

DETERMINATION OF THE ACCURATE VALUES OF THE RATE CONSTANT AND THERMODYNAMIC PARAMETERS FOR THE ROTATION ABOUT THE C(sp²)-C(ARYL) BOND; ADAMANTAN-1-YL 3-BROMO-2,4,6-TRIMETHYL-PHENYL KETONEEva PRIBYLOVA¹ and Miroslav HOLIK^{2,*}

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Received March 25, 1998

Accepted June 23, 1998

Four programs for the ¹H NMR line shape analysis: two commercial – Winkubo (Bruker) and DNMR5 (QCPE 165) and two written in our laboratory – Newton (in Microsoft Excel) and Simtex (in Matlab) have been tested in order to get highly accurate rate constants of the hindered rotation about a single bond. For this purpose four testing criteria were used, two of them were also developed by us. As supplementary determinations the rate constants obtained for the coalescence temperature and for the thermal racemization of chromatographically separated enantiomers were used which fitted well the temperature dependence of the rate constants determined by the line shape analysis. As a test compound adamantan-1-yl 3-bromo-2,4,6-trimethylphenyl ketone was prepared and studied. It was shown that supermodified simplex method used in our algorithm (Simtex), though time consuming, gives the most accurate values of the rate constants and consequently the calculated thermodynamic parameters E_a , ΔH^\ddagger , and ΔS^\ddagger lay in relatively narrow confidence intervals.

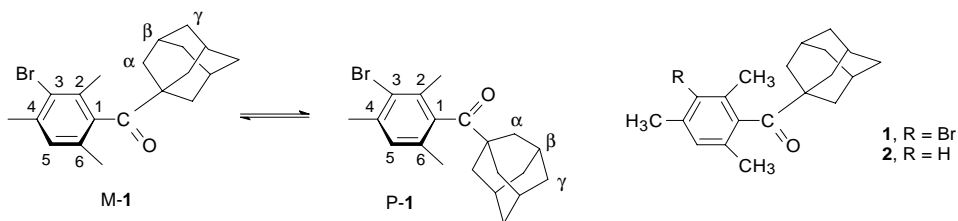
Key words: Rate constants; Thermodynamic parameters; NMR line shape analysis; Dynamic NMR spectroscopy; Thermal racemization; HPLC/polarimetry.

Ortho-disubstituted benzoyl derivatives are non-planar in their ground state with carbonyl group twisted from the molecular plane. When the benzene ring is unsymmetrically substituted, such a derivative exists in two enantiomeric rotamers, which can be assigned with P and M symbols according to the IUPAC rules for helicity^{1,2}.

If the sterical hindrance in planar transition state is high enough, the rate of their interconversion can be investigated by applying various techniques. The rotameric racemates may be resolved³ into their enantiomers, and the energy barrier of enantio-merization investigated by chiroptical methods; an alternative using enantiomeric enrichment or separation is HPLC (refs^{4,5}). Another method of choice is dynamic ¹H NMR spectroscopy^{6,7}. Addition of an optically active auxiliary compound to the racemate

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causes a formation of two diastereomeric complexes with different NMR spectra at low temperature. With increasing temperature, the NMR signals of groups involved in inter-conversion broaden and finally coalesce in an averaged spectrum; the shape of the signals under coalescence can be analyzed and the rate constant for particular temperature obtained by some optimization procedure⁸.



In order to get a wider temperature interval the rate of rotation can be studied by combination of HPLC/polarimetry and NMR spectroscopy^{9,10}. Due to the nature of the processes, the NMR spectroscopy is applied at higher and the polarimetric method at lower temperatures. The possibility to investigate thermodynamic behaviour of the molecule in relatively wide temperature range is a prerequisite for reliable determination of activation parameters like activation energy and enthalpy and entropy of activation. In order to get the results of these two methods as “a sample from the population” it is necessary to calculate rate constants with high accuracy. If this is not done, the confidence intervals of thermodynamic parameters are too wide and the conclusions suggested can be questionable.

In order to find out reliable and precise optimization program for the line shape analysis, we have determined rate constant of the rotation about the C(sp²)-C(aryl) single bond in the adamantan-1-yl 3-bromo-2,4,6-trimethylphenyl ketone (**1**) using four programs; two of them were commercial and two were written in our laboratory.

EXPERIMENTAL

Preparations

Adamantan-1-yl 2,4,6-trimethylphenyl ketone (2). Powdered aluminium chloride (33.5 g, 0.25 mol), in a three-necked flask fitted with a reflux condenser with calcium chloride tube, a stirring rod, and a dropping funnel, was covered with carbon disulfide (50 cm³) freshly distilled from P₂O₅. While cooling the flask in an ice bath, a solution of adamantan-1-yl chloride (49.7 g, 0.25 mol) and 1,3,5-trimethylbenzene (30 g, 0.25 mol) in carbon disulfide (150 cm³) was added dropwise to the stirred mixture over a period of 60 min. After the addition was finished, the mixture was stirred for three additional hours at room temperature. The aluminium complex was decomposed by pouring the reaction mixture into a beaker containing concentrated hydrochloric acid (25 cm³) and crushed ice (about 200 g). The organic layer was separated and the aqueous layer was extracted twice with portions of

ether (100 cm³). The combined organic layers were dried over Na₂SO₄ overnight and solvents were evaporated under reduced pressure. The residue was five times distilled under reduced pressure (133 Pa) from a collar flask filled with glassy fibres. The distillation product, which solidified, was recrystallized from propan-2-ol–water mixture (3 : 1 v/v). The ketone **2** was obtained in yield 26.7 g (41%), m.p. 97 °C. ¹H NMR spectrum (500 MHz, CDCl₃, 303 K): 1.71 m, 6 H (Ad(γ)); 1.91 m, 6 H (Ad(α)); 2.01 m, 3 H (Ad(β)); 2.17 s, 6 H (2-Me, 6-Me); 2.26 s, 3 H (4-Me); 6.81 s, 2 H (3-H, 5-H). ¹³C NMR spectrum (125 MHz, CDCl₃, 303 K): 20.6 s, 2 C (2-Me, 6-Me); 20.9 s, 1 C (4-Me); 28.2 s, 3 C (Ad(β)); 36.5 s, 3 C (Ad(γ)); 39.2 s, 3 C (Ad(α)); 47.1 s, 1 C (C-CO); 128.3 s, 2 C (C-3, C-5); 132.3 s, 2 C (C-2, C-6); 137.3 s, 1 C (C-4); 139.3 s, 1 C (C-1); 218.5 s, 1 C (CO). For C₂₀H₂₆O (282.4) calculated: 85.06% C, 9.28% H; found: 85.06% C, 9.38% H.

Adamantan-1-yl 3-bromo-2,4,6-trimethylphenyl ketone (1). A solution of bromine (20 cm³, 0.039 mol) in chloroform (40 cm³) was added to ketone **2** (9.28 g, 0.033 mol) dissolved in chloroform (80 cm³) and the mixture was left in a hood for three days. After washing with concentrated aqueous NaHCO₃ solution, the chloroform layer was dried overnight with Na₂SO₄. The chloroform was evaporated and the solid residue purified by recrystallization from propan-2-ol–water mixture (3.5 : 1 v/v). The ketone **1** was obtained in yield 11.9 g (79%), m.p. 110 °C. ¹H NMR spectrum (500 MHz, CDCl₃, 303 K): 1.70 m, 6 H (Ad(γ)); 1.89 m, 6 H (Ad(α)); 2.01 m, 3 H (Ad(β)); 2.13 s, 3 H (6-Me); 2.24 s, 3 H (2-Me); 2.24 s, 3 H (4-Me); 6.91 s, 2 H (5-H). ¹³C NMR spectrum (125 MHz, CDCl₃, 303 K): 20.2 s, 1 C (6-Me); 22.7 s, 1 C (2-Me); 23.8 s, 1 C (4-Me); 28.2 s, 3 C (Ad(β)); 36.5 s, 3 C (Ad(γ)); 39.2 s, 3 C (Ad(α)); 47.4 s, 1 C (C-CO); 125.7 s, 1 C (C-3); 130.2 s, 1 C (C-5); 131.2 s, 1 C (C-6); 132.4 s, 1 C (C-2); 137.8 s, 1 C (C-4); 140.7 s, 1 C (C-1); 216.6 s, 1 C (CO). For C₂₀H₂₅BrO (361.3) calculated: 66.48% C, 6.97% H, 22.14% Br; found: 66.54% C, 7.12% H, 21.89% Br.

The assignment of the ¹H and ¹³C signals was checked by 2D heterocorrelated NMR spectrum HSQC. The assignment of the CH₂ and the CH carbon signals in the adamantyl moiety was confirmed by an APT experiment. The assignments of ¹H and ¹³C signals in the adamantyl group are in good agreement with the same signals of structurally related adamantane derivatives¹¹ and the assignments of ¹H and ¹³C signals in the other parts of the studied molecule are in accordance with signals of a structurally similar compound, 3-bromo-2,4,6-trimethylphenyl *tert*-butyl ketone¹².

NMR Spectra

For the structure determinations and the signal assignments, the ¹H, ¹³C and 2D heterocorrelated NMR spectra were measured at 500 MHz on a Bruker Avance DRX-500 spectrometer in chloroform-*d*₁ (*c* = 0.1 mol dm⁻³) with tetramethylsilane as an internal standard. For the ¹H NMR kinetic measurements, 0.05 mol dm⁻³ solutions of compound **1** in hexachlorobutadiene were used, 10 vol.% benzene-*d*₆ serving as a ²H-lock substance; the auxiliary reagent–substrate ratio (L/S) being 0.1. The total volume of the samples was 440 μl. Determination of the rate constant at coalescence temperature, *k_c*, was performed at 80 MHz on a TESLA BS 587 NMR spectrometer.

Variable temperature unit BDTC (Bruker) allows to regulate the sample temperature with a stability of ±0.2 K. The temperature in the NMR probe was checked using proper van Geet equation¹³

$$T(\text{K}) = 466.0 - 101.6 \Delta\delta . \quad (1)$$

Absence of systematic error was controlled by slightly modified procedure of Friebolin¹⁴. The NMR tube containing hexachlorobutadiene, a capillary with ethylene glycol, a capillary with cyclosilane-*d*₁₈ and a capillary with nematic crystal Licristal IV was used for simultaneous determination of Δ*v* (chemical shift difference of CH₂ and OH signals of ethylene glycol) and clearing point of nematic

liquid crystal. Appearance and disappearance of the NMR spectrum of the liquid crystal about the clearing point enables¹⁴ to set the temperature in the range ± 0.2 K.

All chemicals were products of Merck AG, Darmstadt, Germany, only optically active shift reagent tris(3-heptafluorobutyl-(+)-camphorato)europium(III), (+)-Eu(hfbc)₃, was available from Aldrich Chemical Co., Milwaukee, WI, U.S.A.

Liquid Chromatography/Polarimetry

Enantiomers of **1** were separated by high-pressure liquid chromatography at a flow rate of $0.5 \text{ cm}^3 \text{ min}^{-1}$, $\Delta p = 7 \text{ MPa}$, on an optically active sorbent, (+)-poly(triphenylmethyl methacrylate)/SiO₂. Methanol was used as an eluent at 15°C. Injected quantities of racemates were 1 mg in 1 cm^3 . At this conditions complete separation of enantiomers was achieved. The process was monitored by polarimetric detection¹⁵ on a Perkin–Elmer 341 polarimeter and UV detection on an ERC 7210. Kinetics of racemization was performed by an on-line procedure¹⁶, *i.e.*, a run of liquid chromatography was stopped when the polarimetric detection showed maximum. The polarimetric cell, which at that moment contained the solution of an enriched enantiomer, was thermostatted to an appropriate temperature (304 K) and decrease of the angle of rotation with the time was recorded.

Computer Calculations

The calculations of the rate constant of the interconversion from kinetically broadened signals were carried out on a PC computer using the following four programs. The first program written in our laboratory uses Newton method for an iterative procedure, which is included in the commercial program Microsoft Excel. The second program called Simtex was made in our laboratory in programming language Matlab*; its optimization procedure applies a supermodified simplex algorithm¹⁷, which contains the second-order type of vertex and with the expansion factor g restricted to be out of the intervals 0 ± 0.1 and 1 ± 0.1 , to minimize the standard deviation between simulated and experimental spectrum. This program displays an agreement of experimental with theoretical spectrum after each optimization step. The third was the commercial program Winkubo¹⁸ (Bruker, Germany) which also uses some sort of a simplex algorithm. The fourth program¹⁹ was DNMR 5 (QCPE 165); its iterative minimization algorithm being based on a subsequent use of the gradient and Gauss–Newton procedures. The calculation of theoretical line shapes by all the used programs, except the last one, is based on the modified Bloch equations⁸; in the DNMR 5 program, the calculation uses the density matrix formalism²⁰.

RESULTS AND DISCUSSION

Rate Constant of Racemization

Liquid chromatography on (+)-poly(triphenylmethyl methacrylate) monitored by UV and polarimetric detection was used for separation of enantiomers of the compound **1**.

* Matlab is a commercial product of The MathWorks Inc. Natick, U.S.A., supplied in the Czech Republic by Humusoft s.r.o. Prague. Listing of the Simtex program is available from authors on request.

The analytical chromatogram showed a sufficient resolution of enantiomers by LC. The rate constant for rotation about the C(sp²)-C(aryl) bond was obtained by an on-line procedure¹⁶ using the solution of an enantiomerically enriched sample in the polarimetric cell. The overall error in the rate constant calculation can be reduced if the commonly used logarithmic kinetic equation (Eq. (2)) is replaced by the exponential one (Eq. (3))

$$\ln \alpha = a_1 + a_2 t + \varepsilon_a \quad (2)$$

$$\alpha = b_1 + b_2 \exp(b_3 t) + \varepsilon_b, \quad (3)$$

where α is an angle of rotation in mdeg, t is time in seconds and $-a_2$ and $-b_3$ are rate constants of racemization in s⁻¹. In linear equation (2) any possible systematic error is hidden in a constant parameter, a_1 ; however, the exponential equation (3) enables to separate the constant term at the function, b_2 , from the systematic error term b_1 . The results of both calculations showed that, in the accordance with our expectations, the residual sum of squares is about four-times smaller for the exponential regression and the parameter b_1 corresponding to the systematic error, *i.e.* insufficient zeroing of the polarimetric detector, possesses non-zero value (13.7 mdeg).

Rate Constant at the Coalescence Temperature

Addition of the optically active shift reagent, (+)-Eu(hfbc)₃, to the ketone **1** causes shifting of all the signals to the lower field and doubling of methyl signals due to the formation of diastereomeric rotamer complexes. The increase of the rate of rotamer interconversion with increasing temperature causes decrease of the difference between corresponding signals, $\Delta\nu$, connected with their broadening and finally coalescence to one signal. Since the chemical shift difference between signals, $\Delta\nu$, depends on the magnetic field used, the coalescence can be achieved at lower temperature (383 K) on the 80 MHz spectrometer than at 500 MHz; for this measurement a pair of 2-methyl signals was used. As $\Delta\nu$ depends on temperature, the value $\Delta\nu_c$ (difference in chemical shift at the coalescence) must be extrapolated from the kinetically unaffected part of a plot of $\Delta\nu$ vs $1/T$ to the coalescence temperature¹². For the calculation of the rate constant at coalescence temperature, k_c , also the line width without exchange broadening, b_E , must be used²¹ since the addition of shift reagent causes a broadening of the signals, which is no longer negligible with respect to $\Delta\nu_c$. As b_E was found to be independent on temperature at low temperatures, its extrapolation to the $1/T_c$ was not necessary. Rate constant at coalescence was calculated according to the equation (3) from ref.²¹.

In this way calculated value $k_c = 1.43 \text{ s}^{-1}$ does not differ too much from the value $k_c = 1.49 \text{ s}^{-1}$ obtained from the approximative equation (4) from ref.²¹: therefore, last equation was differentiated according to Δv and b_E for estimating of the error in k_c , δk_c (Eq. (4)).

$$\delta k_c = \frac{\partial k_c}{\partial \Delta v} \delta \Delta v + \frac{\partial k_c}{\partial b_E} \delta b_E = 2.22 \delta \Delta v + 1.22 \delta b_E \quad (4)$$

The error in Δv_c extrapolation, $\delta \Delta v_c$, and error due to the line width variation in individual measurements, δb_E , were taken equal to $\pm 0.1 \text{ Hz}$ and the δk_c was calculated to be equal to 0.34.

Rate Constant from the Line Shape Analysis

For the determination of the rate constant of racemization in a temperature interval below coalescence (378–403 K), the change in the shape of the pair of 2-Me signals was analyzed by the line shape analysis. For this purpose, the spectrum of the pair of signals must be digitalized into two vectors – vector of chemical shifts in Hz, v , and vector of corresponding amplitudes, I_{exp} . For each chemical shift in the selected range, v , theoretical amplitude I_{calc} was calculated²² according to Eqs (5) and (6):

$$\mathbf{K} \cdot \mathbf{G} = i \mathbf{C} \cdot \mathbf{P} \quad (5)$$

$$\mathbf{K} = 2\pi i \begin{bmatrix} v_1 & 0 \\ 0 & v_2 \end{bmatrix} - 2\pi i \begin{bmatrix} v & 0 \\ 0 & v \end{bmatrix} + \pi \begin{bmatrix} b_1 & 0 \\ 0 & b_2 \end{bmatrix} - k \begin{bmatrix} -1 & +1 \\ +1 & -1 \end{bmatrix}, \quad (6)$$

where \mathbf{G} is a magnetization vector whose imaginary elements sum up to the amplitude for the frequency v , I_{calc} , i is an imaginary unit, \mathbf{C} is a scaling vector, and \mathbf{P} is a fractional population vector (in this case $[0.5 \ 0.5]'$). Matrix \mathbf{K} includes chemical shifts, v_1 and v_2 , frequency as an independent variable, v , line widths, b_1 and b_2 , and the rate constant k .

Experimental and theoretical spectra (*i.e.*, vectors I_{exp} and I_{calc}) were then normalized and compared with the help of standard deviation. Then the first estimate of the parameters in Eqs (5) and (6) were changed according to some proper algorithm (*e.g.*, Simplex) until the calculated spectrum fitted the experimental one with defined precision. The first estimate of chemical shifts was obtained by extrapolating the linear part of a plot of the Δv vs $1/T$; the estimated line widths were taken from the spectral lines at lower temperature. The determination of the rate constant from each spectrum was divided in two steps. In the first, the iterative procedure contained only the variation of the rate constant (the program was adapted from the Martins' book⁸). Its optimal value

was taken as a starting estimate for the next step which performed the variation of all five parameters by all above mentioned programs. Although optimized as the rate constants of racemization, *i.e.* sum of the values k for forward and reverse reaction, the values given in Table I are rate constants of enantiomerization, *i.e.* $(\Sigma k)/2$.

For comparison of the programs, the following four criteria were chosen:

The first criterion was the above-mentioned *standard deviation* obtained from the fit of normalized calculated and experimental spectra at the temperature 383 K.

The second criterion was a *coefficient of determination*, r^2 , for the linear regression of logarithm of the rate constants on the reciprocal values of temperature (*i.e.*, logarithmic Arrhenius equation). It is based on the fact that the spread of logarithm of rate constants around the expected values characterizes the quality of the rate constant calculation.

The third criterion we called *average error range of the rate constants*. The optimal value of the rate constant was randomly varied and residual sum of squares from optimum spectrum and modified one was evaluated. When the obtained residual sum of squares differed more than one per cent from the value for the optimum rate constant, the result was neglected. For those remaining the difference between maximum and minimum value of the rate constants formed the error range. The error range was calculated for each of six temperatures used and the average value was taken as the fit criterion.

The fourth criterion was also developed in our laboratory and we called it *confidence interval of the rate constants*. It involves rate constant values (only for the temperature 383 K) obtained after a small variation of the all optimized parameters; the optimum

TABLE I
Rate constants of enantiomerization (s^{-1}) of **1** from line shape analysis

T, K	Newton (Excel)	Simtex (Matlab)	Winkubo (Bruker)	DNMR 5
378	0.831	0.852	0.915	0.900
383	1.316	1.337	1.452	1.454
388	2.066	2.067	2.140	2.232
393	3.533	3.233	3.294	3.199
398	4.893	4.895	5.134	5.069
403	7.410	7.412	7.755	7.851
383 ^a			1.43 ± 0.34	
304 ^b			(1.63 ± 0.04) · 10 ⁻⁴	

^a From coalescence at 80 MHz. ^b From polarimetric equilibration.

values were increased (+) or decreased (-) in their 8 combinations according to trials of the Plackett-Burman reduced factorial experiment^{23,24} (Table II). The rate constant was varied (increased or decreased) 20 per cent and all other input values were varied 0.5 Hz. For each combination, new optimization was performed and eight values of rate constant were obtained; their range (the highest minus the lowest value) being taken as this criterion. The results of testing are summarized in Table III.

Four programs used differ in time-demand. The whole optimization takes from a few seconds (DNMR 5) to several hundreds seconds (Simtex) but we believe it is not an important feature at the present. More important is the possibility to put some constraint on the optimized parameter, *e.g.*, non-negativity of the rate constant; it is allowed in all programs except one – Winkubo.

Our program Simtex gives the smallest standard deviation between calculated and experimental spectra, the best coefficient of determination for Arrhenius equation, and the smallest confidence interval of the rate constants. To sum up, we believe that the rate constants determined by our program Simtex with the supermodified simplex can be considered as the best values.

Arrhenius plot in Fig. 1 shows a good agreement among results obtained by line shape analysis, at the coalescence, and by polarimetry. Values of the rate constants determined by NMR spectroscopy fit perfectly the linear dependency of logarithm of the rate constant on the reciprocal value of temperature (see coefficient of determination in Table III), and, moreover, the extrapolated part of this dependency intersects the

TABLE II
Trials according to the Plackett-Burman²³ reduced factorial experiment^a

Parameter	ν_1^b , Hz	ν_2^b , Hz	b_1^b , Hz	b_2^b , Hz	k^c , s ⁻¹
Input values	1 057.40	1 051.57	1.542	1.449	1.337
Trials					
1	+	+	-	+	-
2	+	+	+	-	+
3	+	-	-	-	+
4	-	+	-	+	+
5	+	-	+	+	-
6	-	-	+	+	+
7	-	+	+	-	-
8	-	-	-	-	-

^a From the parameters of the NMR spectrum measured at 383 K and optimized by the Simtex program. ^b Varied ± 0.5 Hz from the input values. ^c Varied $\pm 20\%$ from the input value.

point corresponding to the rate constant determined by polarimetry. Parameters a_1 and a_2 for only NMR points ($n = 7$) and parameters obtained from regression including also the results from polarimetric measurement ($n = 8$) agree very well; *cf.* Eqs (7) and (8).

$$n = 7, \quad \ln y = -13\,062(\pm 184)x + 34.41(\pm 0.47) \quad (7)$$

$$n = 8, \quad \ln y = -13\,282(\pm 40)x + 34.97(\pm 0.11) \quad (8)$$

Indexes in parenthesis in Eqs (7) and (8) are standard deviations of the corresponding parameters. Since both parameters and their standard deviations are inversely proportional to $\Sigma(x - \bar{x})^2$, the broader interval of x values can furnish better estimates of the optimized values.

TABLE III
Criteria for comparison of the optimization programs

Program Criterion	Martin ⁸	Newton (Excel)	Simtex (Matlab)	Winkubo (Bruker)	DNMR5
Standard deviation $\cdot 10^2$	3.041	1.880	1.637	1.883	2.100
Coefficient of determination	0.9771	0.9974	0.9996	0.9989	0.9988
Average error range, s^{-1}	0.341	0.137	0.115	0.095	0.170
Confidence interval of the rate constant, s^{-1}	–	0.135	0.088	0.147	0.109

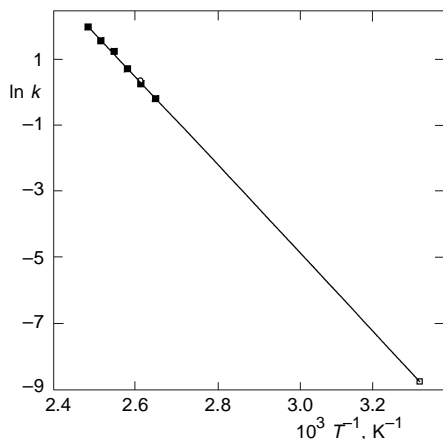


FIG. 1
Arrhenius plot of the rate constants determined by all experimental methods; ■ line shape analysis by the Simtex program, ○ coalescence, □ polarimetry

Determination of the Energy Barrier to Rotation

The activation energy, E_a , for the C(sp²)-C(aryl) rotation was determined according to Arrhenius equation by non-linear regression

$$k = A \exp\left(-\frac{E_a}{RT}\right) + \varepsilon, \quad (9)$$

where k is the first-order rate constant of enantiomerization at temperature T , A is the frequency factor for the rate process, and ε is a residual caused by statistical (random) error. The rate constants obtained by all three experimental methods – line shape, coalescence, and polarimetry – were used for the calculation. A thermodynamical formulation of reaction rates shows that the enthalpy and entropy of activation²⁵ (Table IV) are given by Eqs (10) and (11),

$$\Delta H^\ddagger = E_a - RT \quad (10)$$

$$\Delta S^\ddagger = R \left[\ln \left(\frac{Ah}{k_B T} \right) - 1 \right] = R [\ln A - \ln T - 24.76] \quad (11)$$

TABLE IV
Activation parameters^a of the enantiomerization of **1** for the temperature^b 390.5 K

Program	Newton (Excel)	Simtex (Matlab)	Winkubo (Bruker)	DNMR 5
E_a^c	107.04	109.07	109.89	111.14
ΔE_a^c	0.27	0.09	0.10	0.20
$\ln A$	33.952	34.554	34.846	35.224
$\Delta \ln A$	0.062	0.002	0.029	0.059
$\Delta H^{\ddagger c}$	103.80	105.82	106.65	107.89
$\Delta \Delta H^{\ddagger c}$	0.30	0.28	0.25	0.34
$\Delta S^{\ddagger d}$	26.809	31.814	34.242	37.384
$\Delta \Delta S^{\ddagger d}$	0.065	0.002	0.080	0.150
$\Delta G^{\ddagger c}$	93.327	93.401	93.276	93.296
$\Delta \Delta G^{\ddagger c}$	0.325	0.279	0.281	0.401

^a Calculated from k values in Table I. ^b Harmonic average of temperatures: $1/T_{\text{harm}} = 1/n \sum_{i=1}^n 1/T_i$. ^c In kJ mol⁻¹.
^d In J K⁻¹ mol⁻¹.

respectively, assuming E_a to be temperature independent. In the Eq. (11), h is Planck constant and k_B is Boltzmann constant. The Gibbs energy of activation²⁵, ΔG^\ddagger , is then calculated as $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$ at the harmonic average of temperatures for the NMR measurements with the line shape analysis, *i.e.*, 390.5 K.

The error of activation parameters were calculated using Eqs (12)–(14) (error in entropy of activation as a differentiation from the Eqs (9) and (11) and the error in enthalpy of activation as a differentiation from the Eqs (9) and (10).

$$\Delta\Delta S^\ddagger = \frac{\partial\Delta S^\ddagger}{\partial T} \Delta T + \frac{\partial\Delta S^\ddagger}{\partial k} \Delta k = \frac{-1}{T} \left(\frac{E_a}{T} + R \right) \Delta T + \frac{R}{k} \Delta k \quad (12)$$

$$\Delta\Delta H^\ddagger = R (\ln A - \ln k - 1) \Delta T - \frac{RT}{k} \Delta k \quad (13)$$

$$\Delta\Delta G^\ddagger = \Delta\Delta H^\ddagger + T \Delta\Delta S^\ddagger \quad (14)$$

The error in the temperature measurement, ΔT , was taken as equal to ± 0.5 K (it is a realistic estimate with respect to temperature stability and accuracy of setting, *cf.* Experimental) and the error in the rate constant, Δk , was estimated to be equal to the average error range in the Table III.

From the results in the Table IV, it is evident that activation parameters derived from the rate constant values, which were obtained by the program Simtex, show the smallest errors. The Gibbs energy of activation for the studied compound was found about 3.7 kJ mol^{-1} higher than that for 3-bromo-2,4,6-trimethylpivalophenone¹², *i.e.*, 89.7 kJ mol^{-1} at 390 K. This result is in accordance with our expectation that a more bulky substituent results in increasing of the barrier to rotation.

Conclusion

In order to get accurate values of rate constant of enantiomerization from line shape analysis it is useful to optimize all parameters instead of the rate constant only. From the four optimization programs tested, the Simtex program, written in our laboratory was found as the best one. If the rate constant values are accurate, the value determined by polarimetry can be included in the correlation, which results in a wider temperature interval and more reliable thermodynamic parameters. For the calculation of the rate constant from the polarimetric measurements and also for the calculation of the activation parameters from Arrhenius equation a non-linear regressions are advantageous since in these equations measured values (and not their logarithms) are related directly with values of independent variable. Moreover, the systematic error can be separated

using non-linear equation and the resulting value of the rate constant is not affected. Combining accurate measurements of experimental variables (including temperature) with suitable optimization algorithm and non-linear regression results in increased accuracy of the calculated rate constants and thermodynamic parameters. For instance, error in the free energy of activation, $\Delta\Delta G^\ddagger$, can be about four times smaller than without these precautions (cf. ref.¹⁰).

We acknowledge Prof. A. Mannschreck and Ms N. Pustet, University Regensburg, Germany, for the help with the HPLC/polarimetry measurement. We would like to thank Dr M. Nechvatal, Lachema Brno, for the help with the preparations.

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