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Enantioselective stopped-flow multidimensional gas chromatography Determination of the inversion barrier of 1-chloro-2,2-dimethylaziridine

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Abstract

Enantioselective stopped-flow multidimensional gas chromatography (stopped-flow MDGC) is a fast and simple technique to determine enantiomerization (inversion) barriers in the gas phase in a range of $\Delta G^{\neq}_{gas}(T)=70–200$ kJ mol^{-1}. After complete gas-chromatographic separation of the enantiomers in the first column, gas phase enantiomerization of the heart-cut fraction of one single enantiomer is performed in the second (reactor) column at increased temperature and afterwards this fraction is separated into the enantiomers in the third column. From the observed de novo enantiomeric peak areas a_j, the enantiomerization time t and the enantiomerization temperature T, the enantiomerization (inversion) barrier $\Delta G^{\neq}_{gas}(T)$ is determined and from temperature-dependent experiments, the activation enthalpy $\Delta H^{\neq}_{gas}$ and the activation entropy $\Delta S^{\neq}_{gas}$ are obtained. Enantiomerization studies on chiral 1-chloro-2,2-dimethylaziridine by stopped-flow MDGC yielded activation parameters of nitrogen inversion in the gas phase, i.e., $\Delta G^{\neq}_{gas}(353\ K)=110.5\pm0.5$ kJ mol^{-1}, $\Delta H^{\neq}_{gas}=71.0\pm3.8$ kJ mol^{-1} and $\Delta S^{\neq}_{gas}=-109\pm11$ J mol^{-1} K^{-1}. By the complementary method of dynamic gas chromatography (GC), the apparent enantiomerization (inversion) barrier of 1-chloro-2,2-dimethylaziridine in the gas–liquid biphase system was found $\Delta G^{\neq}_{app}(353\ K)=108$ kJ mol^{-1}. The values obtained by stopped-flow MDGC in the gas phase were used to calculate the activation parameters of nitrogen inversion of 1-chloro-2,2-dimethylaziridine in the liquid phase in the presence of the chiral selector Chirasil–nickel(II), i.e., $\Delta G^{\neq}_{liq}(353\ K)=106.0\pm0.4$ kJ mol^{-1}, $\Delta H^{\neq}_{liq}=68.3\pm1.4$ kJ mol^{-1} and $\Delta S^{\neq}_{liq}=-106\pm3.0$ J mol^{-1} K^{-1}.

Keywords: Stopped-flow multidimensional gas chromatography; Kinetic studies; Dynamic gas chromatography; Computer simulation; Thermodynamic parameters; Enantiomer separation; Aziridine; Chlorodimethylaziridine

1. Introduction

Enantiomerization barriers of configurationally labile chiral compounds can be determined by several methods. Isolation of single enantiomers followed by classical racemization kinetics can be applied universally but this rather tedious method is time consuming and material demanding. Dynamic [1–6] and stopped-flow [7–9] chromatographic techniques are more straightforward since enantiomers are separated and analysed on-line, thus requiring only minute amounts of the unresolved racemic sample. In dynamic methods, enantiomerization occurs during the time scale of chromatographic enantiomer separation and it results in characteristic interconversion profiles such as peak broadening, plateau formation or finally peak coalescence. Experimental interconversion profiles of enantiomerization can be simulated by proper kinetic algorithms [3,5,10,12] based on theories of chromatography [10–14]. The

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computerised comparison of experimental and simulated chromatograms yields apparent rate constants k^{app} of enantiomerization (inversion) occurring in the overall chromatographic biphase partitioning system [1–5,15,16]. By DGC enantiomerization barriers in the range of 70–150 kJ·mol^{-1} can be determined [1,4].

The recently developed single column stopped-flow GC [7–9] does not require a computer simulation. After quantitative separation of the enantiomers on the chiral stationary phase (CSP) in the first part of the column, the flow is stopped and enantiomerization of both fractions is effected at increased temperature by heating the entire column. After a given enantiomerization time, the enantiomerized fractions are separated in the second part of the column. The enantiomerization barriers of each of the two enantiomers are calculated from the four peak areas a_i, the enantiomerization time t and the enantiomerization temperature T. By single column stopped-flow GC enantiomerization barriers of 70–180 kJ mol^{-1} [7] and by single column stopped-flow CZE enantiomerization barriers of 100–130 kJ mol^{-1} [8] can be determined. Unfortunately, by using single column dynamic and stopped-flow methods, enantiomerization proceeds in the environment of the CSP which is required to separate the enantiomers on-line. However, the presence of the CSP clearly affects the enantiomerization barrier. The barrier may be enhanced [8,17,18] or (usually) lowered [1,19]. Efforts have therefore been devoted to combine the advantages of the stopped flow approach with the option to perform enantiomerization in an achiral and inert environment. To this end, multidimensional techniques employing different columns in series in GC and HPLC [20,21] or individual column sections in capillary zone electrophoresis [9] have been employed recently. The novel enantioselective stopped-flow multidimensional gas chromatography (stopped-flow MDGC) [14,15] utilizes three columns in series. The principle of the method is shown in Fig. 1.

The enantiomers are quantitatively separated on a CSP in the first column. Either of the pure enantiomers is then directed in the second uncoated reactor column. Enantiomerization is performed in an achiral and inert environment in the gas phase at increased temperature. Finally, the de novo enantiomeric peak areas a_j are determined on the same CSP in the third column.

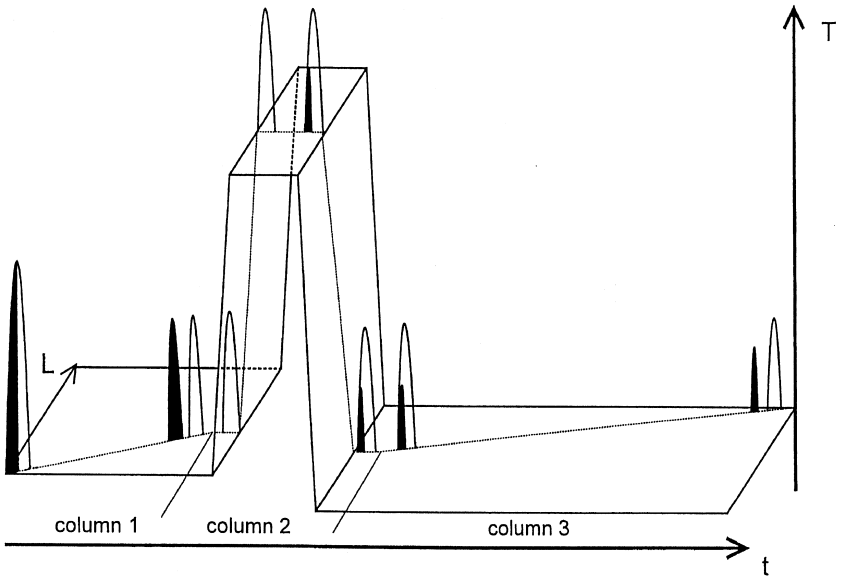

Fig. 1. Schematic representation of the stopped-flow MDGC technique (variables are enantiomerization time t, enantiomerization temperature T, and three columns lengths L). Black: first eluted enantiomer; white: second eluted enantiomer.

An appealing application is provided by compounds containing a stereogenic sp^3-hybridized nitrogen atom with three different ligands. Three-coordinate nonplanar nitrogen is stereochemically labile due to a low energy barrier to pyramidal inversion [23,24]. If the nitrogen atom represents a stereogenic center, molecular inversion leads to enantiomerization. Thus, inversion barriers can directly be obtained by enantiomerization studies. The prerequisite for the separation of the invertomers of chiral amines at ambient temperatures is an inversion barrier of >100 kJ mol^{-1} [25]. By constraining the stereogenic nitrogen atom into a three-membered ring, accompanied by heteroatom bonding, the inversion process of pyramidal nitrogen can be perturbed to such a degree that stable invertomers can be isolated even at room temperature [24–26]. For the invertomers of chiral 1-chloro-2,2-dimethylaziridine (Fig. 2) a lower limit of the enantiomerization (inversion) barrier of $\Delta G^{\#}>89$ kJ mol^{-1} [26] and $\Delta G^{\#}>98.3$ kJ mol^{-1} [27] has been estimated by dynamic NMR spectroscopy. It was subsequently found that the invertomers can be separated by gas chromatography on several chiral stationary phases at elevated temperature [1,28–30]. The inversion barrier was previously determined both by DGC to $\Delta G^{\#}(333\ \text{K})=104.9\pm0.6$ kJ mol^{-1} [1] and by classical enantiomerization kinetics after semipreparative separation of the invertomers to $\Delta G^{\#}(338\ \text{K})=115.5\pm1.2$ kJ mol^{-1} [30].

Here we report in detail on the performance, reliability and applicability of the enantioselective stopped-flow MDGC technique via the determination of activation parameters of enantiomerization (inversion) of chiral 1-chloro-2,2-dimethylaziridine. The results are compared with data measured by conventional racemization kinetics and by new data obtained by DGC using the novel program CHROMWIN 99.

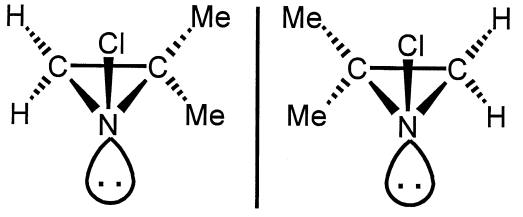

Fig. 2. Structure of 1-chloro-2,2-dimethylaziridine.

2. Experimental

2.1. Materials

1-Chloro-2,2-dimethylaziridine (Fig. 2) was prepared by *N*-chlorination of 2,2-dimethylaziridine according to [29]. The CSPs heptakis-(6-*O*-*tert*.-butyldimethylsilyl-2,3-*O*-dimethyl)-β-cyclodextrin and Chirasil–nickel(II) were synthesized according to Refs. [31] and [32]. The (85–88%)-dimethyl-(12–15%)-diphenylpolysiloxane PS086 was obtained from Gelest/ABCR (Karlsruhe, Germany). Untreated fused-silica capillaries (0.25 mm, I.D.) were obtained from Ziemer (Mannheim, Germany).

2.2. Stopped-flow MDGC

2.2.1. Apparative equipment

The prerequisite for the enantioselective stopped-flow MDGC (Fig. 1) is a gas chromatograph with two ovens, which can be individually heated, two injectors, two detectors and a six-port valve. A Sichromat-2 MDGC instrument (Siemens, Karlsruhe, Germany) was used. Thus, oven 1 contained a split injector, an on-column injector, a flame ionization detector (FID 1) and a pneumatically operating, software controlled six-port valve (Valco). Oven 2 contained another flame ionization detector (FID 2), a ^{63}Ni electron capture detector (ECD) and a cooling device to trap one of the enantiomers on the reactor column.

2.2.2. General procedure

Three capillary columns were installed in the instrument: two enantioselective columns (i.e., columns 1 and 3 coated with the CSP quantitatively separating the enantiomers without enantiomerization at low temperature) and the uncoated reactor column (column 2). Columns 1 and 3 were installed in oven 1 and the reactor column 2 was installed in oven 2. Fig. 3 shows the set-up of the columns in the two valve positions. In position 1 the columns 1 and 3 are separately connected with an injector and a

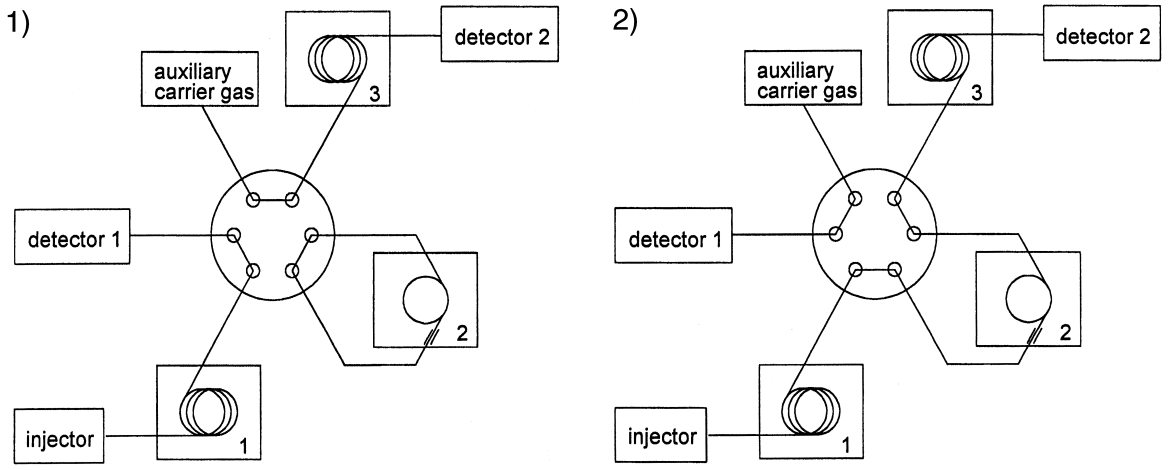

Fig. 3. Experimental set-up of stopped-flow MDGC. Left: switching position 1; right: switching position 2.

detector, while column 2 is part of a closed loop. In position 2 the three columns are operated in series.

The sample injection was performed with the split injector (200°C), the enantiomer separation in column 1 was monitored with FID 2 (250°C) and column 3 with FID 1 (250°C), respectively. Peak integration was carried out with a Chromatopak C-R 6A integrator (Shimadzu).

2.2.3. Capillary columns

Columns 1 and 3 were 25 m (and 50 m, respectively)×0.25 mm I.D., fused-silica capillaries coated with heptakis-(6-*O*-*tert*.-butyldimethylsilyl-2,3-*O*-dimethyl)-β-cyclodextrin [21] (20% dissolved in PS086, 0.2 μm film thickness). Column 2 was a fused-silica capillary (1 m×0.25 mm I.D.) deactivated with hydridopolydimethylsiloxane (2 nm film thickness). Helium was used as carrier gas.

2.2.4. Enantiomerization (inversion) of 1-chloro-2,2-dimethylaziridine

At the beginning of the experiment, racemic 1-chloro-2,2-dimethylaziridine was injected in column 1 (25 m×0.25 mm I.D.) in oven 1 at valve position 1 (Fig. 3) and the invertomers were quantitatively separated on the CSP at 40°C and 0.6 bar helium. The enantiomers were detected with FID 1. The carefully recorded retention times of the initial chromatogram were used to program the subsequent transfer of the first (or second) eluted enantiomer into the reactor column 2. Thus, after the second injection the valve was switched at the appropriate time into position 2 until one single enantiomer was completely transferred into column 2 (oven 2), where it was cryo-focused with the cooling trap. The enantiomerization was started by removing the trap and heating the column 2 rapidly to the enantiomerization temperature whereby no carrier gas was allowed to run through the column ('stopped-flow'). After an adequate enantiomerization time, the enantiomerization of 1-chloro-2,2-dimethylaziridine in column 2 was quenched by placing back the cooling trap. Then the valve was switched into position 2, so that the carrier gas was allowed to run through all three columns. The enantiomerized fraction was separated in column 3 (50 m×0.25 mm I.D.) on the CSP at 40°C and 1.2 bar helium (Fig. 4) and the de novo enantiomeric peak areas a_j were recorded with detector 2.

2.2.5. Calculation of the enantiomerization (inversion) barrier

For the calculation of the enantiomerization (inversion) barrier, the peak area a of the initial enantiomer, the enantiomerization time t and the enantiomerization temperature T obtained by the stopped-flow MDGC experiment were used. As the process of enantiomerization is defined as a reversible first order process [33], the rate constant of enantiomerization [34] in the gas phase k^{gas} was

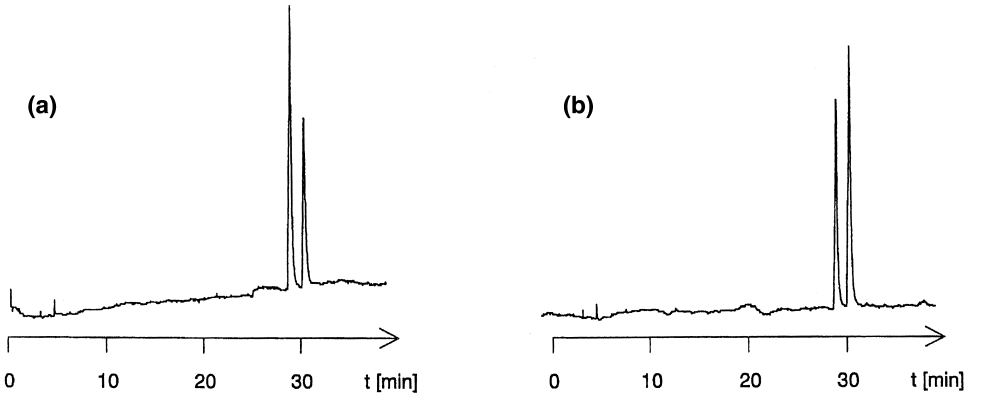

Fig. 4. Gas-chromatographic enantiomer separation of 1-chloro-2,2-dimethylaziridine on heptakis-(6-*O*-*tert*.-butyldimethylsilyl-2,3-*O*-dimethyl)-β-cyclodextrin (20% dissolved in PS086, 50 m, 40°C, 1.2 bar helium) after enantiomerization of (a) first eluted and (b) second eluted enantiomer at 80°C for 1 h.

calculated according to Eq. (1). The Gibbs activation energy $\Delta G^{\#}_{gas}(T)$ was obtained from the rate constant using the Eyring Eq. (2). In calculating $\Delta G^{\#}_{gas}(T)$ a statistical transmission factor κ of 0.5 was used in the Eyring equation due to the definition of enantiomerization as a reversible microscopic interconversion. Enantiomerization studies were performed at different temperatures and according to the Gibbs–Helmholtz equation (3), the activation enthalpy $\Delta H^{\#}_{gas}$ was obtained via the slope and the activation entropy $\Delta S^{\#}_{gas}$ via the intercept of the Eyring plot [T^{-1} *v*ersus ln (k^{gas}/T)]:

$$k = \frac{1}{2t}\ln\left(\frac{a_0}{2a_t - a_0}\right) \quad (1)$$

$$k = \kappa \cdot \frac{k_B T}{h} \cdot e^{-\frac{\Delta G^{\#}(T)}{RT}} \quad (2)$$

$$\Delta G^{\#}(T) = \Delta H^{\#} - T\Delta S^{\#} \quad (3)$$

with:

k^{gas}	rate constant of enantiomerization in the gas phase (s^{-1})
t	enantiomerization time (s)
a_0	peak area of the major peak (%) before enantiomerization ($t=0$)
a_t	peak area of the major peak (%) after the enantiomerization time t
κ	transmission factor; $\kappa=0.5$
k_B	Boltzmann constant; $k_B=1.380662\times10^{-23}$ J K^{-1}
T	enantiomerization temperature (K)
h	Planck's constant; $h=6.626176\times10^{-34}$ J s
$\Delta G^{\#}_{gas}(T)$	activation energy or enantiomerization (inversion) barrier (kJ mol^{-1})
R	gas constant; $R=8.31441$ J K^{-1} mol^{-1}
$\Delta H^{\#}_{gas}$	activation enthalpy (kJ mol^{-1})
$\Delta S^{\#}_{gas}$	activation entropy (J mol^{-1} K^{-1})

2.3. Dynamic GC

2.3.1. Apparative equipment and capillary column

The dynamic GC experiment was performed on a Carlo Erba Fractovap 2150 gas chromatograph equipped with a split injector (250°C), an FID system (250°C) and a Shimadzu Chromatopac C-R 6A integrator, employing a fused-silica capillary coated with Chirasil–nickel(II) (nickel(II)–*bis*[3-heptafluorobutanoyl-10-methylidene-(1*R*)-camphorate]) chemically linked to polydimethylsiloxane) [22] (25 m×0.25 mm I.D., 0.25 μm film thickness). Nitrogen was used as carrier gas.

2.3.2. Computer simulation

Experimental chromatograms featuring enantiomerization were simulated by the novel and fast program CHROMWIN 99 [16] which yields peak profiles of interconversions in dynamic GC via the

discontinuous plate model [1,4,16] and the stochastic model [2,3,16,10–12]. The program runs under Windows on an IBM compatible personal computer. The total retention times t_R, the peak width at half height w_h and the mobile phase hold-up time t_M (using methane as marker) were determined with a Shimadzu C-R 6A integrator. The effective plate numbers N_{eff} were calculated from the modified Eq. (4) [18]:

$$N_{eff} = 5.545 \cdot \frac{t_R(t_R - t_M)}{(w_h)^2} \quad (4)$$

The height of the peaks and of the plateau were obtained from the chromatograms and peak form analysis was performed with CHROMWIN 99 [16] according to the theoretical plate model. The program furnishes the apparent rate constants (k_1^{app} and k_{-1}^{app}; see Fig. 5 and Eq. (5)) of enantiomerization, presupposing that the enantiomerization in the stationary liquid and mobile gas phase are equal:

$$k_1^{app} = \frac{1}{1+k'_A} \cdot k^{gas} + \frac{k'_A}{1+k'_A} \cdot k_1^{liq}$$
$$k_{-1}^{app} = \frac{1}{1+k'_B} \cdot k^{gas} + \frac{k'_B}{1+k'_B} \cdot k_{-1}^{liq} \quad (5)$$

The rate constants were evaluated from as many as thirty chromatograms. The enantiomerization (inversion) barrier has been calculated according to the Eyring Eq. (2) and the transmission factor κ of 0.5 has been applied. The initially injected amounts of the enantiomers were equal for the racemic compound.

By using the rate constant k^{gas} in the mobile gas phase obtained from the stopped-flow MDGC experiment, the simulation was also performed for different values of the rate constant k_1^{liq} in the stationary liquid phase using an improved Newton algorithm in order to find the best agreement of the simulated and experimental elution profiles. The rate constants k_1^{liq} and k_{-1}^{liq} (k_{-1}^{liq} being calculated from k_1^{liq} according to the principle of microscopic reversibility [1]; Fig. 5) in the presence of the liquid chiral stationary phase were obtained with Eq. (5), where k'_A and k'_B are the retention factors of the enantiomers A and B, obtained from the total retention time t_R and the gas hold-up time t_M according to the equation $k' = (t_R - t_M)/t_M$.

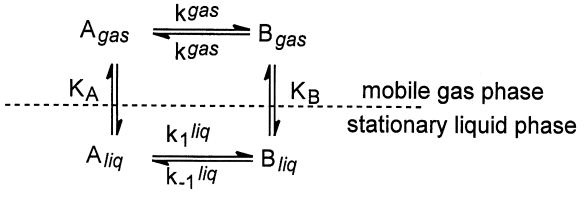

Fig. 5. Principle of microscopic reversibility. Equilibria in a theoretical plate (A) first eluted enantiomer (B) second eluted enantiomer, k represents the rate constant and K the distribution constant [1].

3. Results and discussion

3.1. Determination of the enantiomerization (inversion) barrier of 1-chloro-2,2-dimethylaziridine by stopped-flow MDGC

3.1.1. Activation parameters of enantiomerization (inversion)

The stopped-flow MDGC technique was applied to the determination of the enantiomerization (inversion) barrier of chiral 1-chloro-2,2-dimethylaziridine in the achiral and inert gas phase helium. Enantiomerization conditions as well as values of the observed peak area a, the rate constant k^{gas} and the inversion barrier $\Delta G^{\#}_{gas}(T)$ are listed in Table 1. From these measurements the enantiomerization (inversion) barrier was found $\Delta G^{\#}_{gas}(353\ K) = 110.0 \pm 0.4$ kJ mol^{-1}.

In order to determine the activation enthalpy $\Delta H^{\#}_{gas}$ and the activation entropy $\Delta S^{\#}_{gas}$, enantiomerization studies were performed on the second eluted invertomer at five temperatures between 35 and 95°C. In Table 1 the experimental conditions and the results (mean values and mean deviations at different temperatures) of the enantiomerization experiments are listed. From the Eyring plot (18 experiments; $\ln(k/T) = -8538.75\ T^{-1} + 9.92$; correlation coefficient $r = 0.98$; cf. Fig. 6) $\Delta H^{\#}_{gas}$ was found 71.0 ± 3.8 kJ mol^{-1} and $\Delta S^{\#}_{gas}$ was found -109 ± 11 J mol^{-1} K^{-1} (errors were calculated according to [35]).

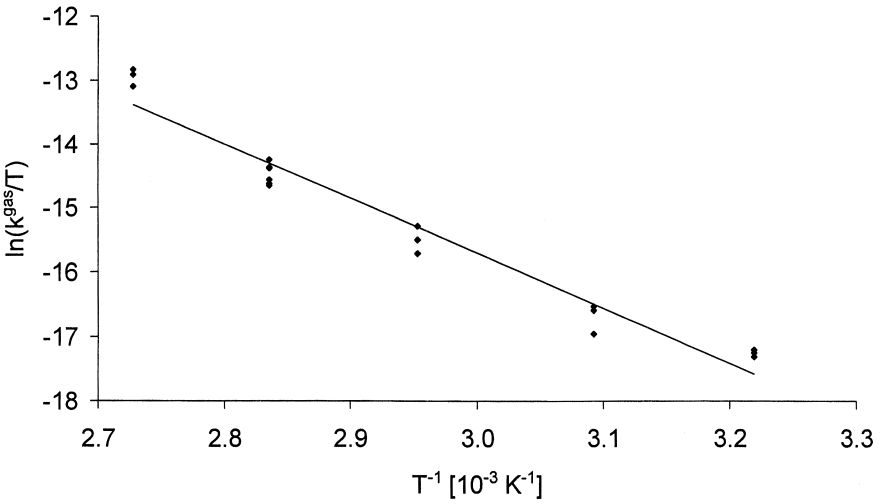

Fig. 6. Eyring-plot from stopped-flow MDGC experiments (26 runs) for determination of $\Delta H^{\neq}_{gas}$ and $\Delta S^{\neq}_{gas}$ of enantiomerization (inversion) of 1-chloro-2,2-dimethylaziridine.

3.1.2. Estimation of the precision and accuracy of enantioselective stopped-flow MDGC

Table 1 lists the mean value and the mean deviation of k^{gas} and $\Delta G^{\neq}_{gas}(T)$ obtained by the stopped-flow MDGC experiments at different temperatures. These mean deviations fit very well with the results calculated by error propagation, which leads to a maximum error of $\Delta G^{\neq}_{gas}$(353 K) of±0.6 kJ mol^{-1}. For the determination of $\Delta G^{\neq}_{gas}(T)$ the constancy of the temperature employed throughout the measurement was assumed. The temperature change measured during a typical enantiomerization experiment (60 min) at 79.5°C (353 K) is shown in Fig. 7. It is estimated that the required time to heat the reactor column 2 to the constant enantiomerization temperature is about 3 min, and the cooling time needed to quench the enantiomerization process is only a few seconds. Assuming that no enantiomeri-

Table 1
Determination of the enantiomerization (inversion) barrier of 1-chloro-2,2-dimethylaziridine by enantioselective stopped-flow MDGC

Run[a]	No.[b]	T (°C)	t (h)	A (%)	k^{gas} (10^{-4} s^{-1})	$\Delta G^{\neq}_{gas}(T)$ (kJ mol^{-1})
1	3	37.5	24	58.9	0.10±0.0[c]	104.1±0.1[c]
	3	50.2	12	60.5	0.19±0.03	106.8±0.5
	3	65.5	4	58.3	0.64±0.11	108.5±0.5
	6	79.5	1	63.4	1.86±0.28	110.0±0.4
	3	93.5	0.25	60.4	8.82±0.93	109.8±0.3
2	2	65.5	1	76.9	0.86±0.03	107.7±0.1
	2	79.5	0.5	68.6		
	2	79.5	0.75	63.5	2.48±0.23[d]	109.2±0.3[d]
	2	79.5	1	59.5		

[a] Run 2: repeated after 3 months.
[b] Number of experiments.
[c] Mean deviation.
[d] Mean of six runs at different enantiomerization times.

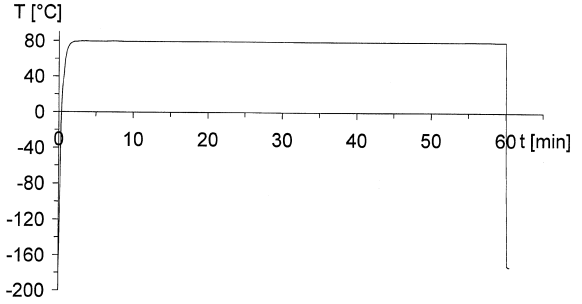

Fig. 7. Time-dependent temperature characteristics of an enantiomerization experiment with 1-chloro-2,2-dimethylaziridine at 80°C (started at −196°C (liquid nitrogen trap).

zation takes place during the heating and cooling time, the rate constant is $k^{gas} = 1.93 \times 10^{-4}$ s^{-1} (enantiomerization time $t = 57$ min) and the inversion barrier is $\Delta G^{\#}_{gas}(353\ K) = 109.9$ kJ mol^{-1}. By comparing these values with the results in Table 1 (assumed $t = 1$ h, $k^{gas} = 1.86 \times 10^{-4}$ s^{-1}, $\Delta G^{\#}_{gas}(353\ K) = 110.0$ kJ mol^{-1}), it can be concluded that the systematic error of heating and cooling of the reactor column 2 is within the mean deviation of the experiment and it does not affect the enantiomerization barrier considerably. However, in case of very short enantiomerization times and/or very high temperatures this systematic error increases and it cannot be ignored.

The error of the activation parameters determined by an Eyring plot via linear regression analysis is related to the correlation coefficient. In the present experiments the scattering of data is small ($r = 0.98$). Nevertheless, in common with other methods, the limited temperature range in the present study and the sensitivity of $\Delta H^{\#}_{gas}$ and $\Delta S^{\#}_{gas}$ toward slight errors in k^{gas} renders any extrapolation difficult.

The precision of enantioselective stopped-flow MDGC was further determined as follows. The enantiomerization experiment with 1-chloro-2,2-dimethylaziridine was repeated six times at exactly the same experimental conditions. The data in Table 1 (set of run 1) show that the repeatability of the method is quite satisfactory ($2.93 \times \sigma$ (standard deviation); error = 1.2 kJ mol^{-1} at 79.5°C (353 K)). The precision of the enantiomerization experiment was then re-checked after a few months when the system was again installed and barriers of $\Delta G^{\#}_{gas}(353\ K) = 109.2 \pm 0.3$ kJ mol^{-1} and $\Delta G^{\#}_{gas}(338\ K) = 107.7 \pm 0.1$ kJ mol^{-1} (see dataset of run 2 in Table 1) were determined. This agrees well (<1%) with the data for the barrier previously determined.

The method of choice to probe the accuracy of the stopped-flow MDGC is the comparison with racemization kinetics of single enantiomers in the gas phase. Previously, an enantiomerization (inversion) barrier of $\Delta G^{\#}_{gas}(338\ K) = 113.6 \pm 1.2$ kJ mol^{-1} (recalculated for $\kappa = 0.5$) was determined for 1-chloro-2,2-dimethylaziridine in the gas phase [30]. This data differs by only 5% from the value of the stopped-flow MDGC experiment ($\Delta G^{\#}_{gas}(338\ K) = 108.5 \pm 0.5$ kJ mol^{-1}).

3.2. Determination of the enantiomerization (inversion) barrier of 1-chloro-2,2-dimethylaziridine by dynamic GC

To validate the enantiomerization (inversion) parameters $\Delta G^{\#}$, $\Delta H^{\#}$ and $\Delta S^{\#}$ obtained by the stopped-flow MDGC experiment, enantiomerization of 1-chloro-2,2-dimethylaziridine was also investigated by temperature-dependent dynamic GC. When enantiomerization of configurationally labile compounds occurs during chromatographic enantiomer separation a characteristic plateau between the terminal peaks of the enantiomers is observed [3]. The plateau height depends on the chromatographic time scale t and the separation temperature T. In dynamic GC the most common models for simulation are the theoretical plate model [1,4,6,15,16] and the stochastic model [2,3,10–12,16]. Kinetic data of interconversion, i.e., the enantiomerization barrier, are obtained by iterative comparison of experimental and simulated chromatograms. This procedure furnishes an apparent rate constant k^{app} which contains the contribution of enantiomerization in the mobile gas and stationary liquid phases. The rates of interconversion are in most cases different in the mobile gas phase and the stationary liquid phase. Moreover, use of the principle of microscopic reversibility [3] requires that the rates of interconversion of the two enantiomers (k^{liq}_1 and k^{liq}_{-1}) are different since the enantiomers reside in a chiral environment as shown in Fig. 5, where A_{gas}, B_{gas}, A_{liq}, B_{liq} are the amounts of enantiomers A and B at equilibrium [3,5,6,8].

As previously reported, the invertomers of 1-chloro-2,2-dimethylaziridine were separated by gas chromatography on nickel(II)–*bis*[3-trifluoroacetyl-(*1R*)-camphorate] in squalane and the enantiomerization barrier was determined at 60°C ($\Delta G^{\#}(338\ K) = 104.9 \pm 0.6$ kJ mol^{-1}) [1]. The present dynamic GC study was modified and was performed on a fused-silica capillary column (25 m × 0.25 mm I.D.), coated with 0.25 μm Chirasil−nickel(II) [[32]] {nickel(II) – *bis*[- heptafluorobutanoyl - 10 - methyl - idene-(*1R*)-camphorate] linked to polydimethylsiloxane} and nitrogen as carrier gas. The invertomers were separated in the temperature range of 50.3–72.2°C. The results of the dynamic GC experiment and simulation are listed in Table 2 and depicted in Fig. 8. By linear regression of the Eyring plot (30

Table 2
Determination of the enantiomerization (inversion) barrier of 1-chloro-2,2-dimethylaziridine by dynamic GC using simulations with CHROMWIN 99

T (°C)	k'_A	k_1^{app} (10^{-4} s^{-1})	$\Delta G^{\neq}_{app}$(T) (kJ mol^{-1})	k_1^{liq} (10^{-4} s^{-1})	$\Delta G^{\neq}_{liq}$(T) (kJ mol^{-1})
50.3	2.27	0.76±0.29	103.1±0.4	0.99	102.4
53.8	1.93	9.81±0.45	103.5±0.5	1.32	102.7
57.7	1.70	1.08±0.25	104.5±0.6	1.45	103.7
62.1	1.35	1.42±0.38	105.2±0.4	1.99	104.3
67.4	1.04	1.96±0.07	106.0±0.1	2.89	104.9
68.4	0.96	2.33±0.05	105.8±0.1	3.65	104.6
72.2	0.89	3.03±0.26	106.3±0.3	4.83	104.9
77.0	0.76	3.99±1.09	107.0±0.8	6.57	105.5
82.6	0.65	6.05±1.85	107.5±0.9	10.7	105.8

experiments; $r=0.99$; Fig. 9) the activation parameters of 1-chloro-2,2-dimethylaziridine in the stationary liquid phase were $\Delta H^{\neq}_{liq}=68.3\pm1.4$ kJ mol^{-1} and $\Delta S^{\neq}_{liq}=-106\pm3$ J K^{-1} mol^{-1} (errors were calculated according to [27]). The data compare well with these obtained by stopped-flow MDGC (3.1.1)

The dynamic GC experiment shows that the inversion process is faster in the presence of the liquid CSP resulting in a decreased enantiomerization (inversion) barrier of $\Delta G^{\neq}_{liq}$, as compared to that in the gas phase. The results of the stopped-flow MDGC and dynamic GC experiments are summarised in Fig. 10.

Extrapolating the values of the activation parame-

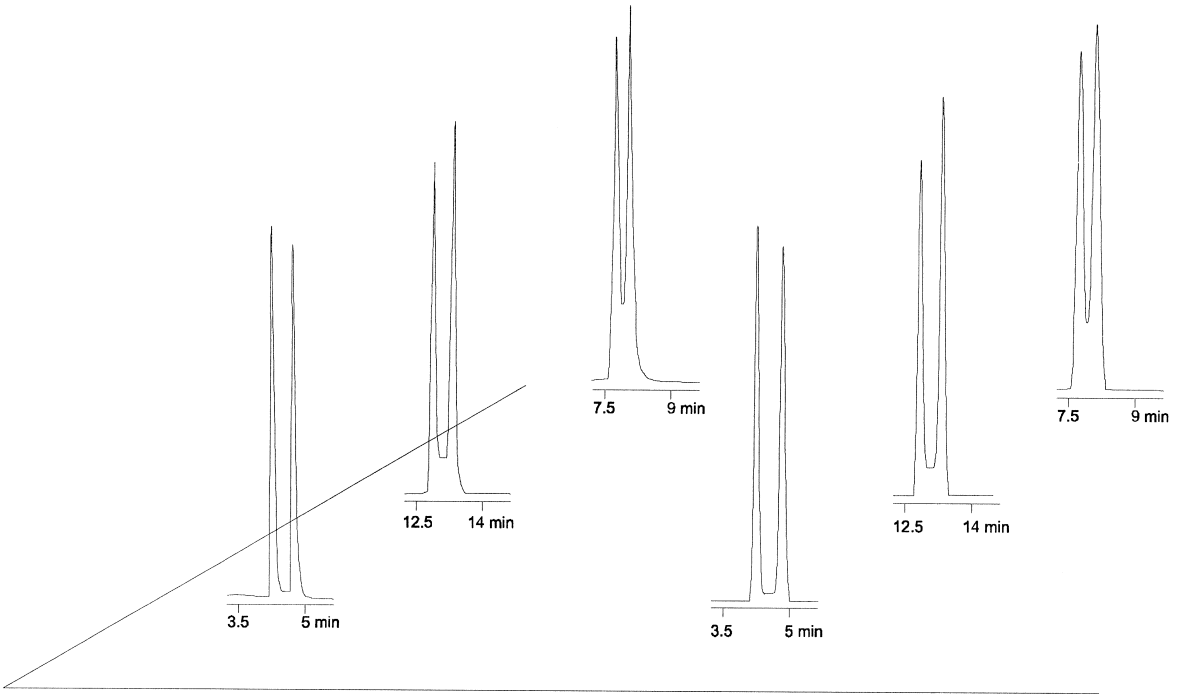

Fig. 8. Comparison of experimental (left) and simulated (right) gas-chromatographic enantiomer separation of 1-chloro-2,2-dimethylaziridine on Chirasil–Nickel(II) with plateau formation due to enantiomerization at 57.7, 67.4 and 77°C (from left to right).

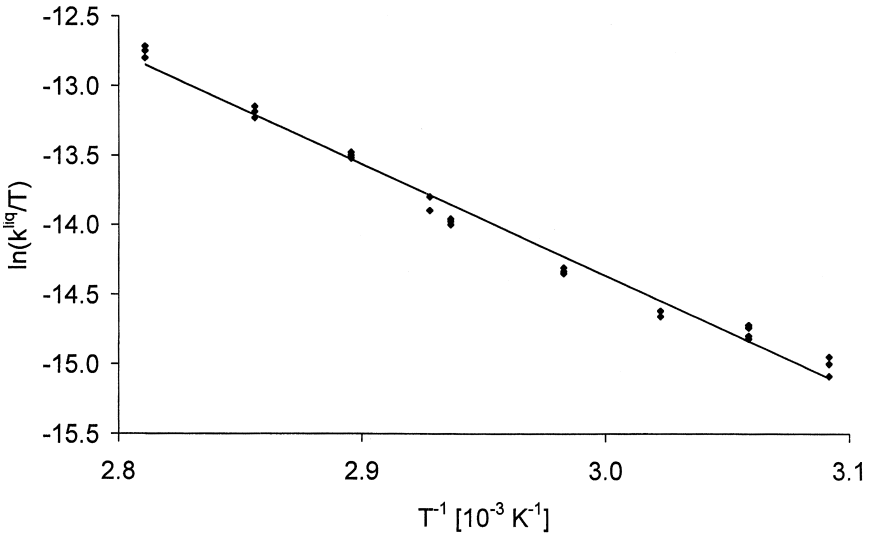

Fig. 9. Eyring-plot from dynamic GC experiments (30 runs) and simulations for determination of $\Delta H^{\#}_{liq}$ and $\Delta S^{\#}_{liq}$ of the enantiomerization (inversion) of 1-chloro-2,2-dimethylaziridine.

ters to standard conditions at 298 K the enantiomerization (inversion) barriers of 1-chloro-2,2-dimethylaziridine are $\Delta G^{\#}_{gas}(298\ K) = 103.5\ kJ\ mol^{-1}$ in the gas phase and $\Delta G^{\#}_{liq}(298\ K) = 99.8\ kJ\ mol^{-1}$ in the stationary liquid phase in the presence of Chirasil–nickel(II), respectively.

4. Conclusion

4.1. Scope of stopped-flow MDGC

Stopped-flow MDGC is a fast and simple method for the determination of activation parameters in the

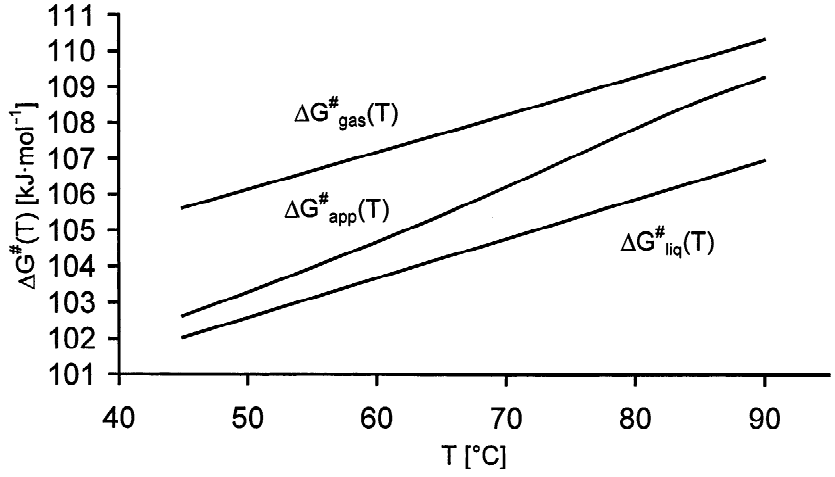

Fig. 10. Calculated inversion barriers $\Delta G^{\#}(T)$ of 1-chloro-2,2-dimethylaziridine at different temperatures in the mobile gas phase ($\Delta G^{\#}_{gas}$), stationary liquid phase ($\Delta G^{\#}_{liq}$) and biphase partitioning system ($\Delta G^{\#}_{app}$).($\Delta G^{\#}_{gas}$) is obtained by stopped-flow MDGC, ($\Delta G^{\#}_{app}$) is obtained by dynamic GC and ($\Delta G^{\#}_{liq}$) is calculated from stopped-flow MDGC and dynamic GC.

inert gas phase not only of enantiomerization processes but also of other interconversions such as epimerizations, *cis*/*trans*- or *syn*/*anti*-isomerizations (diastereomerizations) as well as rearrangements. In the future, even reaction processes may be studied. For certain applications, a two-column multidimensional array is feasible. In contrast to classical kinetics, stopped-flow MDGC does not require a preparative enantiomer separation and ng-amounts of the racemic and unpurified compound are sufficient for analysis. However, an indispensable prerequisite for the investigation of enantiomerization (inversion) processes is the complete on-line separation of the enantiomers by gas chromatography employing a CSP.

4.2. Merits and limitations of enantioselective stopped-flow MDGC

In comparison to dynamic and single column stopped-flow methods, the range of $\Delta G^{\neq}_{gas}(T)$ is larger and enantiomerization is performed in the achiral and inert environment of the gas phase (helium) and data are therefore relevant for physicochemical considerations. In the most favourable temperature and time window, the method yields data in the range of $\Delta G^{\neq}_{gas}(T)=70–200$ kJ mol^{-1}. No computer simulation is necessary as required by dynamic chromatographic methods. Employing an empty reactor column 2, no column bleeding is observed and the reproducibility is therefore better than that for single column stopped-flow GC. The enantiomerization time t and the enantiomerization temperature T can be determined precisely. The error of peak area integration can be minimized by a stable baseline and good peak resolution in column 3. The fluctuation of the temperature within the enantiomerization experiment is very small ($<\pm 1$°C). The temperature is measured directly at the reactor column 2 in order to minimize the systematic error. As outlined before, the small systematic error caused by heating the reactor column 2 to the enantiomerization temperature (ca. 2–3 min, depending on the enantiomerization temperature) and by cooling the reactor column 2 to quench enantiomerization (only a few seconds) is within the mean deviation of the enantiomerization barrier. In stopped-flow MDGC enantiomerization temperatures between 35 and 320°C can be applied. When analysing chiral compounds with low enantiomerization barriers it should be ascertained that the compound does not enantiomerize during the gas-chromatographic enantiomer separation in column 1 and 3. Enantiomerization times of a few minutes up to several hours can be applied. At very short enantiomerization times, systematic errors due to the finite heating and cooling period of the column are more pronounced. Very long enantiomerization times may be accompanied by diffusion or secondary reactions including decomposition.

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