## Kurzmitteilung / Short Communication

# Investigation of the Enantiomerization Barrier of Homofuran by Computer Simulation of Interconversion Profiles Obtained by Complexation Gas Chromatography

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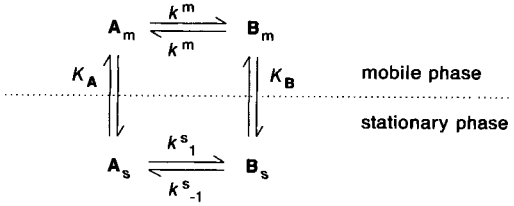
By computer simulation of experimental interconversion profiles, obtained by complexation gas chromatography, rate constants of enantiomerization have been determined for homofuran between 95 and 130°C. Since enantiomerization proceeds at similar rates in the mobile and stationary phase, the rate constants obtained by an Arrhenius plot are in excellent agreement with values determined independently by polarimetry between 60 and 90°C. We thus demonstrate that dynamic chromatography can be an easy means for the rapid determination of enantiomerization (or isomerization) barriers of ca. 70–120 kJ mol$^{-1}$ requiring only minute amounts of racemic sample.

In analogy to dynamic NMR spectroscopy[1], dynamic chromatography has in recent years increasingly been employed for the determination of rate constants of dynamic molecular processes, particularly enantiomerization ("racemization")[2]. As early as 1984, we used a computer program based on the theoretical plate model for the simulation of experimentally observed interconversion profiles in complexation gas chromatography[3]. Veciana and Crespo[4] as well as Zinner and Mannschreck[5] have recently simulated experimental interconversion profiles in HPLC with a program using the stochastic model (calculating peak shapes according to Gauss).

The interconversion of configurationally labile enantiomers during chromatography on a chiral stationary phase (enantiomerization) yields plateaus between the peaks of the resolved antipodes[6] if enantiomerization proceeds at a suitable rate relative to the chromatographic time scale (enantiomerization barrier of ca. 70–120 kJ mol$^{-1}$), the plateau height being temperature-dependent. The rates of interconversion may be different in the mobile and stationary phase[3]. Whereas the forward and backward rate constant in the (achiral) mobile phase must be equal, the equilibrium constant of enantiomerization in the stationary phase is different from unity and is determined by the other three equilibrium constants according to Scheme 1 and the principle of microscopic reversibility[3,7].

Scheme 1




The overall rate constants $k_1$ and $k_{-1}$, which determine the observed interconversion profile, are influenced by the rate constants of both phases according to the capacity factors of the enantiomers $k'_A$ and $k'_B$ (i.e., according to their residence times)[4,5]:

$$k_1 = \frac{1}{1+k'_A} + \frac{k'_A}{1+k'_A}k^s_1 \quad \text{and} \quad k_{-1} = \frac{1}{1+k'_B} + \frac{k'_B}{1+k'_B}k^s_{-1} \qquad \text{(a)}$$

where it is necessary that

$$k_1/k_{-1} = k_1(k'_A+1)/(k'_B+1) = t_{R_B}/t_{R_A} \qquad \text{(b)}$$

(ratio of the uncorrected retention times)[8]. If $k^m$ and $k^s_1$ are not too different, the average of the overall rate constants $k_1$ and $k_{-1}$, obtained by computer simulation of experimental interconversion profiles, can be used for the simple and rapid estimation of the enantiomerization barriers[9], traces of (optically not enriched) racemate being sufficient. Thus, for cyclodextrin stationary phases in GC[7] and for poly(triphenylmethacrylat)[4] and triacetylcellulose[5] in HPLC the values of $\Delta G^{\neq}$ calculated from the average of $k_1$ and $k_{-1}$ according to the Eyring equation were found to be no more than 1–3 kJ mol$^{-1}$ lower than $\Delta G^{\neq}$ values determined by independent methods (dynamic NMR methods, polarimetry after optical enrichment).

In our previous simulation experiments[3] enantiomerization in the mobile phase was neglected. In the investigated example (1-chloro-2,2-dimethylaziridine at 60°C on the stationary phase {nickel(II)-bis[3-(trifluoroacetyl)-(1*R*)-camphorate]} in squalane) this simplification was acceptable since the enantiomerization barrier of 104.9 kJ mol$^{-1}$ thus obtained for the stationary phase was significantly reduced in comparison to 115 kJ mol$^{-1}$ in the gas phase (independent determination[10]). The resulting increase of the

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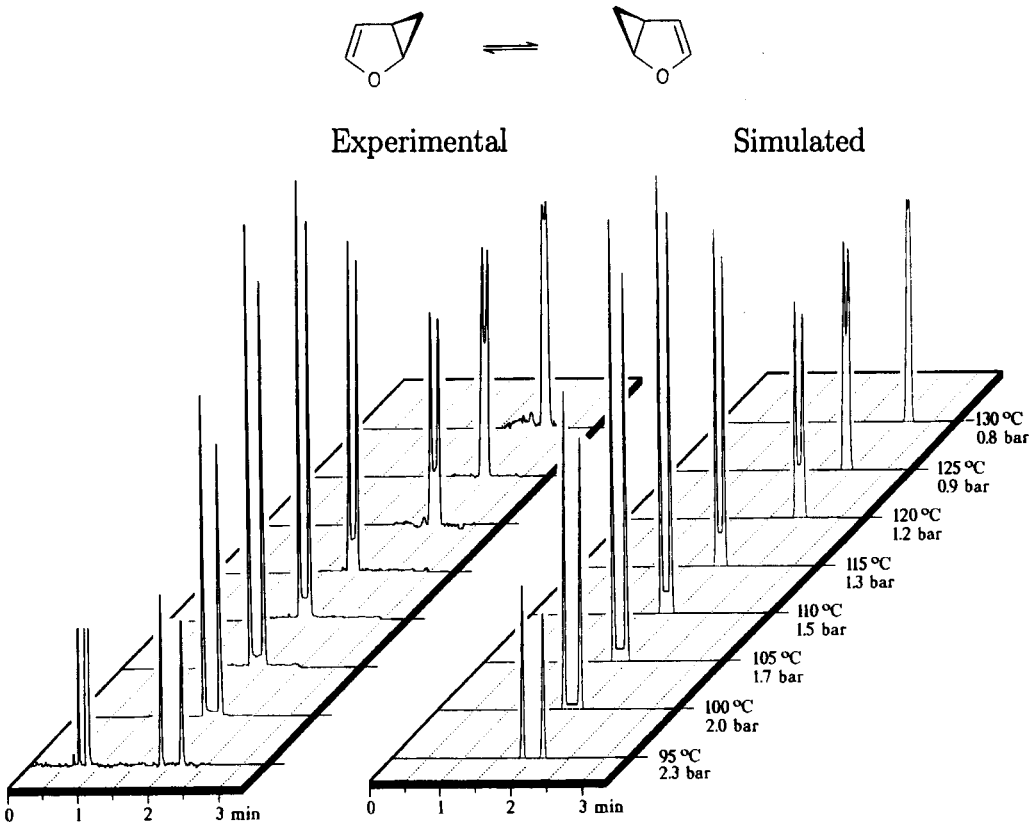


Figure 1. Elution profiles of homofuran at different temperatures and inlet pressures ($N_2$); left: experimental chromatograms (column: 10 m × 0.1 mm i.d., coated with Ni[II]-Chirasil-Metal[12]; film thickness: 0.25 μm), injected amounts of homofuran varying (split injection); right: simulated chromatograms (parameters see ref.[14])

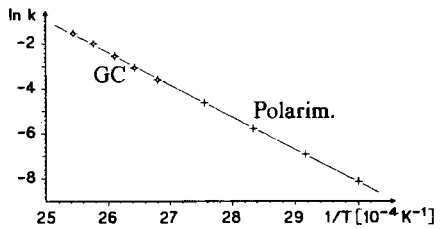


Figure 2. Arrhenius plot for homofuran (GC: average of $k_1$ und $k_{-1}$ in Table 1 determined by simulation; polarimetry: 0.5 $k_{rac}$ from ref.[13], cf. also ref.[2])

rate of inversion by a factor of 40 was attributed to the activating influence of the metal ion[3].

We now demonstrate that a recently developed universal chromatogram simulation program[7,11] based on the theoretical plate model can be used for the determination of enantiomerization barriers which excellently agree with values obtained by chiroptical methods.

In this paper an example is presented where also in complexation gas chromatography the rate constants of enantiomerization in the mobile and stationary phase are surprisingly similar. Figure 1 shows experimental and simulated elution profiles of homofuran on polysiloxane-anchored nickel(II)-bis[3-(heptafluorobutanoyl)-(1*R*)-camphorate] (Ni[II]-Chirasil-Metal[12]) at 95–130 °C. An excellent agreement of experimental and simulated gas chromatograms was achieved. The overall rate constants $k$ obtained by simulation (average of $k_1$ and $k_{-1}$, Table 1) fit surprisingly well with the values that Klärner and Schröer[13] measured in solution by polarimetry between 60 and 90 °C (0.5 $k_{rac}$; cf. ref.[2]). The rate constants thus determined by independent methods show a linear increase ($\ln k$ vs. $T^{-1}$) over the entire temperature range from 60 to 120 °C which can be expressed by the Arrhenius equation (c) (cf. Figure 2).

$$k = (1.5 \pm 0.3) \times 10^{15} \exp[-(119.6 \pm 0.6)\,\mathrm{kJ\,mol^{-1}}(RT)^{-1}]\,\mathrm{s^{-1}} \quad \text{(c)}$$

For the formation of the ylide intermediate[9,13] we obtain $\Delta G^{\neq}$ = 113.8 ± 0.4 kJ mol$^{-1}$ (at 90 °C), $\Delta H^{\neq}$ = 116.6 ± 0.6 kJ mol$^{-1}$, and $\Delta S^{\neq}$ = 7.7 ± 1.5 J K$^{-1}$ mol$^{-1}$.

This result demonstrates that dynamic chromatography significantly extends the temperature range for the acquisition of kinetic data of enantiomerization (and isomerization) which can be determined without previous enantiomer (or generally, isomer) enrichment.

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## Experimental

Homofuran was prepared as previously described[13].

*Gas Chromatography:* Fused silica tubing (100 μm i.d., manufactured by Chromopack International, The Netherlands) was purged with hydrogen at 250 °C for 2 h. A capillary of 10 m in length was statically coated at room temperature by using a carefully filtered 1.0% Chirasil-Metal solution in diethyl ether. The film thickness was approximately 0.25 μm. The column was conditoned for ca. 12 h at 190 °C with nitrogen (1 bar). Nitrogen was used as a carrier gas. The measurements were performed with a Carlo-Erba MEGA gas chromatograph equipped with a flame-ionization detector and a Shimadzu C-R 3A integrator.

Table 1. Rate constants[a] and barriers[b] of enantiomerization for homofuran obtained from the simulation experiments shown in Figure 1

| $T$ [°C] | 100 | 105 | 110 | 115 | 120 | 125[c] | 130[c] |
|---|---|---|---|---|---|---|---|
| $k_1$ [min$^{-1}$][d] | 0.029 | 0.048 | 0.080 | 0.134 | 0.215 | (0.35) | (0.54) |
| $k_{-1}$ [min$^{-1}$][d] | 0.025 | 0.044 | 0.074 | 0.126 | 0.205 | (0.33) | (0.52) |

[a] Referring to the enantiomer interconversion ($R$) $\rightleftharpoons$ ($S$) (cf. ref.[9]). — [b] Referring to the first step of enantiomerization, i.e. formation of an ylid intermediate (cf. ref.[9]). — [c] No plateau because of insufficient peak resolution (peak coalescence of the second kind)[6], value is therefore inaccurate. — [d] For the entire chromatographic system; determined by simulation of the experimental gas chromatograms (see Figure 1) under the condition $k_1/k_{-1} = t_{R_B}/t_{R_A}$ (cf. text); ±10%.

*Computer Simulation:* The calculations were performed with a CONVEX C 220[11]. The following data taken from the experimental chromatograms were used as a basis for the simulation: the dead time $t_M$, the retention times $t_{R_A}$ and $t_{R_B}$ and the theoretical plate numbers $n_A$ and $n_B$, the latter being practically equal. The initial amounts of the enantiomers **A** and **B** were equal (racemate). Given the rate constants $k^m$ in the mobile phase, the simulation experiment was performed for different values of the rate constant $k_1^s$ in the stationary phase [$k^s_{-1}$ being calculated from $k_1^s$ according to the principle of microscopic reversibility (cf. Scheme 1 and ref.[8])] in order to find the best agreement of simulated and experimental curves. Another possible procedure, yielding the same results, is to perform the simulation experiments for different values of $k_1$, to calculate $k_{-1}$ from $k_1$ in agreement with eq. (b), initially assuming the same rate constants in both phases, i.e. $k_m = 1/2\,(k_1^s + k^s_{-1}) = 1/2\,(k_1 + k_{-1})$, in order to obtain $k_1$ and $k_{-1}$, and then to evaluate according to eq. (a). $\Delta G^{\neq}$ was calculated from the corresponding rate constant $k$ (mean of forward and backward reaction) according to the Eyring equation

$$k = f\frac{k_B T}{h} e^{\Delta G^{\neq}/RT} \qquad \text{(d)}$$

where the transmission coefficient $f = 0.5$ for a two-step reaction[9] (cf. remarks in the text).

[1] *Dynamic NMR Spectroscopy* (Eds.: L. M. Jackman, F. A. Cotton) Academic Press, New York, **1975**.

[2] "Racemization" is defined as the irreversible formation of a racemate from an optically enriched mixture [i.e., (+) or (−) → (±)]. The term "enantiomerization" refers to a reversible interconversion of the enantiomers [i.e., (+) $\rightleftharpoons$ (−)]. Since interconversion of *one* (+) molecule to *one* (−) molecule reduces the enantiomer excess of (+) by *two* molecules, the $k_{rac}$ vaue thus defined and used in ref.[12] is related to $k^m$ by $k_{rac} = 2\,k^m$; cf.: E. L. Eliel, *Stereochemistry of Carbon Compunds*, McGraw-Hill Book Company Inc., New York **1962**, p. 34.

[3] W. Bürkle, H. Karfunkel, V. Schurig, *J. Chromatogr.* **1984**, *288*, 1–14.

[4] J. Veciana, M. I. Crespo, *Angew. Chem.* **1991**, *103*, 85–88; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 74.

[5] H. Zinner, Dissertation, Universität Regensburg, **1991**, chapter 8; cf. also: B. Stephan, H. Zinner, F. Kastner, A. Mannschreck, *Chimia* **1990**, *44*, 336–338.

[6] V. Schurig, W. Bürkle, *J. Am. Chem. Soc.* **1982**, *104*, 7573–7580.

[7] For a detailed description of the theoretical and experimental procedure see: M. Jung, V. Schurig, *J. Am. Chem. Soc.*, **1992**, *114*, 529–534.

[8] This is a direct consequence of eq. (a) and the principle of microscopic reversibility[3,7], i.e. $k_1^s/k^s_{-1} = t'_{R_B}/t'_{R_A}$ (ratio of the corrected or net retention times).

[9] It has to be noted that inaccuracies of the rate constants only have a small influence on the calculation of the respective $\Delta G^{\neq}$ value, e.g., $k = 0.05$ min$^{-1}$ ± 10% only yields an error of 0.4 kJ mol$^{-1}$ in the respective $\Delta G^{\neq}$ value. Since enantiomerization of homofuran proceeds via an ylide intermediate[13], and half of the intermediate formed reacts back to the starting material, a statistical factor $f = 0.5$ has to be used in the Eyring equation when converting the rate constant of the total reaction ($k^m$, $k_1$, and $k_{-1}$) into the activation barrier of the first step (cf. also: H. Häkli, M. Mintas, A. Mannschreck, *Chem. Ber.* **1979**, *112*, 2028–2038).

[10] V. Schurig, U. Leyrer, *Tetrahedron: Asymmetry* **1990**, *1*, 865–868.

[11] The program on the basis of the theoretical plate model, written in FORTRAN 77 and usable with any large computer, is available from the authors upon request as a source code and has been accepted by the Quantum Chemistry Program Exchange (QCPE). It can be adapted to various problems in dynamic chromatography. An unlimited number of solutes may be injected in variable amounts, and a special procedure allows different plate numbers to be used within one chromatogram. An application of a variation of the described program to a problem that requires a Runge-Kutta routine for the kinetic calculations will be discussed in a forthcoming publication (M. Jung, V. Schurig, *J. Chromatogr.*, paper accepted for publication).

[12] V. Schurig, D. Schmalzing, M. Schleimer, *Angew. Chem.* **1991**, *103*, 994–996; *Angew. Chem. Int. Ed.Engl.* **1991**, *30*, 987–989.

[13] F.-G. Klärner, D. Schröer, *Angew.Chem.* **1987**, *99*, 1295–1297, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1294.

[14] Plate numbers (depending on the inlet pressure; above 125 °C the low capacity factor requires measurements below the Van Deemter optimum): 18000 (averaged value) at 95–120 °C, 10400 at 125 °C und 12000 at 130 °C; (dead time $t_M$, uncorrected retention times $t_R$ [min] of the enantiomers **A** and **B**): 0.61, 1.84, 2.13 at 95 °C, 2.3 bar $N_2$; 0.67, 1.75, 1.97 at 100 °C, 2.0 bar $N_2$; 0.83, 1.81, 2.00 at 105 °C, 1.7 bar $N_2$; 0.96, 1.82, 1.96 at 110 °C, 1.5 bar $N_2$; 1.11, 1.93, 2.04 at 115 °C, 1.3 bar $N_2$; 1.47, 2.37, 2.48 at 120 °C, 1.2 bar $N_2$; 1.59, 2.38, 2.46 at 125 °C, 0.9 bar $N_2$; 1.83, 2.62, 2.67 at 130 °C, 0.8 bar $N_2$.

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