Probing the Stereointegrity of Tröger's Base—A Dynamic Electrokinetic Chromatographic Study

Oliver Trapp,[a] Gabriele Trapp,[a] Jingwu Kong,[a] Uwe Hahn,[b] Fritz Vögtle,*[b] and Volker Schurig*[a]

Abstract: Under acidic conditions the enantiomers of Tröger's base **1** (2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazozine) are subject to enantiomerization. During enantioselective dynamic electrokinetic chromatography using 10 mM hydroxypropyl-β-cyclodextrin as the chiral mobile phase additive in 50 mM tris/phosphate buffer at pH 2.2, enantiomerization of Tröger's base gives rise to characteristic elution profiles featuring plateau formation and peak broadening. Introduction of a permanent positive charge attributed to quaternization in the monobenzylated derivative of Tröger's base **2** (5-benzyl-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazozinium bromide) decreases the enantiomerization barrier significantly. To determine the rate constants of enantiomerization the experimental chromatograms were evaluated by a direct calculation method and by using the computer simulation program ChromWin. From temperature-dependent measurements the Eyring activation parameters for **1** and **2** were determined: **1**: $\Delta G^{\neq}$ (298 K) $= 100.9 \pm 0.5$ kJ mol^{-1}, $\Delta H^{\neq} = 89.5 \pm 2.0$ kJ mol^{-1}, $\Delta S^{\neq} = -42 \pm 10$ J K^{-1} mol^{-1}; **2**: $\Delta G^{\neq}$ (298 K) $= 90.2 \pm 0.5$ kJ mol^{-1}, $\Delta H^{\neq} = 91.4 \pm 2.0$ kJ mol^{-1}, $\Delta S^{\neq} = 9.8 \pm 10$ J K^{-1} mol^{-1}.

Keywords: chirotopic nitrogen · ChromWin · computer simulation · electrophoresis · kinetics

Introduction

For more than a century Tröger's base has been one of the most fascinating and stimulating chiral molecules in organic chemistry. Ever since its first synthesis by J. Tröger in 1887[1, 2] it has been a lucid subject of intensive analytical and synthetic research. After several unsuccessful attempts to elucidate the structure of Tröger's base, Spielman finally determined the correct structure in 1935 by synthesis and elemental analysis.[3] Contrary to Meisenheimer's suggestion that chirotopic nitrogen compounds fail to display optical activity due to pyramidal inversion, Prelog and Wieland achieved the successful enantioseparation of constrained Tröger's base by liquid chromatography on a 0.9 m column containing lactose hydrate, followed by fractional crystallization in 1944.[4] This separation not only constitutes the first separation of an asymmetrically substituted compound containing trivalent nitrogen but also represents the first reproducible chromatographic separation of an enantiomeric pair. The relative stability of Tröger's base against inversion lies in its molecular architecture which contains trivalent nitrogen as bridgehead atoms. Owing to the blocked configuration of the two stereogenic nitrogen atoms and the C_2 symmetry of the molecule only one pair of enantiomers is observed.

In recent developments, the theoretical and practical application of Trögers base as a chiral solvating agent,[5, 6] a molecular receptor,[7] and an auxiliary in enantioselective reactions was revisited. Tröger's base and its analogues are mostly derived in a one-step synthesis from the reaction of toluidines or substituted anilines with formaldehyde, but in the past few years, new Tröger's base analogues derived from heterocyclic compounds have been reported.[8, 9] Some of these Tröger's base analogues have been shown to interact with DNA.[10–12] One reason for the increasing popularity of Tröger's base is the rigid concave structure of the molecule which provides an ideal chiral molecular armature[13] for the construction of chelating and biomimetic systems[8, 14–23] or for the synthesis of chiral molecular tweezers.[24] However, the utilization as chiral agent, receptor, or auxiliary requires stereointegrity under the desired conditions. As already reported by Prelog and Wieland,[4] Tröger's base is prone to racemization in presence of an acidic medium. Greenberg and Molinaro proposed an enantiomerization mechanism via an iminium intermediate but were unable to prove its existence by NMR spectroscopy.[25]

Several groups tried to enhance the chromatographic enantioseparation of Tröger's base; Prelog and Wieland only

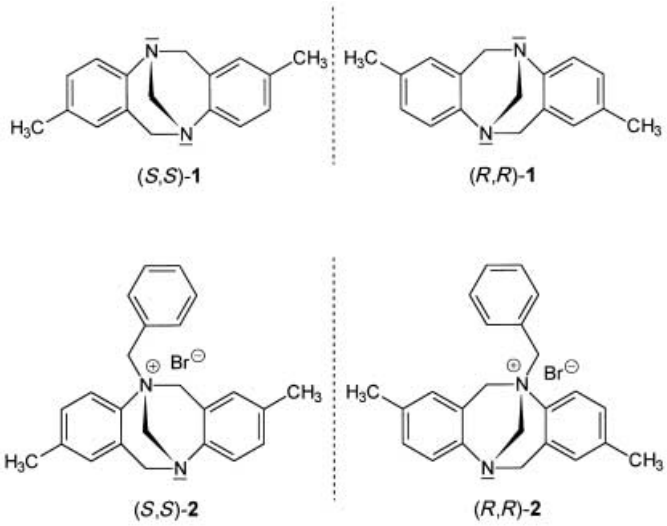
[a] Prof. Dr. V. Schurig, Dr. O. Trapp, Dr. G. Trapp, Dr. J. Kong
Universität Tübingen
Institut für Organische Chemie
Auf der Morgenstelle 18, 72076 Tübingen (Germany)
Fax: (+49) 7071-29-5538
E-mail: volker.schurig@uni-tuebingen.de

[b] Prof. Dr. F. Vögtle, Dipl.-Chem. U. Hahn
Kekulé Institut für Organische und Biochemie
Rheinische Universität
Gerhard-Domagk-Strasse 1, 53121 Bonn (Germany)
Fax: (+49) 22873-5662
E-mail: voegtle@uni-bonn.de

 © 2002 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 0947-6539/02/0816-3629 $ 20.00+.50/0

obtained 5.5% of both enantiomers from the racemate. Successful methods were developed by using cellulose triacetate[26, 27] or (+)-poly(triphenylmethylmethacrylate)[28, 29] as chiral selectors in high-performance liquid chromatography (HPLC) or capillary electrochromatography (CEC), respectively. The application of supercritical fluid chromatographic (SFC) and gas chromatographic (GC) separations using modified cyclodextrins (Chirasil-β-Dex)[30, 31] or the simulated moving bed (SMB) separation of Tröger's base on amylose carbamate derivatives (Chiralpak-AS) have also been reported.[32]

Herein, we describe the determination of rate constants k_1^{app}, enantiomerization barriers $\Delta G^{\neq}(T)$, and activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of Tröger's base **1** (2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazozine) and its N-monobenzylated derivative **2** (5-benzyl-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazozinium bromide; Scheme 1). For the determination of these parameters an elektrokinetic chromatographic (EKC) separation method was developed in which hydroxypropyl-β-cyclodextrin was used as a chiral mobile phase additive. By dynamic measurements in acidic buffer medium (tris/phosphate buffer, pH 2.2) and subsequent analysis of the experimental chromatographic data by direct calculation[33] or computer simulation,[34] the rate constants k_1^{app} of the enantiomerization reaction were obtained. From temperature-dependent measurements the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated by using the Eyring equation. The enantiomerization mechanism was then elucidated by comparison of the enantiomerization barrier $\Delta G^{\neq}(T)$ and the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of the permanently charged and uncharged compounds.



Scheme 1. Enantiomeric pairs of Tröger's base **1** and its N-monobenzylated derivative **2**.

Results and Discussion

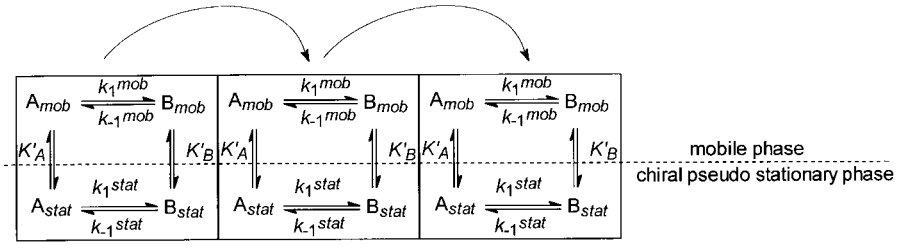
Molecular interconversion occurring during the time scale of chromatographic separation gives rise to characteristic elution profiles featuring plateau formation and/or peak broadening, evident in peak fronting of the first and peak tailing of the second eluted enantiomer.[35–40] The application of peak form analysis through iterative comparison of experimental and simulated chromatographic elution profiles allows the determination of kinetic data for the enantiomerization process. Generally a sophisticated computer simulation program such as ChromWin[34] is required for the analysis of these dynamic elution profiles. An approximation function (AF) that allows the direct calculation of enantiomerization rate constants of racemic mixtures from chromatographic parameters has recently been described.[33]

The application of the principle of microscopic reversibility requires that the rates of enantiomerization of the corresponding enantiomers are different in the presence of the chiral stationary or pseudo stationary phase ($K_B' > K_A'$), that is $k_1^{stat} > k_{-1}^{stat}$. This phenomenon arises from the fact that the stereoisomers are discriminated, and hence separated, due to a different thermodynamic Gibbs energy of the diastereomeric analyte–selector complexes ($-\Delta_{B,A}\Delta G = RT \ln(K_B/K_A)$) as shown in Scheme 2 for a series of consecutive theoretical plates.

Thus, whereas the second eluted enantiomer B is enriched during the chromatographic time scale of separation, because in the presence of the chiral pseudo stationary phase, that is hydroxypropyl-β-cyclodextrin, it is formed more rapidly than the first eluted enantiomer A ($k_1^{stat} > k_{-1}^{stat}$), no displacement of the equilibrium between A and B occurs at constant temperature as the second eluted enantiomer B is depleted to a greater extent due to its longer residence time in the column.

In dynamic chromatography individual rate constants in the achiral mobile phase and in the chiral stationary or pseudo stationary phase cannot be distinguished. Therefore the apparent rate constants k_1^{app} and k_{-1}^{app}, a weighted mean of the rate constants in the mobile phase k_1^{mob} (with $k_1^{mob} = k_{-1}^{mob}$ for enantiomerization) and the different rate constants in the chiral pseudo stationary phase (CPSP) k_1^{stat} and k_{-1}^{stat}, are determined. The apparent rate constants k_1^{app} and k_{-1}^{app} are defined as in Equation (1), with the retention factor k'

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



Scheme 2. Equilibria in a series of theoretical plates: A is the first eluted enantiomer, B is the second eluted enantiomer, k represents the rate constant and K the distribution constant.

© 2002 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
0947-6539/02/0816-3630 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 16

being $k' = (t_R - t_M)/t_M$ and t_R as the total retention time and t_M as the migration time of the neutral marker dimethylformamide.

Provided that the rate constant in the mobile phase is accessible by an independent method, that is stopped-flow experiments or polarimetric studies, it is possible to calculate the rate constants in the stationary liquid phase and to quantify the influence of the chiral selector on the enantiomerization process as previously described.[31, 43–45]

A prerequisite for the successful determination of rate constants k_1^{app} is the quantitative on-column separation of the enantiomers in the respective chromatographic setup. The enantiomeric pairs of **1** and **2** could be separated by enantioselective electrokinetic chromatography[46] (EKC) in the presence of 10 mM hydroxypropyl-β-cyclodextrin as the chiral mobile phase additive. The use of 50 mM tris/phosphate buffer at pH 2.2, which enhanced the enantiomerization process described by Prelog and Wieland,[4] was found to be suitable for the separation. The elution order of **1** was determined to be (*S*,*S*) before (*R*,*R*) by coinjection of enantiomerically pure **1**.

From Figure 1 it is evident that **1** displays distinct plateau formation between 30 and 60 °C, whereas **2** demonstrates this typical elution profile already between 0 and 30 °C. Even though plateau heights and enantiomerization barriers cannot be correlated directly,[47, 48] the similar elution times at 30 °C and the dramatic difference in the elution profile (almost baseline separation for **1** and a single broadened peak for **2** suggests a lower enantiomerization barrier for **2**.

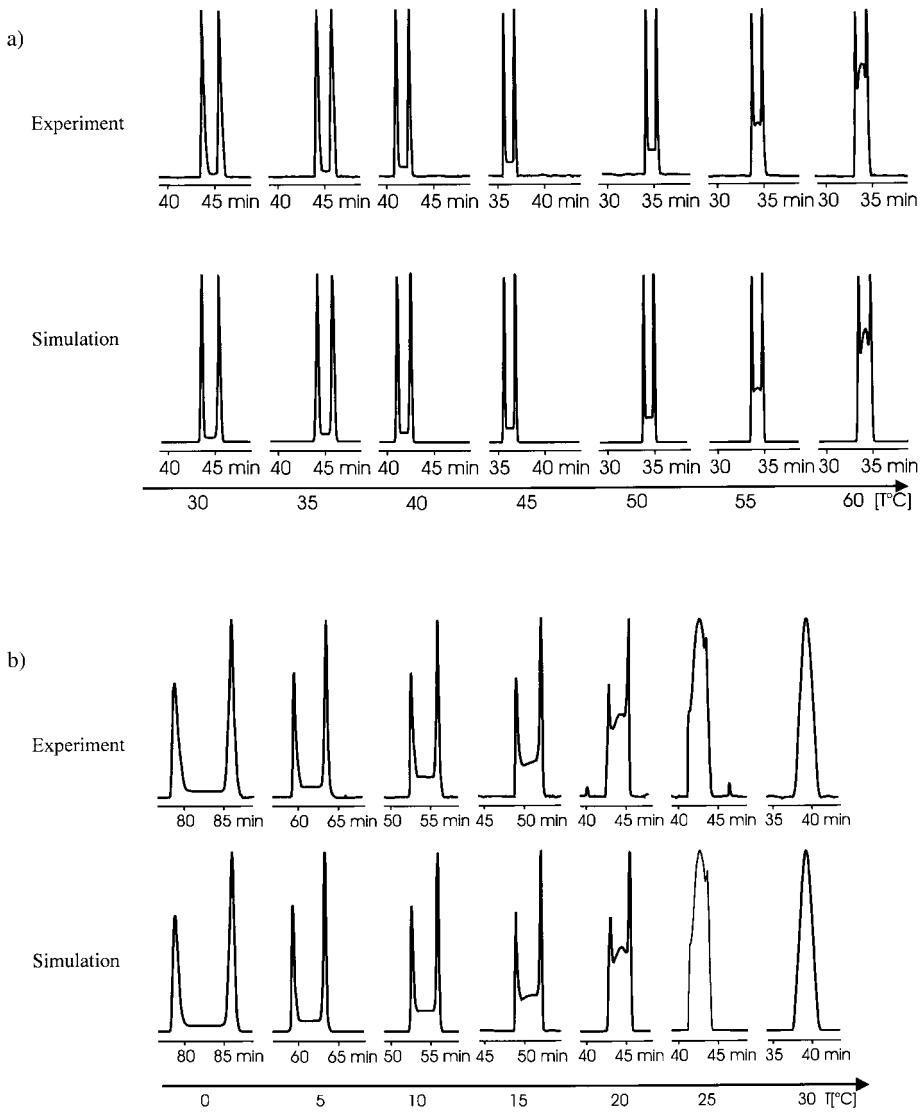


Figure 1. Enantiomerization of **1** (a) and **2** (b) at different temperatures: experimental chromatograms (top) versus simulated chromatograms (bottom).

Table 1. Selected experimental data and rate constants obtained by direct calculation (AF) and computer simulation (SM+) of Tröger's base **1** and the N-monobenzylated derivative **2**.

Compound	T [°C]	t_R^A [min]	t_R^B [min]	$N_{Aeff.}$	$N_{Beff.}$	$h_{Plateau}$ [%]	k_1^{app}(SM+) [s^{-1}]	k_1^{app}(AF) [s^{-1}]
1	30	50.5	52.5	331000	287000	2	2.3×10^{-5}	2.3×10^{-5}
1	35	44.0	45.6	130000	117000	5	4.9×10^{-5}	4.8×10^{-5}
1	40	40.0	41.5	186000	174000	6	6.8×10^{-5}	6.3×10^{-5}
1	45	35.7	36.9	286000	263000	9	1.3×10^{-4}	1.2×10^{-4}
1	50	34.1	35.3	282000	236000	15	2.2×10^{-4}	1.9×10^{-4}
1	55	33.7	34.9	290000	242000	30	3.8×10^{-4}	3.7×10^{-4}
1	60	33.1	34.4	267000	169000	67	7.0×10^{-4}	6.7×10^{-4}
2	0	76.2	82.5	58000	96000	4	3.6×10^{-2}	3.6×10^{-2}
2	5	59.9	63.0	80000	131000	6	7.4×10^{-2}	7.4×10^{-2}
2	10	53.3	56.8	201000	169000	9	1.4×10^{-1}	1.4×10^{-1}
2	15	50.6	53.9	415000	375000	17	3.1×10^{-1}	3.1×10^{-1}
2	20	42.5	44.9	143000	237000	47	5.6×10^{-1}	5.5×10^{-1}
2	25	41.4	43.6	–	–	–	–	–

Selected experimental data and apparent rate constants of the forward reaction k_1^{app} obtained by the direct calculation with the approximation function (AF) and computer simulation with the improved stochastic model (SM+) of ChromWin are given in Table 1.

For the calculation of the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ the mean values of $\ln(k/T)$ from at least six experiments per temperature were plotted as a function of T^{-1} according to the Eyring equation (Figure 2).

 © 2002 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 0947-6539/02/0816-3631 $ 20.00+.50/0

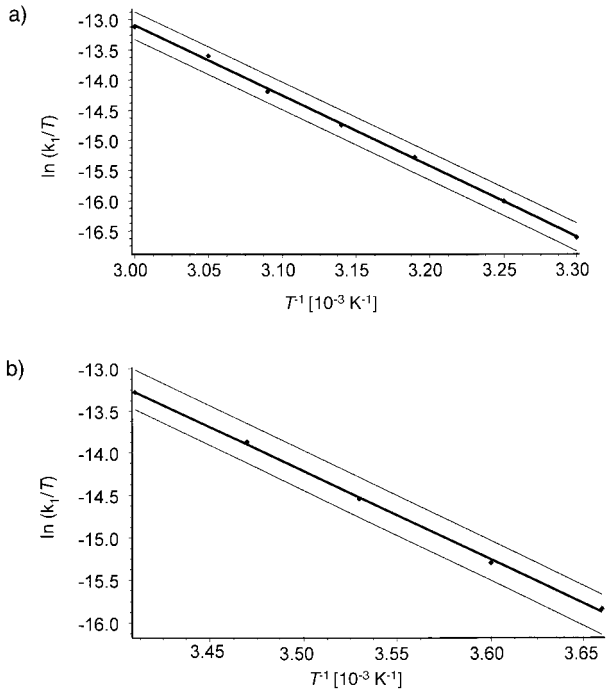


Figure 2. Eyring plots for the determination of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for **1** (a) and **2** (b) from the DEKC experiment.

The activation parameters, evaluated by linear regression of the Eyring plots (agreement factors: **1**: $r^2 = 0.9995$, **2**: $r^2 = 0.9994$), are given in Table 2 and Table 3. Owing to the imprecision of the peak width caused by the data acquisition system, chromatograms expressing plateau heights of more than 60% were not used for the calculation of the activation parameters. As expected from the experimental chromatograms as well as from theoretical considerations, the permanently charged, N-monobenzylated derivative of Tröger's base **2**, shows a significant decrease in its stereochemical stability ($\Delta G^{\neq}$ (298 K) $= 90.2 \pm 0.5$ kJ mol^{-1}) as compared to the parent compound Tröger's base ($\Delta G^{\neq}$ (298 K) $= 100.9 \pm 0.5$ kJ mol^{-1}). Taking into account the yet unproved enantiomerization mechanism of Tröger's base via an iminium intermediate (Scheme 3), as already proposed by Greenberg and Molinaro,[25] a charge separation requiring a higher activation energy would occur for Tröger's base **1**, whereas a charge shift requiring less activation energy would apply for the N-monobenzylated derivative **2**. Taking the acidic environment of the buffer medium into account a protonated species of Tröger's base is expected. In this case a pre-equilibrium of protonation can be assumed.

Table 2. Eyring activation parameters obtained for Tröger's base **1** and its N-monobenzylated derivative **2** by temperature dependent measurement and computer simulation (SM +) of the experimental chromatograms.

Compound	$\Delta G^{\neq}$ (298 K) [kJ mol^{-1}]	$\Delta H^{\neq}$ [kJ mol^{-1}]	$\Delta S^{\neq}$ J K^{-1}mol^{-1}
1	100.9 ± 0.5	89.5 ± 2.0	-42 ± 10
2	90.2 ± 0.5	91.4 ± 2.0	10 ± 10

Table 3. Activation parameters for Tröger's base described in literature.

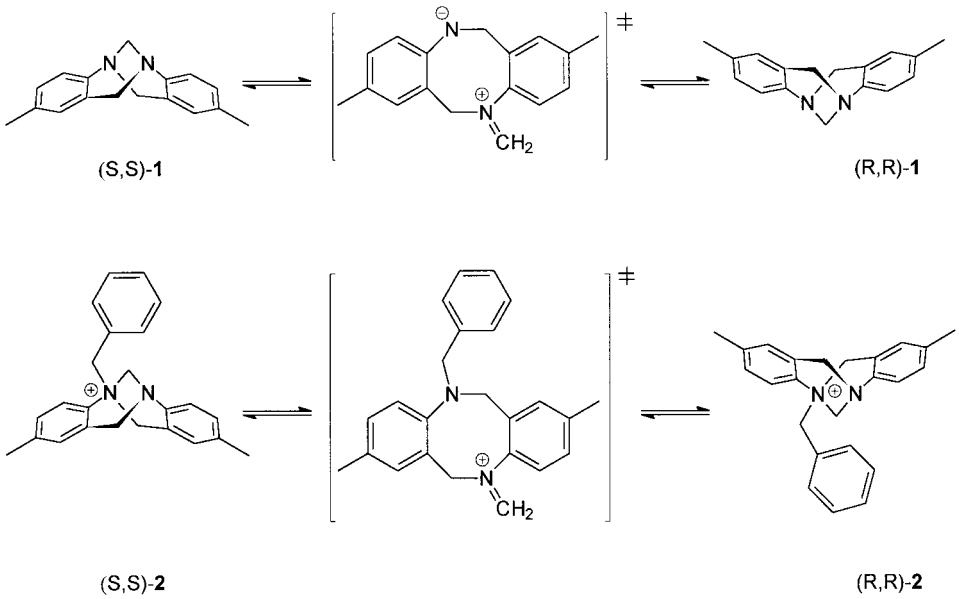
Method/conditions	T [°C]	$\Delta G^{\neq}$ [kJ mol^{-1}]	k_1^{app} [s^{-1}]	Ref.
racemization/water	25	98.5 ± 2	8.4×10^{-5}	[4]
DGC, Chirasil-β-Dex	25	117.8 ± 0.5	7.6×10^{-9}*	[31]
sfMDGC, gas phase	25	112.8 ± 0.5	5.4×10^{-8}*	[31]

[a] Calculated from the Gibbs free energy given in literature.

Experimental Section

Materials: The racemate of Trögers base **1** was obtained from Aldrich (Steinheim, Germany). The N-monobenzylated derivative **2** was prepared by one of us (U.H.). Hydroxypropyl-β-cyclodextrin was obtained from Fluka (Buchs, Switzerland), tris(hydroxymethyl)aminomethane (tris) from ICN (Irvine, CA, USA), sodium dihydrogenphosphate (99%) from Sigma (Deisenhofen, Germany). HPLC grade methanol was purchased from Merck (Darmstadt, Germany) and 18.2 MΩ high purity water used to prepare the buffer solutions was obtained from a Millipore-Q system (Millipore, Marlborough, MA, USA). Before use, all buffer and sample solutions were passed through a 0.45 μm disposable filter cartridge (Chromafil, Machery and Nagel, Düren, Germany).

Synthesis of 5-benzyl-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazozinium bromide (2): Benzyl bromide **3** (0.12 mL, 1 mmol) was added dropwise under argon atmosphere to a solution of (−)-5,6,11,12-tetrahydro-2,8-dimethyl-5,11-methanodibenzo[*b*,*f*][1,5]diazozine (**1**; 250.4 mg, 1 mmol) in benzene (4 mL). The mixture was stirred for 48 h, and the resulting colorless solid filtered off, washed with small amounts of hot benzene, and dried under high vacuum to give **2** (328.6 mg) as a colorless solid in 78% yield; m.p. 176.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta =$ 2.04 (s, 3H; CH_3), 2.12 (s, 3H; CH_3), 3.92 (d, $^2J_{H,H} = 17.0$ Hz, 1H; Ar-CH_aH_b-N), 4.49 (d, $^2J_{H,H} = 17.0$ Hz, 1H; Ar-CH_aH_b-N), 5.06 (d, $^2J_{H,H} =$ 11.3 Hz, 1H; Ph-CH_aH_b-N^+), 5.24 (d, $^2J_{H,H} = 11.3$ Hz, 1H; Ph-CH_aH_b-N^+),



Scheme 3. Proposed enantiomerization mechanism of Tröger's base via an iminium transition state.

© 2002 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
0947-6539/02/0816-3632 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 16

5.29 (d, $^2J_{H,H}$ = 15.5 Hz, 1H; N-CH_aH$_b$-N$^+$), 5.75 (d, $^2J_{H,H}$ = 15.5 Hz, 1H; N-CH$_a$$H_b$-N$^+$), 6.05 (d, $^2J_{H,H}$ = 13.3 Hz, 1H; Ar-CH_aH$_b$-N$^+$), 6.29 (d, $^2J_{H,H}$ = 13.3 Hz, 1H; Ar-CH$_a$$H_b$-N$^+$), 6.55 (s, 1H; H$_{ar}$), 6.62 (s, $^4J_{H,H}$ = 1.0 Hz, 1H; H$_{ar}$), 6.91 (s, $^4J_{H,H}$ = 1.0 Hz, 2H; H$_{ar}$), 7.15–7.29 (m, 4H; H$_{ar}$), 7.58 (d, $^3J_{H,H}$ = 7.1 Hz, 2H; H$_{ar}$), 8.77 ppm (d, $^3J_{H,H}$ = 8.9 Hz, 1H; H$_{ar}$); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 20.7 (CH_3), 20.9 (CH_3), 57.5 (N-CH_2-Ar), 65.7, 66.3 (N$^+$-CH_2-Ar, N$^+$-CH_2-Ph), 74.6 (N$^+$-CH_2-N), 121.8, 123.9, 124.1, 127.4, 127.5, 128.1, 128.4, 128.9, 130.1, 130.3, 130.4, 133.6, 135.5, 136.2, 139.9, 140.8 ppm (C_{ar}); FAB-MS, *m*-NBA, *m/z* (%): 341.2 (100) $[M]^+$.

Instrumentation: The separation of enantiomers was carried out with a Prince Unicam Crystal 300/31 capillary electrophoresis system equipped with on-column UV-detector (Bischoff Lambda 1000, Leonberg, Germany) and a thermostated laboratory-built water-cooling system with integrated temperature control (Haake D8-GH, Haake, Karlsruhe, Germany).[48, 49] Peak integration was carried out with a Chromatopak C-R6A integrator (Shimadzu, Kyoto, Japan).

Dynamic electrokinetic chromatography: Separation of racemic Tröger's base **1** and its N-monobenzylated derivative **2** was performed by employing a fused silica capillary (Microquartz, Munich, Germany). The effective length of the capillary was 95 cm (total length 112 cm), the temperature regulated length was 76 cm, and the inner diameter was 50 μm. For all separations 50 mM tris/phosphate buffer of pH 2.2 and 10 mM (14 mg mL^{-1}) hydroxypropyl-β-cyclodextrin as chiral mobile phase additive were used. The temperature of the thermostated zone ranged from 30 °C to 60 °C for Tröger's base **1** and from 0 °C to 30 °C for the benzylated derivative **2**. Both compounds were dissolved in methanol and stored at 4 °C for a maximum of 14 days. Sample concentration was adjusted to 0.1 mg mL^{-1}.

Injection was performed hydrodynamically by applying a pressure of 70 mbar for 2 s at the anodic side. A voltage of 30 kV was used for separation. UV detection was performed at 210 nm. Between runs, the capillary was conditioned by flushing with 0.1 M sodium hydroxide solution (5 min, 1 bar) followed by buffer solution for 10 min at 1 bar.

Direct calculation (AF): For the direct calculation of the approximated apparent rate constant of the forward reaction and the enantiomerization barrier the recently described approximation function $k_1^{approx} = f(t_R^A, t_R^B, w_h^A, w_h^B, h_{plateau}, N)$ [Eq. (2)] was used.[34] The validation of the approximation function (AF) for DEKC experiments is described in reference [49].

$$k_1^{approx} = -\left[\frac{1}{t_R^A}\ln\left[\frac{1}{\Delta t_R}\left(1-\frac{h_{plateau}}{100}\left(0.5-\frac{1}{\sqrt{2\pi N}}\right)\right)\right]\right] - \frac{1}{t_R^A}\ln\left[\begin{array}{l}\left[\frac{1}{\Delta t_R}\left(1-\frac{h_{plateau}}{100}\left(0.5-\frac{1}{\sqrt{2\pi N}}\right)\right)\right] \\ + \frac{0.01 h_{plateau} e^{-\frac{\Delta t_R^2}{2\sigma_A^2}} - e^{-\frac{\Delta t_R^2}{8\sigma_A^2}}}{2\sigma_A\sqrt{2\pi}} \\ + \frac{0.01 h_{plateau} - e^{-\frac{\Delta t_R^2}{8\sigma_B^2}}}{2\sigma_B\sqrt{2\pi}}\end{array}\right] \quad (2)$$

In Equation (2) $\sigma_i = \frac{w_h^i}{\sqrt{8\ln 2}}$ with $i = \{A, B\}$ and $\Delta t_R = t_R^B - t_R^A$.

Computer simulation (SM+): Computer simulation was performed with the stochastic model plus (SM+) of ChromWin.[34] For the calculation of the enantiomerization barrier and the apparent rate constants k_1^{app}, the plateau height $h_{plateau}$, peak width at half height w_h, the total retention times t_R of the enantiomers and the hold-up time t_M (using dimethylformamide as a marker) were used as experimental input parameters.

As the enantiomerization process is defined as a reversible first-order reaction, a statistical transmission factor κ of 0.5[31, 50, 51] was used in the Eyring equation for calculation of the enantiomerization barrier (or Gibbs activation energy) $\Delta G^{\neq}(T)$. Enantiomerization studies were performed at different temperatures and according to the Gibbs–Helmholtz equation, the activation enthalpy $\Delta H^{\neq}$ was obtained from the slope and the activation entropy $\Delta S^{\neq}$ from the intercept of the Eyring plot (ln (k/T) as a function of T^{-1} [Eq. (3)].

$$\Delta G^{\neq}(T) = -RT\ln\left(\frac{k_1^{app} h}{\kappa k_B T}\right) \quad (3)$$

In Equation (3), R is thes gas constant (R = 8.31441 J K^{-1} mol^{-1}), T is the enantiomerization temperature [K], k_1^{app} is the apparent rate constant of the forward reaction, h is the Planck constant ($h = 6.626176 \times 10^{-34}$ J s), κ is the transmission factor (κ = 0.5), and k_B is the Boltzmann constant ($k_B = 1.380662 \times 10^{-23}$ J K^{-1}).

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der chemischen Industrie. G.T. thanks the Graduiertenkolleg "Chemistry in Interphases" for a doctorate scholarship

[1] J. Tröger, *J. Prakt. Chem.* **1887**, *36*, 225–245.
[2] F. Vögtle, *Fascinating Molecules in Organic Chemistry*, Wiley, Chichester **1989**.
[3] M. A. Spielman, *J. Am. Chem. Soc.* **1935**, *57*, 583.
[4] V. Prelog, P. Wieland, *Helv. Chim. Acta* **1944**, *27*, 1127–1134.
[5] E. Weber, U. Müller, D. Worsch, F. Vögtle, G. Will, A. Kirfel, *J. Chem. Soc. Chem. Commun.* **1985**, 1578.
[6] S. H. Wilen, J. Z. Qi, P. G. Willard, *J. Org. Chem.* **1991**, *56*, 485–487.
[7] S. Goswami, K. Ghosh, S. Dasgupta, *J. Org. Chem.* **2000**, *65*, 1907–1914.
[8] F. C. Cooper, M. W. Partridge, *J. Chem. Soc. (C)* **1955**, 991–994.
[9] C. S. Wilcox, *Tetrahedron Lett.* **1985**, *26*, 5749–5752.
[10] E. Yashima, M. Akashi, N. Miyauchi, *Chem. Lett.* **1991**, 1017.
[11] A. Tatibouët, M. Demeunynck, J. Lhomme, *Synth. Commun.***1996**, *26*, 4375.
[12] H. Salez, A. Wardani, M. Demeunynck, A. Tatibouët, J. Lhomme, *Tetrahedron Lett.* **199**5, *36*, 1271.
[13] I. Sucholeiki, V. Lynch, L. Phan, C. S. Wilcox, *J. Org. Chem.* **1988**, *53*, 98–104.
[14] C. S. Wilcox, M. D. Cowart, *Tetrahedron Let*t. **198**6, *27*, 5563.
[15] M. D. Cowart, I. Sucholeiki, R. R. Bukownik, C. S. Wilcox, *J. Am. Chem. Soc.* **198**8, *110*, 6204.
[16] J. C. Adrian Jr, C. S. Wilcox, *J. Am. Chem. Soc.* **198**9,*111*, 8055.
[17] D. R. Bond, J. L. Scott, *J. Chem. Soc. Perkin Trans. 2,* **199**1, 47.
[18] J. Adrian Jr, C. S. Wilcox, *J. Am. Chem. Soc.* **199**2, *114*, 1398.
[19] M. J. Crossley, T. W. Hambley, L. G. Mackay, A. C. Try, R. Walton, *J. Chem. Soc. Chem. Commun.* **1995**, 1077.
[20] E.-I. Kim, S. Paliwal, C. S. Wilcox, *J. Am. Chem. Soc.* **1998**, *120*, 11192.
[21] S. Goswami, K. Ghosh, S. Dasgupta, *J. Org. Chem.* **2000**, *65*, 1907.
[22] M. Harmata, M. Kahraman, *Tetrahedron*: *Asymmetry* **2000**, *11*,2875.
[23] A. A. Ibrahim, M. Matsumoto, Y. Miyahara, K. Izumi, M. Suenaga, N. Shimizu, T. Inazu, *J. Heterocyclic Chem.* **1998**, *35*, 209–215.
[24] C. Pardo, E. Sesmilo, E. Gutiérrez-Puebla, A. Monge, J. Elguero, A. Fruchier, *J. Org. Chem.* **2001**, *66*, 1607–1611.
[25] A. Greenberg, N. Molinaro, M. Lang, *J. Org. Chem.* **1984**, *49*, 1127–1130.
[26] G. Hesse, R. Hagel, *Chromatographia* **1973**, *6*, 277.
[27] K. R. Lindner, A. Mannschreck, *J. Chromatogr.* **1980**, *193*, 308.
[28] Y. Okamoto, I. Okamoto, H. Yuki, *Chem. Lett.* **1981**, 835.
[29] K. Krause, B. Chankvetadze, Y. Okamoto, G. Blaschke, *Electrophoresis* **1999**, *20*, 2772–2778.
[30] V. Schurig, D. Schmalzing, M. Schleimer, *Angew. Chem.* **1991**, *103*, 994–996; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 987–989.
[31] O. Trapp, V. Schurig, *J. Am. Chem. Soc.* **2000**, *122*, 1424–1430.
[32] E. Huthmann, M. Juza, *J. Chromatogr. A* **2001**, *908*, 185–200.
[33] O. Trapp, V. Schurig, *J. Chromatogr. A* **2001**, *911*, 167–175.
[34] O. Trapp, V. Schurig, *Comput. Chem.* **2001**, *25*, 187–195.
[35] L. C. Craig, *J. Biol. Chem.* **1944**, *155*, 519–534.
[36] J. Kallen, E. Heilbronner, *Helv. Chim. Acta* **1960**, *43*, 489–500.
[37] V. Schurig, W. Bürkle, *J. Am. Chem. Soc.* **1982**, *104*, 7573–7580.
[38] W. Bürkle, H. Karfunkel, V. Schurig, *J. Chromatogr.* **1984**, *288*, 1–14.
[39] A. Mannschreck, H. Zinner, N. Pustet, *Chimia* **1989**, *43*, 165–166.

[40] M. Reist, B. Testa, P.-A. Carrupt, M. Jung, V.Schurig, *Chirality* **1995**, *7*, 396 – 400.
[41] G. Weseloh, C. Wolf, W. A. König, *Chirality* **1996**, *8*, 441 – 445.
[42] K. P. Scharwächter, D. H. Hochmuth, H. Dittmann, W. A. König, *Chirality* **2001**, *13*, 679 – 690.
[43] V. Schurig, S. Reich, *Chirality* **1998**, *10*, 316 – 320.
[44] S. Reich, O. Trapp, V. Schurig, *J. Chromatogr. A* **2000**, *892*, 487 – 498.
[45] O. Trapp, G. Schoetz, V. Schurig, *Chirality* **2001**, *13*, 403 – 414.
[46] S. Terabe, K. Otsuka, K. Ichikawa, A. Tsuchia, T. Ando, *Anal. Chem.* **1984**, *56*, 111 – 113.
[47] O. Trapp, G. Trapp, V. Schurig, *J. Biochem. Biophys. Methods* **2002**, submitted.
[48] G. Schoetz, O. Trapp, V. Schurig, *Anal. Chem.* **2000**, *72*, 2758 – 2764.
[49] G. Schoetz, O. Trapp, V. Schurig, *Electrophoresis* **2001**, *22*, 3185 – 3190.
[50] K. J. Laidler, *Chemical Kinetics*, Harper&Row, New York, **1987**, pp. 98 – 116.
[51] M. Jung, V. Schurig, *J. Am. Chem. Soc.* **1992**, *114*, 529 – 534.

Received: March 13, 2002 [F3940]

 © 2002 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 0947-6539/02/0816-3634 $ 20.00+.50/0