Activation Parameters for Inversion of 1-(1-Naphthyl)-isoquinoline. II.* Determination of the Enthalpy and Entropy of Activation for the Free Base

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The activation parameters for inversion of 1-(1-naphthyl)-isoquinoline in methanol solution have been determined from the temperature dependence of the rate of racemization of the levorotatory enantiomer in the temperature interval -36.2 to -5.9°C . The results obtained from 113 runs correspond to a $\Delta H^{\ddagger}$ for inversion of $80.4 \pm 1.7 \text{ kJ mol}^{-1}$ and a $\Delta S^{\ddagger}$ for inversion of $7.1 \pm 6.7 \text{ J mol}^{-1} \text{ K}^{-1}$.

The concept of "size" of the lone electron pair on nitrogen is a subject of some controversy.^{1,2} This is partly due to the fact that it is difficult to design an experiment which will measure only this factor, resulting in different "operational" definitions of the van der Waals volume of the lone pair. Another reason is that the concept of "size" of the lone pair is classical in nature and lacks precise theoretical definition.

It has recently been shown³ that the "size" of an electron pair (*i.e.* a localized two-electron group) can be related to the expectation values of two quantum mechanical operators corresponding to the first and second moments of the electronic charge distribution of localized molecular orbitals. This hopefully brings the discussion of "size" of the lone pair on a sounder foundation.

In Part I of this series⁴ it was suggested that the optical stability of 1-(1-naphthyl)-isoquinoline **1** relative to that of 1,1'-binaphthyl **2** can be used to gauge the van der Waals volume of the lone pair in comparison to that of hydrogen. The basis for this rationale is the

success of the classical model for calculating the barriers to inversion as introduced by Westheimer *et al.*⁵⁻⁷ and later used by Howlett.⁸ In their model the major part of the barrier to inversion comes from the van der Waals interaction between interfering atoms and the bending of the bonds of these atoms. In addition, Hill has suggested that the barriers to inversion of biphenyls can be used to obtain information on the van der Waals volumes of substituents in the interfering positions.⁹ The two molecules **1** and **2** are so similar that one may hope that they are inverted through similar transition states and that comparison of their respective $\Delta H^{\ddagger}$ values for inversion will yield an estimate of the difference in "size" between

* For Part I of this series, see Ref. 4.

the lone pair and hydrogen. The activation parameters for inversion of **2** in dimethylformamide solution are already known with high precision.^{10,11} It is not appropriate to compare the free energies of activation for inversion of **1** and **2**, as the entropies of activation for inversion of biphenyls and biphenyl-like compounds are known to range between +42 and -63 J mol⁻¹ K⁻¹.¹² In addition, due to differences in solubility of **1** and **2**, and the method used to obtain optically active **1**, the rates of racemization of **1** and **2** must necessarily be determined in different solvents.

EXPERIMENTAL

Kinetic runs were made on a Perkin-Elmer 141 polarimeter placed in a "dry box" filled with nitrogen. The polarimeter cells were standard Perkin-Elmer 1 ml and 5 ml "micro cells", and the cell windows were kept free of frost by a stream of dry nitrogen. The nitrogen was pre-dried by passing through a column of Drierite, and the residual water was then frozen out in a trap cooled by liquid nitrogen. The error in each reading, determined by measurements on pure methanol, was $\pm 0.003^\circ$.

The temperature in the cells was measured using a calibrated thermistor and a Fluke 8300A digital voltmeter. The thermistor was calibrated against a Hewlett Packard 2801 A quartz thermometer to a precision of ± 0.1 K.

The cooling liquid was supplied by a Hetofrig cooling bath, type CB 6, together with a Heto thermostat, type 01 PT 623, capable of keeping the preset temperature at $\pm 0.05 - \pm 0.001$ K depending on the temperature chosen. Due to the non-optimal design of the polarimeter cells and the cell compartment, the temperature in the cell fluctuated somewhat, at most ± 0.1 K during any run. The temperature range was from 237.0 K to 267.3 K. The measurements were distributed fairly evenly throughout the interval with the largest density of measurements at higher temperatures. The largest temperature difference between two runs occurred at low temperatures and was slightly less than one degree.

The solvent used was Merck "Methanol zur Analyse" which was used without further purification.

The individual rate constants were calculated using the least squares method. The activation parameters for inversion were then calculated from an Eyring-plot using a weighted least squares method to find the best line through the points. The calculations were done on an IBM 365/65 computer using standard linear regression analysis routines.

(-)-1-(1-Naphthyl)-isoquinoline. A solution of (-)-1-(1-naphthyl)-isoquinolinium α -bromo-

camphor- π -sulfonate⁴ (5 mg ml⁻¹ in methanol) was added to Amberlite IRA 400 ion exchange resin in the OH-form (0.5 g per ml of the salt solution) in a test tube inserted in a cooling medium kept at $-20 \pm 1^\circ\text{C}$. After stirring for 2 min, the solution was filtered into the cooled polarimeter cell. The initial rotation was measured 5 min after contact with the ion exchange resin. In each run the rotation was followed to zero and remained there, within experimental error. After completion of the first 10 runs the solutions were evaporated to dryness. The IR-spectra (in KBr) of these residues were identical to the spectrum of racemic 1-(1-naphthyl)-isoquinoline.

RESULTS AND DISCUSSION

The initial rotations obtained for the different (-)-1-(1-naphthyl)-isoquinoline solutions seemed to vary at random. It was found very difficult to get rotations higher than 1° , even with higher initial concentrations of optically active salt, apparently because the free base **1** is adsorbed or trapped to some extent in the polymer matrix of the ion exchange resin at the low temperatures used. Out of the 113 runs 79 had an initial rotation between 0.5 and 1° and the other 34 had rotations between 0.1 and 0.5° .

The standard errors in the rate constants did not show any correlation with the magnitude of the rotations obtained. Although the relative errors tend to be larger at higher temperatures, this trend is not constant. The range of the standard errors was from 0.2 to 3.5 % with the majority of the errors less than 1 %. Table 1 shows results obtained in a few typical runs taken from the whole temperature range.

Table 1. Rate constants for racemization of (-)-1-(1-naphthyl)-isoquinoline obtained in some typical runs.

Temp. K	$k \times 10^4$ sec ⁻¹	Standard deviation $\times 10^6$ sec ⁻¹
242.8	1.35	0.48
246.6	2.80	0.49
253.2	7.18	2.5
258.2	11.8	6.3
262.7	41.0	80.0
266.4	57.0	100.0

Table 2. Enthalpy and entropy of activation for inversion of 1-(1-naphthyl)-isoquinoline (1) and 1,1'-binaphthyl (2).

Compound	Solvent	Temp. range K	$\Delta H^\ddagger$ kJ mol ⁻¹	$\Delta S^\ddagger$ J mol ⁻¹ K ⁻¹
1	methanol	237.0–267.3	80.4 ± 1.7	7.1 ± 6.7
2 ^a	DMF	295.3–337.2	89.9 ± 0.8	–33.4 ± 2.4
2 ^b	DMF	—	91.6	–21.8

^a Calculated from the values given in Ref. 11 in kcal mol⁻¹ and corresponding e.u. ^b Calculated from the values given in Ref. 10 in kcal mol⁻¹ and corresponding e.u., no error limits are available from this work.

All runs were included in an Eyring-plot and were weighted statistically by the inverse of the variance (σ^2) resulting from the least-squares calculation of the rate constant. A least-squares treatment of the rate data, plotted as $\ln(k/T)$ vs. $1/T$ and weighted by $1/\sigma^2$, yielded a $\Delta H^\ddagger$ for inversion of 80.4 ± 1.7 kJ mol⁻¹ and a $\Delta S^\ddagger$ for inversion of 7.1 ± 6.7 J mol⁻¹ K⁻¹. The errors are given here as twice the standard error derived from the weighted least-squares treatment. Table 2 contains $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for 1 and the corresponding data available for 2.^{10,11}

The results show that the large difference in optical stability between 1 and 2, $\Delta \Delta G^\ddagger = -20$ kJ mol⁻¹ at -20°C ,⁴ is to a large extent due to the difference in $\Delta S^\ddagger$.

No information exists, of course, about the exact path of racemization of 1 and 2, i.e. whether they undergo inversion through the transoid or the cisoid transition state. Cooke and Harris assumed that 2 and similar compounds undergo inversion through two transoid transition states (with the interfering atoms passing each other one pair at a time) but point out that this choice is arbitrary.¹⁰

If one makes the reasonable but perhaps erroneous assumption that both compounds undergo inversion through similar transition states, then the conclusion is that the steric volume of the free electron pair on nitrogen, while less than that for hydrogen, is still of the same order of magnitude. This is supported by crystallographic work on SbOF.¹³ The configuration around antimony in the crystal structure is typical for an element having a stereochemically active lone pair and similar to the structures of Sb₂O₄, SbNbO₄ and SbPO₄.^{14,15}

In these structures the stereochemically active lone pair is more extended than a bonding pair and requires more room on the surface of the atom.

Finally, even if 1 and 2 undergo inversion through different transition states, the non-bonded interaction between hydrogen and the lone pair must be appreciable. If the barrier consisted only of H...H non-bonded interaction and no contribution from interactions involving the lone pair, then the former interaction would probably be almost completely relieved in the transition state by bending of the pivot bond, and the rate of racemization would be too fast for observation.

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