intramolecular O-H···O hydrogen bonding.



Scheme 1. Enantiomerization of the inherently chiral tetrabenzoxazine resorcarene derivative **1**.

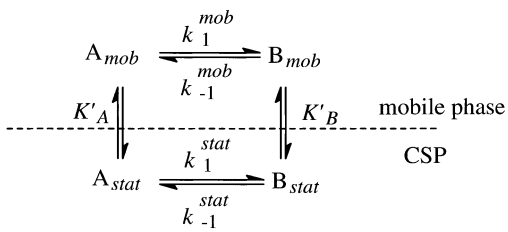
simulation program like ChromWin[14] is necessary. This program applies the theoretical plate model,[7b,15] the stochastic model[16] and the novel derived approximation function[17] for direct calculation of the rate constants of enantiomerization from chromatographic parameters (Scheme 2).

Yet only apparent rate constants (k_1^{app} and k_{-1}^{app})[18] can be determined, which represent a weighted mean of the rate constants in the mobile phase k_1^{mob} (k_{-1}^{mob} is equal for enantiomerization) and the rate constants in the chiral stationary phase k_1^{stat} and k_{-1}^{stat} (cf. Eq. (1) with the retention factor $k' = (t_R - t_M)/t_M$).

$$k_1^{app} = \frac{1}{1+k'_A} k_1^{mob} + \frac{k'_A}{1+k'_A} k_1^{stat}$$

$$k_{-1}^{app} = \frac{1}{1+k'_B} k_1^{mob} + \frac{k'_B}{1+k'_B} k_{-1}^{stat} \qquad (1)$$

The forward and backward rate constants in the chiral stationary phase are distinct, i.e. $k_1^{stat} > k_{-1}^{stat}$ because the enantiomers A and B have a different thermodynamic Gibbs free energy ($-\Delta_{B,A}\Delta G$) in the presence of the chiral stationary phase ($k'_B > k'_A$). The apparent rate



Scheme 2. Equilibria of interconverting enantiomers in a single chromatographic theoretical plate. A is the first eluted enantiomer, B is the second eluted enantiomer, k represents rate constants and K′ the distribution constants between the mobile phase and the chiral stationary phase.

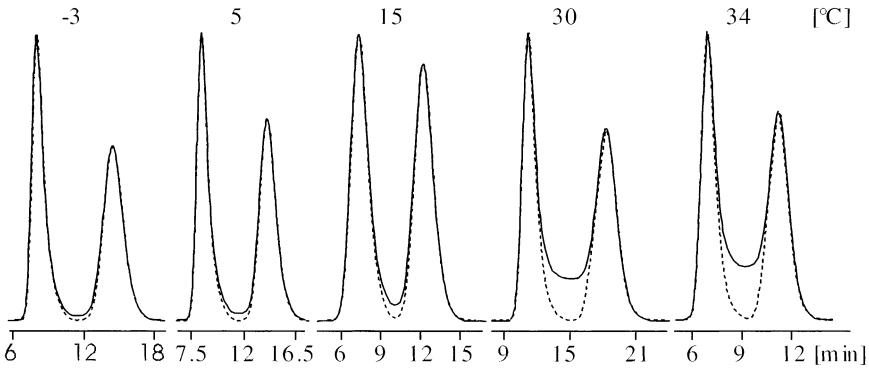


Figure 2. Results of the simulation with ChromWin of the experimental elution profiles, obtained by temperature dependent DHPLC of **1** (plain line: separation with enantiomerization; dotted line: theoretical separation considering tailing). Model: Stochastic model plus (SM+). Method: "Find enantiomerization barrier II".

Table 1. Apparent forward rate constant of enantiomerization and enantiomerization barrier in *n*-hexane/2-propanol (9:1), obtained by peak form analysis of the elution profiles

T (°C)	k_1^{app} (10^{-5} s^{-1})	$\Delta G^{\#}$ (kJ mol^{-1})
−3.0	5.0	88.2
5.0	10.3	89.2
15.0	17.8	91.2
30.0	69.5	92.6
31.0	68.0	92.9
34.0	106.0	92.8

constants themselves are varied by the simulation program until the simulated chromatogram coincides with the experimental chromatogram.

Since the experimental elution profiles of the enantioselective HPLC separation of **1** show peak tailing, the stochastic model plus (SM+)[14] of ChromWin has been improved by introduction of an exponentially modified Gaussian function[19] for the simulation of the unchanged peaks of the enantiomeric fractions. Therefore, the simulation procedure additionally considers peak tailing by iterative comparison of the experimental and simulated elution profile. The results of the simulations are depicted in Fig. 2 and the rate constants obtained are summarized in Table 1. To distinguish between the enantiomerization process taking place during partitioning and poor chromatographic separation caused by strong tailing, the theoretical elution profiles for the latter case were simulated considering tailing and are shown in Fig. 2 as a dotted line.

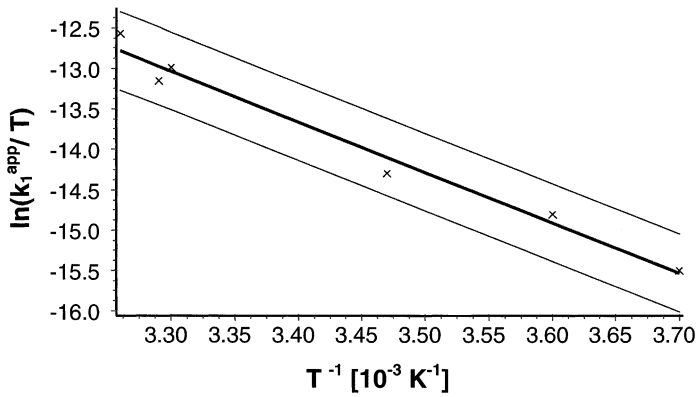
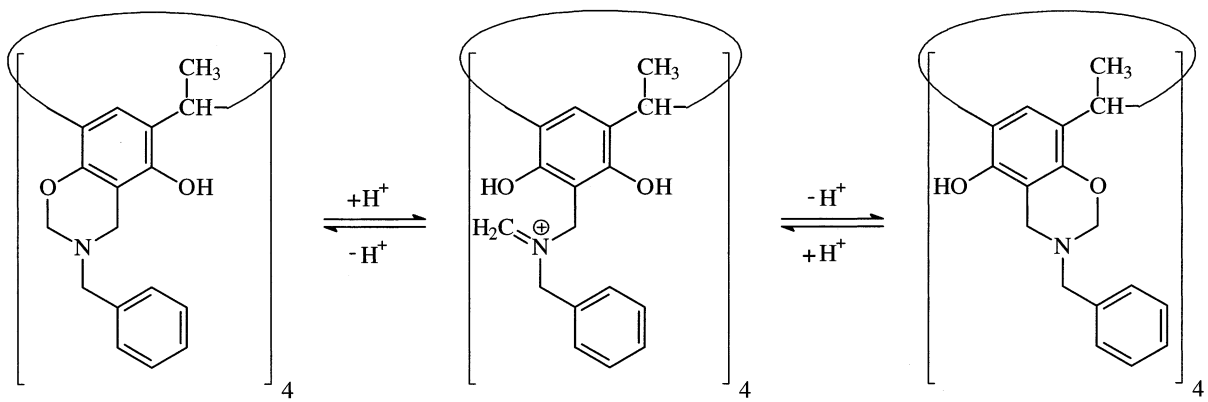


Figure 3. Eyring plot for the determination of $\Delta H^{\#}$ and $\Delta S^{\#}$ from the computer simulated elution profiles of the DHPLC experiment. The upper and lower curves represent the error bands of the linear regression with a level of confidence of 95%.

The mean values of $\ln(k_1^{app}/T)$ were plotted as a function of T^{-1} according to the Eyring equation (Fig. 3). The activation parameters were evaluated by linear regression of the Eyring plot (agreement factor $r=0.990$): $\Delta H^{\#}=53.0\pm1.8$ kJ mol^{-1} and $\Delta S^{\#}=-131\pm14$ J (K mol)$^{-1}$.



Scheme 3. Proposed mechanism of enantiomerization of **1** via acid catalyzed ring cleavage and formation of an iminium intermediate.

The low value of the activation enthalpy $\Delta H^{\#}$ and the high negative activation entropy $\Delta S^{\#}$, obtained by the evaluation of the temperature dependent DHPLC experiment of **1**, corroborate the proposed enantiomerization mechanism via acid catalyzed ring cleavage and formation of an iminium intermediate.[5] High negative values of the activation entropy $\Delta S^{\#}$ can be considered as evidence for a dissociative mechanism of the inversion process[20] (Scheme 3).

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References

1. (a) Timmermann, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663–2704; (b) Böhmer, V. *Angew. Chem. Int. Ed.* **1995**, *34*, 713–745.
2. (a) Arnecke, R.; Böhmer, V.; Paulus, E. F.; Vogt, W. *J. Am. Chem. Soc.* **1995**, *117*, 3286–3287; (b) Arnecke, R.; Böhmer, V.; Friebe, S.; Gebauer, S.; Krauss, G. J.; Thondorf, I.; Vogt, W. *Tetrahedron Lett.* **1995**, *36*, 6221–6224; (c) Airola, K.; Böhmer, V.; Paulus, E. F.; Rissan, K.; Schmidt, C.; Thondorf, I.; Vogt, W. *Tetrahedron* **1997**, *53*, 10707–10724.
3. Iwanek, W. *Tetrahedron: Asymmetry* **1998**, *9*, 4289–4290.
4. (a) Pickard, S. T.; Pirkle, W. H.; Tabatabai, M.; Vogt, W.; Böhmer, V. *Chirality* **1993**, *5*, 310–314; (b) Kusano, T.; Tabatabai, M.; Okamoto, Y.; Böhmer, V. *J. Am. Chem. Soc.* **1999**, *121*, 3789–3790.
5. Böhmer, V.; Caccamese, S.; Principato, G.; Schmidt, C. *Tetrahedron Lett.* **1999**, *40*, 5927–5930.
6. Okamoto, Y.; Kawasaki, M.; Hatada, K. *J. Am. Chem. Soc.* **1984**, *106*, 5357.
7. (a) Schurig, V.; Bürkle, W. *J. Am. Chem. Soc.* **1982**, *104*, 7573–7580; (b) Bürkle, W.; Karfunkel, H.; Schurig, V. *J. Chromatogr.* **1984**, *288*, 1–14; (c) Veciana, J.; Crespo, M. I. *Angew. Chem. Int. Ed.* **1991**, *30*, 74–77; (d) Jung, M.; Schurig, V. *J. Am. Chem. Soc.* **1992**, *114*, 529–534; (e) Schurig, V.; Jung, M.; Schleimer, M.; Klärner, F.-G. *Chem. Ber.* **1992**, *125*, 1301–1303; (f) Jung, M.; Fluck, M.; Schurig, V. *Chirality* **1994**, *6*, 510–512; (g) Wolf, C.; König, W. A.; Roussel, C. *Liebigs Ann.* **1995**, 781–786; (h) Hochmuth, D. H.; König, W. A. *Liebigs Ann.* **1996**, 947–951; (i) Schurig, V.; Keller, F.; Reich, S.; Fluck, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3475–3480; (j) Hochmuth, D.; König, W. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1089–1097; (k) Trapp, O.; Schurig, V. *J. Am. Chem. Soc.* **2000**, *122*, 1424–1430; (l) Reich, S.; Trapp, O.; Schurig, V. *J. Chromatogr. A* **2000**, *892*, 487–498.
8. Wolf, C.; Pirkle, W. H.; Welch, C. J.; Hochmuth, D. H.; König, W. A.; Chee, G.-L.; Charlton, J. L. *J. Org. Chem.* **1997**, *62*, 5208–5210.
9. (a) Mannschreck, A.; Zinner, H.; Pustet, N. *Chimia* **1989**, *43*, 165–166; (b) Stephan, B.; Zinner, H.; Kastner, F.; Mannschreck, A. *Chimia* **1990**, *10*, 336–338; (c) Cabrera, K.; Jung, M.; Fluck, M.; Schurig, V. *J. Chromatogr. A* **1996**, *731*, 315–321; (d) Wolf, C.; Hochmuth, D. H.; König, W. A.; Roussel, C. *Liebigs Ann.* **1996**, 357–363; (e) Gasparrini, F.; Lunazzi, L.; Misiti, D.; Villani, C. *Acc. Chem. Res.* **1995**, *28*, 163–170; (f) Gasparrini, F.; Misiti, D.; Pierini, M.; Villani, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2069–2073; (g) Oxelbark, J.; Allenmark, S. *J. Org. Chem.* **1999**, *64*, 1483–1486; (h) Lorenz, K.; Yashima, E.; Okamoto, Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 1922–1925.
10. (a) Schoetz, G.; Trapp, O.; Schurig, V. *Anal. Chem.* **2000**, *72*, 2758–2764; (b) Schoetz, G.; Trapp, O.; Schurig, V. *Enantiomer* **2000**, *5*, 391–396.
11. Reist, M.; Testa, B.; Carrupt, P.-A.; Jung, M.; Schurig, V. *Chirality* **1995**, *7*, 396–400.
12. Trapp, O.; Schurig, V. *Chem. Eur. J.* **2001**, *7*, 1495–1502.
13. (a) Marriott, P. J.; Lai, Y.-H. *J. Chromatogr.* **1988**, *447*, 29–41; (b) Marriott, P. J.; Lai, Y.-H. *Chem. Australia* **1994**, 386–389; (c) Melander, W. R.; Lin, H.-J.; Jacobson, J.; Horvath, C. *J. Phys. Chem.* **1984**, *88*, 4527–4536; (d) Jacobson, J.; Melander, W.; Vaisnys, G.; Horvath, C. *J. Phys. Chem.* **1984**, *88*, 4536–4542; (e) Wutte, A.; Gübitz, G.; Friebe, S.; Krauss, G.-J. *J. Chromatogr. A* **1994**, *677*, 186–191; (f) Rathore, A. S.; Horvath, C. *J. Chromatogr. A* **1997**, *787*, 1–12.
14. Trapp, O.; Schurig, V. *Comput. Chem.* **2001**, *25*, 187–195.
15. (a) Craig, L. C. *J. Biol. Chem.* **1944**, *155*, 519–534; (b) Kallen, J.; Heilbronner, E. *Helv. Chim. Acta* **1960**, *43*, 489–500.
16. (a) Keller, R. A.; Giddings, J. C. *J. Chromatogr.* **1960**, *3*, 205–220; (b) Kramer, R. *J. Chromatogr.* **1975**, *107*, 241–252; (c) Cremer, E.; Kramer, R. *J. Chromatogr.* **1975**, *107*, 253–263.
17. (a) Trapp, O.; Schurig, V. *J. Chromatogr. A* **2001**, *911*, 167–175; (b) Trapp, O.; Schurig, V. submitted.
18. The defined rate constants represent the experimentally observed interconversion from one enantiomer to the other. Nothing is known about the exact mechanism (concerted or stepwise) of this enantiomerization and of potential intermediates.
19. (a) Foley, J. P.; Dorsey, J. G. *Anal. Chem.* **1983**, *55*, 730; (b) Yau, W. W. *Anal. Chem.* **1977**, *49*, 395; (c) Barber, W. E.; Carr, P. W. *Anal. Chem.* **1981**, *53*, 1939; (d) Foley, J. P.; Dorsey, J. G. *J. Chromatogr. Sci.* **1984**, *22*, 40.
20. Kostyanovsky, R. G.; Kadorkina, G. K.; Kostyanovsky, V. R.; Schurig, V.; Trapp, O. *Angew. Chem. Int. Ed.* **2000**, *39*, 2938–2940.