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Semi-preparative Enantiomer Separation of 1-Chloro-2,2-dimethylaziridine by Complexation Gas Chromatography - Absolute Configuration and Barrier of Inversion

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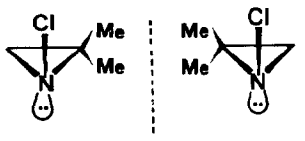
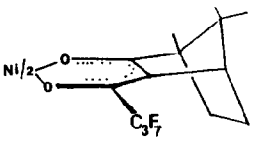
Summary. 1-Chloro-2.2-dimethyl-aziridine has been resolved into its enantiomerically pure invertomers by semi-preparative complexation gas chromatography at 25°C. The absolute configuration has been correlated with the chromatographic elution order. An inversion barrier of $\Delta G^{\ddagger}$ = 115.5 kJ/mol was determined in the gas phase at 338.6 K.

In 1-chloro-2,2-dimethylaziridine **1** the three-coordinated, pyramidal nitrogen constitutes the chiral center as well as a potential coordination center. Consequently, the gas chromatographic enantiomer separation of **1** on nickel(II) *bis*[(3-heptafluorobutanoyl)-(*1R*)-camphorate] **2** in squalane leads to the large separation factor of α = 1.5 at 60°C (corresponding to a difference of the free association enthalpy between the invertomers of **1** and *1R*-**2** of -$\Delta(\Delta G°)$ = 1.2 kJ/mol (333K)) [2,3].





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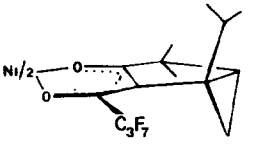

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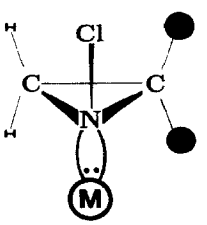
The inversion of configuration of **1** during its chromatographic enantiomer separation gives rise to characteristic interconversion profiles (observed for the first time for labile enantiomers by chiral chromatography [3]) from which kinetic activation data of enantiomerization are readily accessible by peak form analysis (*dynamic gas chromatography* [4]). In order to refine the mathematical treatment used [4] the knowledge of the inversion barrier of **1** in the gas phase is indispensable.

Employing an analytical 7.5 m x 3 mm (i.d.) stainless steel column containing 250 mg **2** in 6.25 g OV-101 impregnated on 43 g Chromosorb (W-AW-DMCS, 60-80 mesh) [5,6], the pure invertomers of **1** have been separated and isolated in mg-quantities (Fig. 1). The high enantiometric purity of the invertomers was corroborated by complexation gas chromatography employing an analytical column (Fig. 2). It should be noted that both the semi-preparative and the analytical separation of the labile invertomers of **1** can be achieved at room temperature.

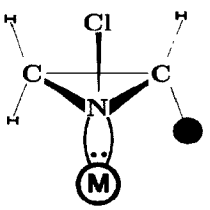
The amount of isolated enantiomerically pure invertomers (appr. 2 mg) was sufficient for the determination of chiroptical data in n-pentane and of measuring the enantiomerization kinetics in the gas phase employing an analytical column for screening ee by complexation gas chromatography (cf. Fig. 3, racemization at 82°C). The lowest rate of inversion of **1** in the *gas phase* at 338.6 K (65.3°C, boiling methanol) found was $k = 6.9 \quad 10^{-6}$ sec^{-1}, $t_{1/2} = 842$ min, $\Delta G^{\ddagger} = 116.7$ kJ/mol (mean value for $\Delta G^{\ddagger}$ in four measurements at $T = 338.6 \pm 0.3$ K: 115.5 ± 1.2 kJ/mol) [7,8].

The invertomer of **1**, eluted as the second fraction on nickel(II) *bis*[(3-heptafluorobutanoyl)-(*1R*) - camphorate] *(1R)*-**2**, shows a positive optical rotation at all wavelengthes and a positive Cotton effect at 217 and 260 nm in n-pentane. By indirect evidence we previously assigned configuration *S* to the invertomer of **1** eluting as the second peak on *(1R)*-**2** because *(1S,2S)*-1-chloro-2-methyl-aziridine **4** [3], which differs from **1** only by the absence of a methyl group in anti-position to the coordinating nitrogen lone pair, is also eluted as the second peak [3].



S

1



1S,2S

4

This assignment is in contradiction to that given by Kostyanovsky et al. [10] and others [11], based on the octant rule, but is in agreement with that proposed by Snatzke [12] and with the recent correction of the misassignment by Kostyanovsky et al. [13]. Thus, by gas chromatographic and chiroptic evidence the absolute configuration of (+)-1-chloro-2,2-dimethylaziridine **1** is *S*.

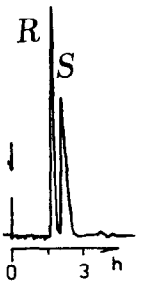


Figure 1: Semi-preparative separation of the invertomers of **1** by complexation gas chromatography on nickel(II) *bis*[(3-heptafluorobutanoyl)-(*1R*)-camphorate] **2** at 22°C (*S* is eluted after *R* on *(1R)*-**2**). Column: 7.5 m x 0.3 cm stainless steel, packed with 250 mg **2** in 6.25 g OV-101 impregnated on 43 g Chromosorb (W-AW-DMCS, 60-80 mesh). Carrier gas: 1.5 bar nitrogen. Injected amount of **1**: 6 μl. Analysis time: 3 h.

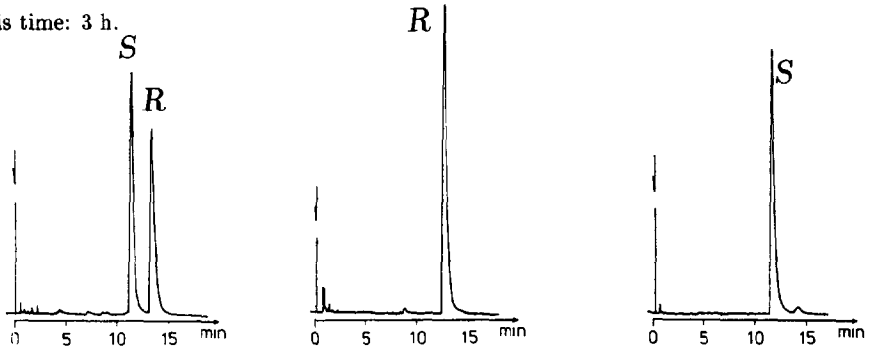


Figure 2: Enantiomeric purity of the isolated invertomers **1**. Left: racemic sample; middle: pure *R*-**1**; right: *S*-**1** (contaminated with appr. 1% *R*-**1** originating from uncomplete cutting of the preparative fractions (cf. Fig. 1). Analytical column: 25 m 0.25 mm glass capillary column coated with nickel(II)-*bis*-[(2-heptafluorobutanoyl)-*(1S,5S)*-4-methylthujonate] **3** [14] (0.125 **m** in OV-101, 50°C (*R* is eluted after *S* on *(1S,5S)*-**3**).

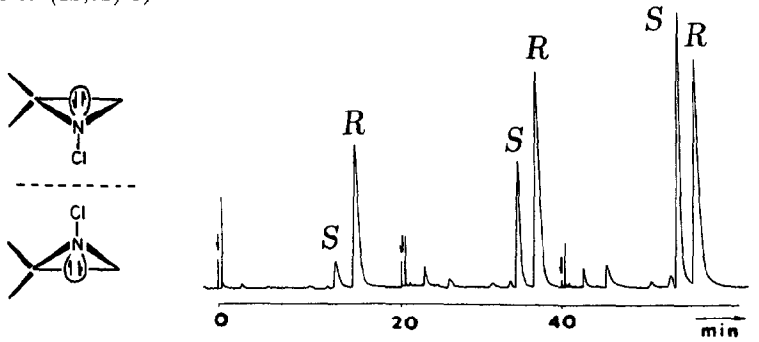


Figure 3: Rapid racemization of *R*-**1** at 82°C monitored by complexation gas chromatography (conditions cf. Fig. 2).

Acknowledgment

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7 Calculated according to 2t k = $\ln(ee_{(o)}/ee_{(t)})$ using the program KINMIK (A. Eiglsperger, Dissertation, Universität Regensburg, 1985, p. 76).

8 By dynamic ^{1}H-NMR spectroscopy the free enthalpy of inversion of **1** has been estimated > $\Delta G^{\ddagger}$ = 98.4 kJ/mol at 180°C since no coalescence of the diastereotopic methyl proton resonances were observed at this temperature [9]. From the *dynamic* chromatographic coalescence phenomenon caused by inversion of **1** during gas-chromatographic enantiomer separation on **2**, k = 23.5 · 10^{-5}sec^{-1} and $\Delta G^{\ddagger}$= 105.1 kJ/mol has been determined by peakform analysis [4] In this treatment, a decrease of the barrier of inversion of **1** being different for the two invertomers in the presence of chiral **2**, has been inferred and, consequently, $\Delta G^{\ddagger}$ also represents a lower limit. An optically enriched sample of **1** (ee < 5%) [10,11] showed a half-time of inversion $t_{1/2}$ = 45 min (80°C, CCl_4). According to $t_{1/2}$ = ln2/2k and $\Delta G^{\ddagger}$= 4.57 T(10.32 + log(T/k), $\Delta G^{\ddagger}_{353}$ = 113 2 kJ/mol is calculated.

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