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On- and off column enantiomerization of 4,4′-bisquinolin-2-ones: A comparison of Auto-, DHPLcy2k and DCXplorer calculated thermodynamic data generated by dynamic high, performance liquid chromatography with theoretically calculated data

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ABSTRACT

Fast semipreparative HPLC enantioseparation of four axially chiral biscarbostyrils (4,4′-bisquinoline-2-ones) using ULMO as a π-acidic Pirkle type chiral stationary phase leads to two racemizing pairs (**1**,**2**; k_{obs} 1.6×10^{-4} and 3.0×10^{-4} s^{-1} at 28 °C) and two stable ones (**3**,**4**). **3** was stabilized by a crown ether linkage from pos. 6 to 6′, and **4** had sterically demanding bromo substituents in pos. 3 and 3′. On-column generated temperature-dependent chromatograms of **1** and **2** were fitted with Auto-DHPLCy2k and DCXplorer. For cpd **2** both programs delivered similar ΔG values of 90 and 93 kJ/mol, well comparable with the 99 kJ/mol calculated with the B3LYP/6-31G (d) procedure. At temperatures of high conversion DCXplorer delivered inconsistent series of rate constants for the more tailing and less resolved tetramethoxy derivative **1**. We connect this problem with an almost impossible halfwidth calculation of tailing peak pairs which are weakly resolved. However, this problem could be observed only in the case of tetramethoxy derivative **1**. Stochastic generated data of Auto-DHPLCy2k could be used at a lower percentage of conversion only while the theoretical plate model did not deliver useful data at temperatures of very low conversion but fitted well high conversion chromatogram series of **1** and **2**.

1. Introduction

Temperature dependence of rate constants of enantiomerization can be conveniently studied chromatographically using peak shape analysis of racemic analytes, if a continuous re-racemization occurs during the separation process on a chiral stationary phase (CSP). Numerous publications about dynamic racemization during chromatographic resolution on CSP's have been published during the last 30 years. Comprehensive references can be found in recent papers [1–5] and reviews [6]. Since the seminal publication of Bürkle et al. [7] such a process on a CSP is called enantiomerization. Kinetically it is a simple case of a reversible monomolecular reaction and has also the advantage, that for enantiomers the response of chromatographic detectors is completely equal. Racemization during the separation process occurs continuously. An overlapping zone ("plateau") between the two peaks of enantiomers can be observed due to a continuous dynamic inversion of already separated enantiomers at any part of the column. It is a kinetic process, thus it is enhanced by increased temperature. Since the first FORTRAN programs [7,8] a number of computations to analyze dynamic peak shapes have been advanced, e.g. MIMESIS [9,10], SIMUL [11] and its Fortran77 modification to allow direct input of ASCII chromatogram data [12], CHROMWIN [13]. The latter allows simulating elution profiles by the theoretical plate model and the stochastic model [2,14] and includes an acceleration algorithm to find the correct reaction rate constant. Its further development led to a unified equation and the free available Windows program DCXplorer [5,15]. Another further developed program is Auto-DHPLCy2k implementing both stochastic and theoretical plate models but allowing separate evaluations of both approaches. It is claimed to take into account tailing effects [1] which has been advanced previously by Trapp et al. [15c] by iterative comparison of the experimental and simulated elution profile.

Recently we separated a number of axially chiral 4,4′-biscarbostyrils [16] on our Pirkle-type π acidic ULMO CSP [17] and found, that some HPLC enantiomer separations of 6- and 7-methoxy substituted species got rather large separation factors (1.5–2.5) but exhibited significantly tailing peaks. In order to investigate the elution order and thus comparing the experimental CD data with calculated ones, we found that of four enantiopure species (Fig. 1) compounds **1** and **2** racemized within hours

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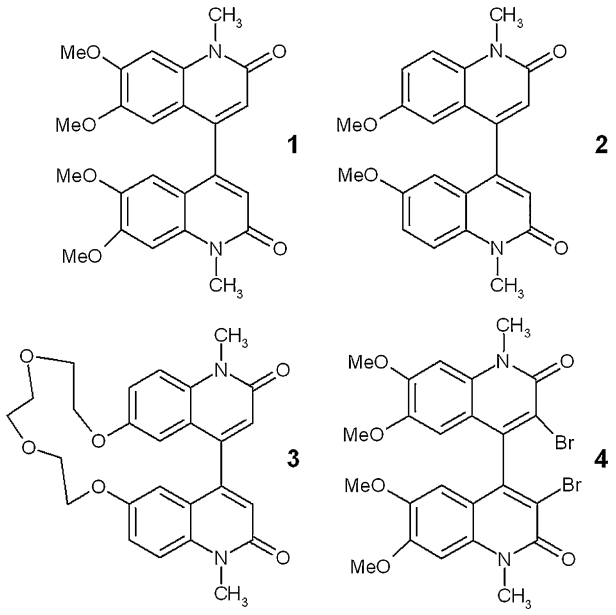

Fig. 1. Bisquinoline-2-ones **1**–**4**.

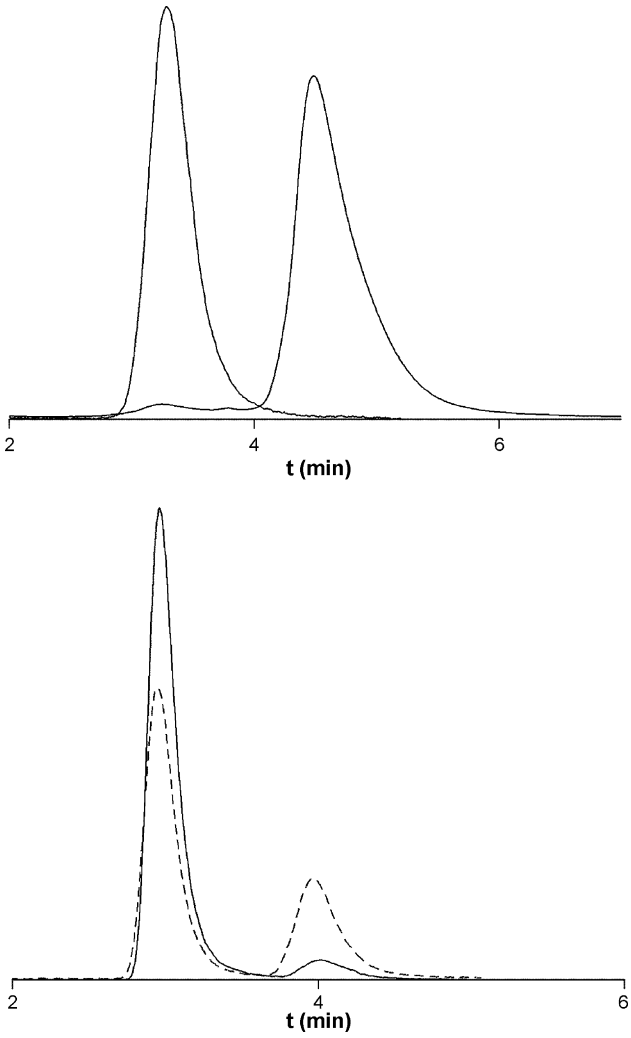

Fig. 2. Lower part: Fraction 1 of 6,6′-dimethoxybiscarbostyril **2**, (—) shortly after isolation and (···) after 6 h at 13 °C; upper part: HPLC of the isolated enantiomers of crown ether **3**.

at room temperature. This publication describes results of three different calculation methods of dynamic peak shape analysis, DCXplorer and Auto-DHPLcy2k allowing a separate stochastic and theoretical plate model calculation. Results are compared with kinetically measured and with theoretically calculated thermodynamic parameters.

2. Experimental

Chiral HPLC measurements were performed using a HEWLETT PACKARD series HP1050 instrument consisting of a pumping system, a multiple wavelength detector and an auto-sampler and the HPChemstation software. The chiral stationary phase (CSP) was an (S,S)-ULMO [17] column (125 × 4 mm) from REGIS, Morton Grove, IL, USA. Temperature of the column was maintained by Lauda RM6—RMS Brinkmann Refrigerating Circulating Bath. CD measurements were carried out on a Jasco J-715 spectropolarimeter at room temperature using a 2-cm (volume 4 mL) cell with the following parameters: bandwidth 1 nm; step resolution 0.2 nm; accumulation 1; sensitivity 20 mdeg; speed, 100 nm/min; response 2 s; bandwidth 1.0 nm.

2.1. Chromatography and solutions for CD spectra

The experiments were performed with isocratic elution at a flow rate of 1 mL/min. Conditions were optimized regarding solubility and speed. The latter being important for compounds **1** und **2** since the enantiomers interconverted notably within 1 h, while enantiopure compounds **3** and **4** were stable in solution for at least 2 weeks. The mobile phase always consisted of a v/v/v mixture of n-heptane/dioxane/dichloromethane 45:45:10. The column temperature was between 13 and 75 °C. Semipreparative HPLC runs: 1 μL of an about 0.1 M stock solution (crown ether **3**: 0.03 M) of racemic sample in chloroform was injected (repeated 5–10 times). Yield was about 0.1–0.3 mg of >98ee fractions **1** and **2** in 5 and 9 mL respectively. For CD measurements isolated peaks of labile **1** and **2** were measured immediately after two separations. Mobile phase of enantiopure **3** and **4** was removed in vacuo and compounds were redissolved in methanol. For kinetic HPLC analysis, 30 μL mobile phase was directly injected after single 1 μL runs.

2.2. Kinetic data and interversion barriers

Collected individual fractions of both enantiomers of **1** and **2** were used for kinetic studies. Vials were thermostatted at different temperatures and taken out only for the short time of HPLC injection.

2.3. Dynamic peak shape analysis

The computer program DCXplorer was downloaded from the Internet [15]. Calculations using the program Auto-DHPLCy2k [1] were done by Marco Pierini (Sapienza Università di Roma, Italy). This program implements both stochastic and theoretical plate models according to mathematical equations and procedures described within refs. [13,11]. Algorithm including the stochastic approach was adapted to also allow simulation of non-enantiomeric isomerizations [18a–c]. Functionality of the program was validated on several kinds of first-order processes by comparing its evaluations with those obtained by either DNMR technique [18a,d–f] or classical kinetic measurements based on the batchwise approach [1,18b,c]. Both the cited algorithms may take tailing effects into account. In addition, chromatographic and kinetic parameters can be automatically optimized by driving their variation by simplex algorithm, until the best agreement between experimental and simulated dynamic chromatograms is obtained.

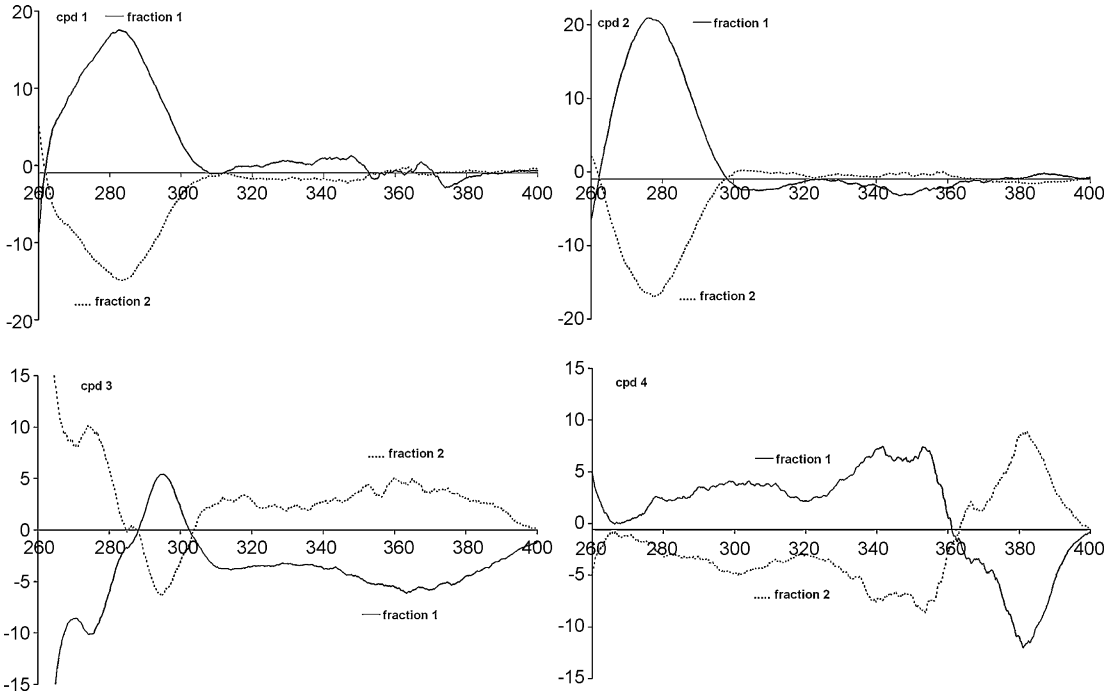

Fig. 3. Experimental CD spectra of enantiomerically enriched or pure compounds **1**–**4**.

Comparison between such dynamic profiles is done objectively by evaluating the root mean square differences (RMSD) between the two normalized chromatograms. Convergence of simplex procedure was considered acceptable when the RMSD gradient was below 0.001. Errors associated to the so evaluated rate constants were estimated less than 2%.

2.4. Computational details

The geometries of compounds **1**, **2**, and **4** were optimized using the BP86 density functional [19] and the SVP basis set [20]. Electronic excitation energies and rotational strengths (electronic circular dichroism) were obtained by time-dependent density functional theory [21–27] (B3PW91/TZVP) [28,29]. Rotational barriers were calculated with the B3LYP/6-31G(d) procedure [30–32]. This method has been found to give good results for the enantiomerization of chiral biphenyl derivatives [4]. Solvent effects (methanol, dioxane) were approximated by the IEF-PCM variant of the polarizable continuum solvation model [33]. Programs used were Turbomol [34], Gaussian 03 [35], and MOLDEN [36] for visualization, and SHAPE [37] for the simulation of CD spectra (halfwidth 10 nm).

3. Results and discussion

3.1. Semipreparative enantioseparation of biscarbostyrils and CD spectra

Fig. 2 shows in the lower part the chromatograms of the collected first fractions of compound **2** shortly after isolation and after 6 h in the mobile phase at 13 °C. Even at this temperature some enantiomerization is visible as a small plateau. Enantiomers of thermodynamically stable compound **3** are shown in the upper part.

The preparatively isolated fractions of the 2nd eluting enantiomers of crown ether **3** were sufficiently enantiopure to measure almost mirror image CD spectra. Up to 10 runs were collected and fractions were pooled. In case of unstable **1** and **2**, CD measurements were done immediately after the chromatographic runs in the heptane–dioxane–dichloromethane solution. Because of the absorption of the solvents the curves in the range 270–260 nm are somewhat incorrect. Since biscarbostyrils **3** and **4** do not racemize, the mobile phase was evaporated and these CD-spectra were measured in the more UV transparent methanol (Fig. 3).

3.2. Determination of the absolute configuration

One of the most powerful tools to determine the absolute configuration, especially of natural products, is HPLC resolution of the individual enantiomers, combined with measurement of electronic circular dichroism spectra and comparison with those simulated on the basis of quantum chemical calculations [38,39]. Computed chiroptic properties, mainly electronic CD spectra, have been successfully applied to assign the absolute configuration of axially chiral compounds [40–48]. In these investigations the conformational sensitivity of simulated CD spectra, i.e. their dependence on the inter-ring torsional angle, has been pointed out. The calculated potential energy curve for rotation around the central C4–C4′ bond, described by the torsional angle τ (C3–C4–C4′–C3′) is rather flat in the vicinity of the global minimum [$\tau \sim 100^{\circ}$ (BP86/SVP)]. Hence, several rotamers within 5 kJ/mol of the minimum energy structure were taken into account with appropriate Boltzmann averaging of the respective simulated CD curve. The experimental CD spectrum of biscarbostyril **3** (Fig. 3) is characterized by two broad overlapping bands of like sign, extending from 300 to 400 nm (peaks at ~315 and ~360 nm) and a relatively sharp peak of opposite sign at ~295 nm. 3,3′-Dibromo-6,6′,7,7′-tetramethoxy-4,4′-biscarbostyril **4** shows a rather sharp long wavelength CD band at ~380 nm and broad features extending from 280 to 360 nm. The simulated spectra for compounds **2** and **4** (a*S* configuration) resulting from calculated rotational strengths are displayed in Fig. 4. For comparison, experimental curves of fractions **1**, and in the case of **4** both fractions are added. The general feature of the experimental CD spectrum of **2** is quite nicely reproduced by the simulations.

On the basis of a comparison between the experimental CD spectra and those simulated for the a*S* enantiomer, the first eluted

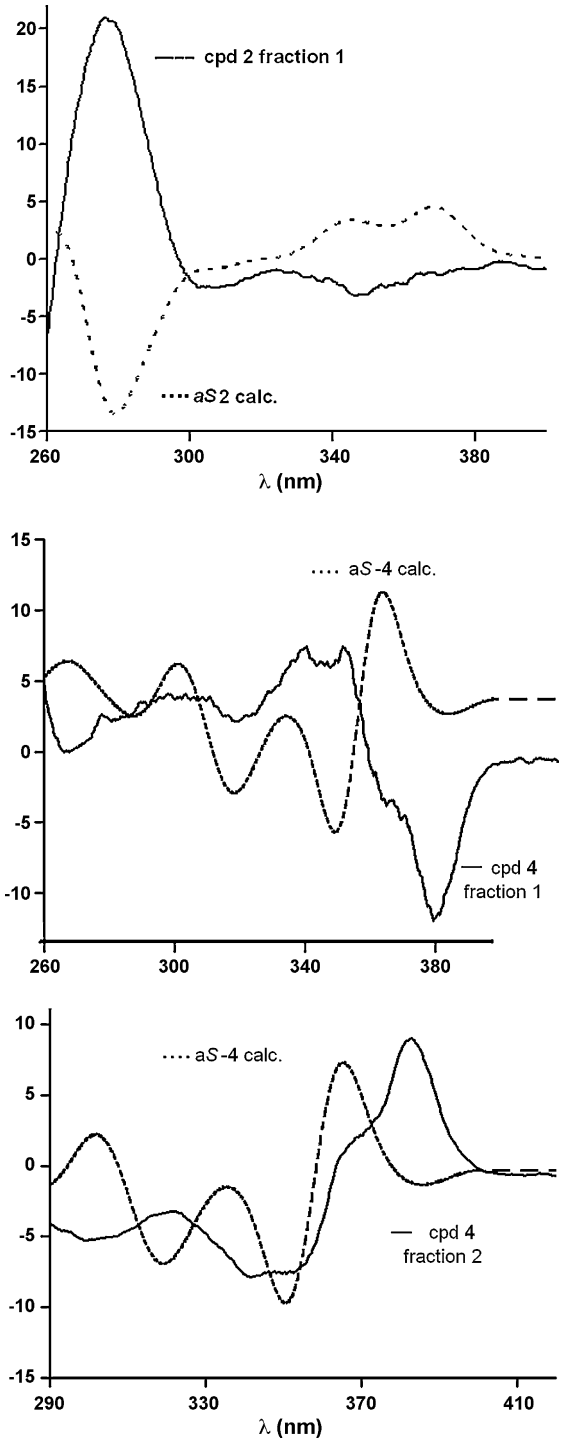

Fig. 4. Experimental vs. calculated a*S*-CD-spectra of 6,6′-dimethoxybiscarbostyril **2** (upper) and both fractions of 3,3′-dibromo-6,6′,7,7′-tetramethoxycarbostyril **4**.

enantiomer of biscarbostyrils **2** and **3** has to be assigned the absolute configuration a*R*. However, the calculated CD spectrum of a*S* dibromo compound **4** could be almost equally well fitted to the CD spectra of both HPLC fractions, which are different from **2** and **3**.

3.3. Rate constants and activation parameters

Table 1 contains all experimental and calculated thermodynamic parameters for biscarbostyrils **1** and **2**. Original and fitting

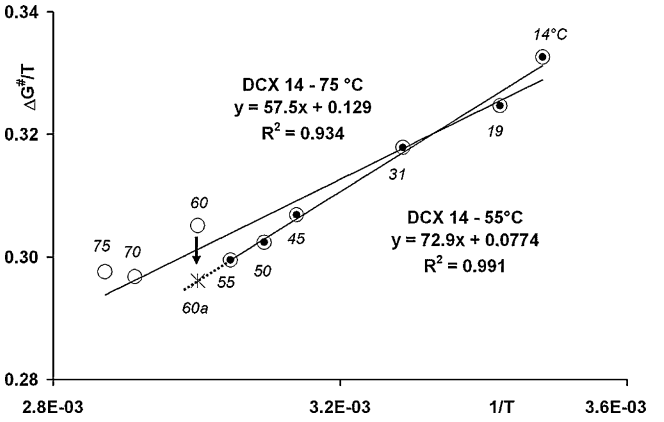

Fig. 5. Compound **1**: DCXplorer Eyring plot 14–55 °C vs. 14–75 °C. Note that the modified 60 °C value 60a fits exactly the 14–55 °C plot. Slope is $\Delta H^{\#}$ and intercept is $-\Delta S^{\#}$.

curves for temperature-dependent coalescing HPLC peaks are collected in the supporting information.

3.3.1. DCXplorer

The Windows® program DCXplorer, which contains a unified theoretical plate and stochastic equation is available free of charge at the Internet site of Oliver Trapp [15]. It is easy to install and to use directly XY files from the .CSV format. Therefore we used it first to study the interconverting biscarbostyrils **1** and **2**. While there was no problem to get linear Eyring plots from 6,6′-dimethoxy compound **2** (HPLC resolution 2.40 at 20 °C; $R^2 = 0.992$, $\Delta H^{\#} = 37$ kJ/mol, $\Delta S^{\#} = 180$ J/mol K (Table 1), the very similarly structured but not so well HPLC resolved 6,6′,7,7′-tetramethoxy analogue **1** (res = 1.54) showed remarkable diverging data in the upper temperature range. However, in the temperature range 14–55 °C there was an equally good linear correlation coefficient of 0.992, giving $\Delta H^{\#} = 73$ kJ/mol and $\Delta S^{\#} = -77$ J/mol K. Note that we generated data by setting plateau positions to the minima between peaks 1 and 2 (for a comparison with the automatically generated mean position see S2–S8).

Fig. 5 shows two trend lines: one with values up to 55 °C and an R^2 value of 0.992 and a second trend line representing all temperatures up to 75 °C ($R^2 = 0.934$, values not in Table 1). Highly notable is a *decrease* in the DCXplorer calculated rate constants from 55 to 60 °C (1.56×10^{-3} to 7.85×10^{-4}), although the interconverting middle plateau is raised at 60 °C as expected compared with the one at 55 °C (Fig. 6). A closer examination shows that 55–60 °C is just the temperature range where the 100% maxima change from the first to the second peak. Looking at the published calculation method, the program switches after this point to a modified equation. We modified the 60 °C chromatogram in order to get the second maximum just smaller than the first one *and kept everything else unchanged* (Fig. 6, right). Note that this "manipulation" is not at all used to correct results and that such values are not included in linear regression calculations and are not in the table. However, we show that in the case of tailing the program DCXplorer can have a weak spot in switching formulas at the temperature which changes the maxima.

The calculated 60 °C rate constant (2.4×10^{-3}) would fit exactly to the linear 14–55 °C expression (Fig. 5) because the DCXplorer program uses continuously the published first equation. However, after consultation with DCXplorer coauthor Oliver Trapp he would not recommend the use of only the first equation. We can support this by the observation that calculation with our very similar analogue **2** *did show the expected rate constant increase* shifting the intensity ratios from peak 1 to peak 2 (55–60 °C, Fig. 7).

Table 1
Summary of thermodynamic data for enantiomerization of biscarbostyrils **1** and **2**.

	DCXplorer	Theoretical plates	Stochastic	Mean[a]	Combined[b]	Kinetics	B3LYP/6-31G(d)
cpd **1**							
T range (°C)	14–55	45–75	31–60		31–75	9–31	
R^2	0.992	0.979	0.996		0.979	0.989	–
$\Delta G^{\#}$ (kJ/mol)[c]	103	95	100	100	100	96	101
$\Delta H^{\#}$ (kJ/mol)	73 ± 3.5	61 ± 4	84 ± 3	77 ± 12	98.7 ± 6	81 ± 7	89
$-\Delta S^{\#}$ (J/mol K)	77 ± 12	114 ± 14	54 ± 10	71 ± 32	5.2 ± 20	48 ± 20	40
cpd **2**							
T range (°C)	22–75	55–75	22–55		22–75	9–39	
R^2	0.992	0.998	0.999		0.994	0.997	–
$\Delta G^{\#}$ (kJ/mol)[c]	90	94	94	93	100	94 ± 4	99
$\Delta H^{\#}$ (kJ/mol)	37 ± 1.5	55 ± 1.9	49 ± 1.2	47 ± 9	61.4 ± 5.5	63.2 ± 3.5	89
$-\Delta S^{\#}$ (J/mol K)	180 ± 5	130 ± 6	150 ± 4	153 ± 25	129 ± 6	103 ± 12	32

[a] Does not contain the combined approach.
[b] DHPLCy2k stochastic 31–55; theoretical plates 60–75 °C.
[c] 25 °C.

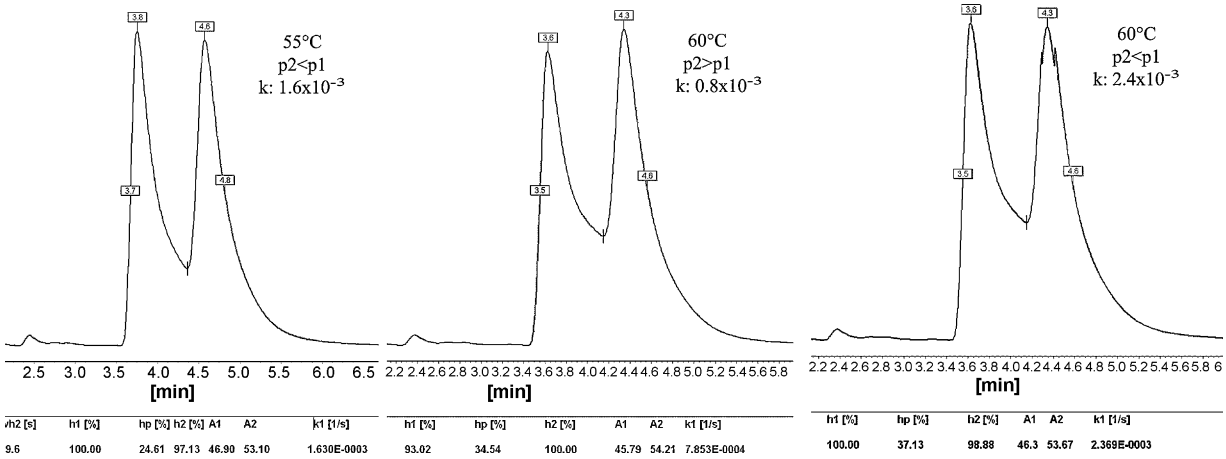

Fig. 6. Compound **1**: Comparison of DCXplorer results for enantiomerization of **1** at 55 and 60 °C after slight modification of the 2nd peak switching intensity ratios (arrows see text).

3.3.2. DHPLCy2k

A number of recent publications describe the use of the program Auto-DHPLCy2k to calculate enantiomerization rate constants and thermodynamic parameters [1,18,49]. Since a "ready to use" program is not freely available, it is thankfully acknowledged that calculations were done by Marco Pierini at the University of Rome, Italy. Three $\Delta G^{\#}/T$ vs. $1/T$ plots are shown in Fig. 8.

Calculating with the theoretical plate model leads to a linear plot (open squares) in the temperature range from 45 to 75 °C. The stochastic model worked well in the range from 31 to 60 °C

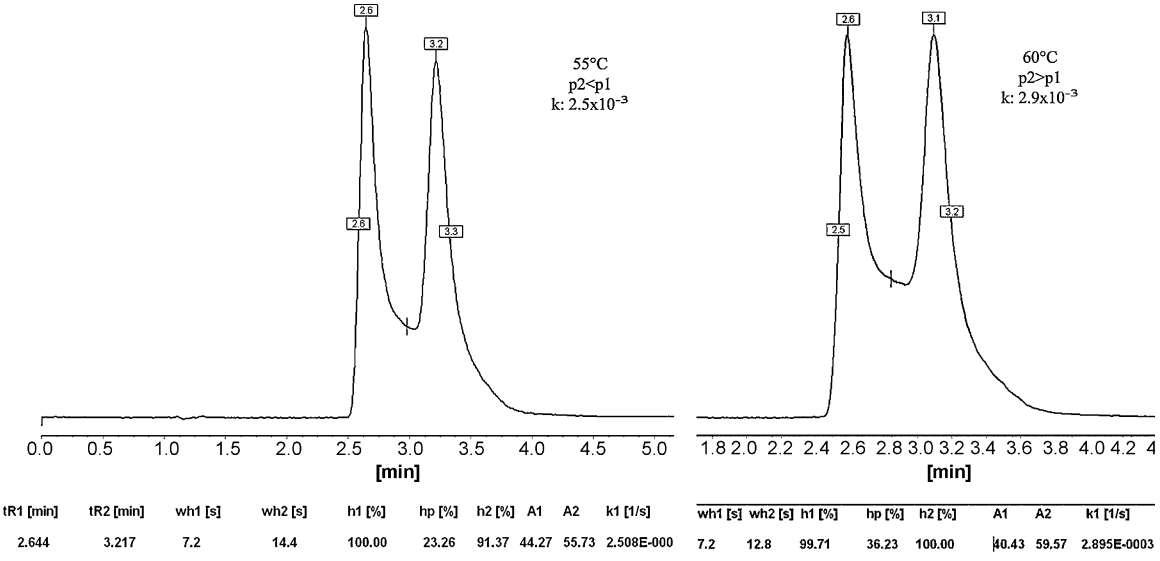

Fig. 7. Compound **2**: Comparison of DCXplorer results for enantiomerization at 55 and 60 °C just as intensity ratios switch. Calculated rate constants increase from 2.5 to 2.9×10^{-3}.

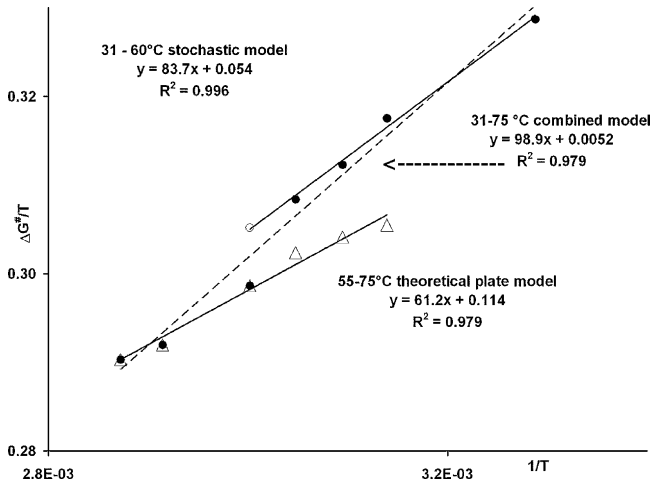

Fig. 8. Compound **1**: Auto-DHPLCy2k generated (○) stochastic and (△) theoretical plate model data and the best combination (●) as Eyring plots.

(Table 1). Good linearity (R^2 = 0.979) for the large range 31–75 °C could be found combining the 60, 70 and 75 °C values from the theoretical plate model with 31–55 °C values from the stochastic model (Fig. 7). However, the DCXplorer results (Fig. 5) for temperature range 14–55 °C were $\Delta H^{\#}$ = 73 kJ/mol and $\Delta S^{\#}$ = −77 J/mol K, just in between the stochastic and the theoretical plate model, namely $\Delta H^{\#}$ = 84 kJ/mol and $\Delta S^{\#}$ = -54 J/mol K and $\Delta H^{\#}$ = 61 kJ/mol and $\Delta S^{\#}$ = −114 J/mol K respectively. The theoretical plate model fits very well at high interconversion rates but seems to be not useful to analyze the rather small changes in peak shape at lower temperatures when the conversion just begins. It delivers with 61 kJ/mol the lowest $\Delta H^{\#}$ and the largest (negative) $\Delta S^{\#}$ value, −114 J/mol K. In contrast, the stochastic model fits the lower temperature chromatograms pretty well. Marco Pierini suggests a combination of both methods which leads to an activation enthalpy of almost 100 kJ/mol, the very small $\Delta S^{\#}$ term of −5 J/mol K and a good correlation coefficient R^2 = 0.979 over the range 31–75 °C.

As already found with DCXplorer, for 6,6′-dimethoxybiscarbostyril **2** linear correlation coefficients are much better than for tetramethoxy analogue **1**. Eyring plots for the three discussed calculation methods are shown in Fig. 9. In contrast to tetramethoxy analogue **1** (Table 1), DCXplorer calculated $\Delta H^{\#}$ of **2** (37 kJ/mol) is somewhat lower than theoretical plate (55 kJ/mol) and stochastic model (49 kJ/mol) activation enthalpies calculated with DHPLCcy2k. $\Delta H^{\#}$ values are lower for **2** than **1** (mean 47 kJ/mol vs. 77 kJ/mol which can be also estimated visually from the higher temperature of peak height inversion (ca. 62 °C vs. 57 °C for **1**).

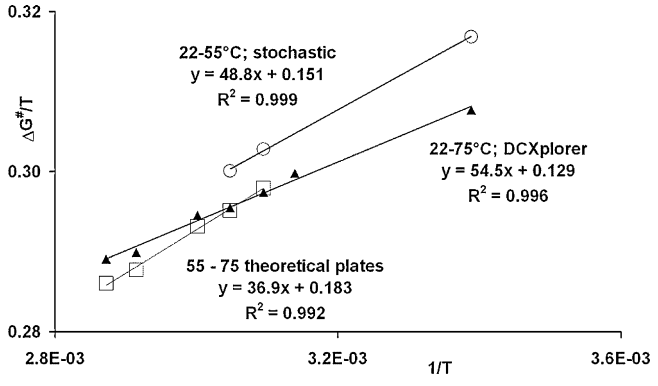

Fig. 9. Compound **2**: Eyring plots Auto-DHPLCy2k generated (○) stochastic and (□) theoretical plate model vs. (▲) DCXplorer.

Calculated (negative) entropy parameters for the inversion of **2** are higher than for **1** (mean −153 J/mol K vs. −71 J/mol K).

3.3.3. Kinetics

In order to compare peak shape generated thermodynamic data with first-order enantiomerization rate constants, almost pure enantiomers of 6,7,6′,7′-tetramethoxy- and 6,6′-dimethoxybiscarbostyrils **1** and **2** were isolated with semipreparative HPLC and the rate of enantiomerization was monitored in the temperature range 9–39 °C with the same analytical column. We see a small difference in the kinetically measured activation parameters of **1** and **2** (Table 1). Activation enthalpies are 81 and 63 kJ/mol. This trend is also shown by the averaged dynamic HPLC generated values (Table 1, 77 kJ/mol vs. 47 kJ/mol). The entropic parameters are −48 J/mol K vs. −103 J/mol K. The theoretically calculated values fit into this scheme reasonably well (Table 1). Gibbs free energies are in all cases around 100 kJ/mol, average values observed for this kind of atropisomerism [9].

4. Conclusion

Our observations of rather diverging energy parameters calculated from experimental HPLC curves with three different methods are valid only for our experimental results with tailing biscarbostyrils **1** and **2**. Therefore this paper does not have a universal appeal as the procedure is best suited for this specific case. Data do not contain multiple repeated and averaged measurements. DCXplorer and Auto-DHPLCy2k both get about the same quality of data, but not equal results. DCXplorer is containing an unified equation and therefore it fits peak shapes over a large temperature range. However, DCXplorer can deliver strange results raising the intermediate plateau above 50% (in case of compound **1**). Despite the excellently linear low conversion rate constant calculation of DCXplorer, for tailing peaks the program's built in peak width feature is not optimal. Note the way the program calculates peak half-widths: doubling of the difference to the maximum from the start side of the first peak and the outside of the second peak results in incorrect half width values. This could be improved by including weighted tailing factors.

Auto-DHPLCy2k has a theoretical plate program part which is fitting coalescing chromatograms extremely well. The stochastic part of Auto-DHPLCy2k seems to be valuable in the medium temperature range only.

Experimental generation of data for dynamic peak shape analysis is straightforward. The classical method of measuring rate constants requires at least five chromatograms during racemization and values at four or more different temperatures. This is much more work, even if one does not consider the necessity of preparative enantioseparation. Therefore, from our experience with the (tailing) dynamic chromatograms of biscarbostyrils **1** and **2** we assume that a combination of two peak shape analysis methods would get reliable results with less experimental work than the classical single enantiomer method.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.chroma.2009.12.001.

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