Activation Parameters for Inversion of 1-(1-Naphthyl)-isoquinoline. III.* Dependence on Acidity of the Rate of Inversion of 1-(1-Naphthyl)-isoquinolinium Chloride

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The rate of inversion of 1-(1-naphthyl)-isoquinolinium chloride has been determined at 20 °C in ethanol solutions of different H_0 . The results give a limiting rate corresponding to a free energy of activation for inversion of 95.9 ± 0.3 kJ mol⁻¹ at $H_0 \approx -0.8$. This is compared with the barrier to inversion of 1,1'-binaphthyl and interpreted as support for the assumption that the two systems undergo inversion through similar transition states.

1-(1-Naphthyl)-isoquinoline **1** presents an interesting case of biphenyl-like atropisomerism in which the barrier to inversion partly consists of steric interaction between hydrogen and the lone electron pair on nitrogen. The successful resolution of **1** depends on the fact that its conjugate acid has a considerably higher barrier to inversion than has the free base.¹ Preliminary data on the racemization of (–)-1-(1-naphthyl)-isoquinolinium chloride show that, due to the rather low basicity of **1** ($pK_a \approx 3.8$ in 95 % v.v. aqueous ethanol), the rate of racemization is acidity dependent.¹ The measured rate of racemization appeared to be a composite of the rate of racemization *via* the cation and *via* the free base.

The protonation of **1** affects the rate of racemization in two ways, partly due to the assumed increase in steric interaction and partly due to an inductive effect similar to that found on protonation of 4,4'-biquinolyl **2**.² The latter effect probably changes the rate of

racemization to a minor extent only. Crawford and Ingle² have shown that *monoprotonated 2* racemizes only 20 % slower than does the free base.

The rate of inversion of **1** compared to that of its conjugate acid could therefore be expected to yield a qualitative estimate of the difference in steric "size" between the lone pair and hydrogen. Contrary to the earlier comparison between the activation parameters for inversion of **1** and those for 1,1'-binaphthyl,³ such a comparison would be independent of an assumed similarity between the latter molecule and **1**. On the other hand, the difference in charge between **1** and its conjugate acid is an inevitable fact tending to obscure the interpretation of the experimental evidence.

In order to measure separately the rate of racemization of the hydrochloride of **1**, the rate was studied as a function of H_0 . The limiting rate of racemization of the hydrochloride at low H_0 values should yield the rate of racemization of the cation.

* For Part I and II of this series see Refs. 1 and 3.

EXPERIMENTAL

Kinetic runs were performed on a ZEISS OLD 5 polarimeter with digital output at the wave-length 436 nm. The polarimeter cell was a 10 cm microcell with vacuum windows custom-made by LKB-BECKMAN Instruments AB. The error in each reading determined on the pure H_0 solutions was $\pm 0.001^\circ$. The temperature in the cells was measured using a calibrated thermistor and a Fluke 8300 A digital voltmeter with BCD outlet. The thermistor was calibrated against a Hewlett Packard 2801 A quartz thermometer to a precision of ± 0.1 K and was capable of measuring temperature changes of ± 0.0013 K. The constant-temperature medium was supplied by a Heto-therm Ultrathermostat 02 Pt 623 UO. The temperature setting was adjusted to 293.16 K using a mercury thermometer calibrated to ± 0.01 K. The polarimeter and the voltmeter were interfaced on-line to a Compucorp 425 Scientist programmable calculator providing automatic data collecting and statistical treatment of the data using the least squares method. In addition the highest and the lowest temperature in each run were recorded. The temperature fluctuation did not exceed ± 0.1 K in any run and in 87 % of the runs it was less than 0.03 K. The interface was custom-made by Scandia Metric.

The H_0 solutions were prepared from 99.5 % ethanol diluted to 95 % v.v. ethanol with distilled water using a stock solution of 12.5 M HCl in 95 % v.v. ethanol. The molarity of each solution was determined by titration with 0.1 M NaOH solution on a Radiometer Titri-graph automatic titrator. The H_0 of the solution was then calculated by interpolation using the data given in Refs. 4 and 5.

All attempts to obtain crystalline optically active 1-(1-naphthyl)-isoquinolinium chloride have failed as previously reported.¹ Solutions of (–)-1-(1-naphthyl)-isoquinolinium chloride at different H_0 were prepared in the following way: A methanolic solution of (–)-1-(1-naphthyl)-isoquinoline was prepared at -20°C from (–)-1-(1-naphthyl)-isoquinolinium α -bromo-camphor- π -sulfonate by the method previously described.^{1,3} The solution was immediately added to a slight excess of HCl in absolute methanol kept at -80°C and then quickly freeze-dried to a viscous yellow glass by means of a mercury diffusion pump and a vapor trap cooled with liquid nitrogen. Ethanolic HCl solution (5 ml), with the desired H_0 and kept at -80°C , was then added, and the sample was kept at dry-ice temperature until used. Samples kept in this way were sufficiently optically stable for 3–5 days even in solutions of the highest H_0 used. In 81 % of the samples the absolute rotation was between 1.4 and 0.5° , only one sample had starting rotation below 0.3° . From each batch one run was followed until no further change in optical activity could

be observed. This was done in order to check that no residual impurity due to optically active anion was present. All runs from batches with residual rotation were discarded.

The resulting H_0 of a batch was subject to small errors due to the method of preparation. Because of the tendency of the hydrochloride of 1 to form a glass on freeze-drying rather than crystals, complete removal of residual methanol was found to be impossible. The amount of residual methanol, however, is probably very small and certainly less than 1 % of the final volume of the batch. The freeze-drying was monitored by visual inspection and the H_0 solution was not added until the glass was too viscous to flow. In addition, the solutions of H_0 lower than -0.3 did not wet the polarimeter cell directly. In order to fill the cell without bubbles in the light-path, it was necessary to wet it first with ethanol and then wash it out a number of times with reference solution of the desired H_0 . The error produced by this practice is also assumed to be quite small, and in view of the approximate character of the H_0 function, the total error in H_0 is certainly unimportant in the present context.

The racemization reactions appeared to follow strictly first-order kinetics, $\ln(\alpha_0/\alpha_t)$ plotted against time yielding straight lines with regression coefficients larger than 0.995 in 93 % of the

Fig. 1. Logarithmic plot of the rate of racemization of (–)-1-(1-naphthyl)-isoquinolinium chloride at 293.16 K as a function of H_0 . (Uncertainty in H_0 not represented.) Dotted line shows rate of racemization of 1,1'-binaphthyl in DMF solution at the same temperature, computed from the activation parameters in Ref. 6.

Table 1. Kinetic data on the racemization of (-)-1-(1-naphthyl)-isoquinolinium chloride in solutions of different H_0 .

H_0	No. of runs	$k_{\text{rac}} \times 10^4$ s^{-1}	S.D. of $k_{\text{rac}} \times 10^4$ s^{-1}	Largest deviation of $k_{\text{rac}} \times 10^4$ s^{-1}	Largest deviation of mean temperature of any run from 293.16 K.
+2.43	7	33.0	1.8	2.9	0.01
+1.52	5	4.39	0.31	0.43	0.02
+1.04	7	4.15	0.27	0.29	0.01
+0.51	5	1.53	0.08	0.09	0.03
-0.27	5	1.10	0.03	0.05	0.01
-0.60	11	0.99	0.11	0.21	0.03
-0.79	7	0.91	0.01	0.02	0.01
-0.99	5	0.90	0.04	0.05	0.01
-1.38	6	1.08	0.05	0.07	0.04
-2.38	5	1.39	0.04	0.06	0.10
-3.26	4	1.23	0.10	0.21	0.10
-3.35	6	1.39	0.03	0.04	0.01

runs. Lower regression coefficients were generally connected with large deviations from the mean temperature of the run.

RESULTS AND DISCUSSION

The kinetic data were obtained for eleven values of H_0 between +2.43 and -3.35 with the greatest density of measurements in the region with limiting racemization rates. The results are listed in Table 1 along with the largest deviations of the mean temperatures of the runs from 293.16 K. The presence of residual impurity of the optically active anion was shown to alter the kinetic results but, as mentioned in the Experimental Section, each batch of (-)-1-(1-naphthyl)-isoquinolinium chloride solution was checked for residual rotation and runs from batches with permanent optical activity were discarded. This criterion of purity is quite sensitive since the specific rotation of sodium (+)- α -bromocamphor- π -sulfonate is above 200° at the wavelength 436 nm and the corresponding acid has an even higher specific rotation.

A few large interexperimental deviations occur, as can be seen from Table 1. In the region of interest, $H_0 \approx -0.2$ to -1.4, however, the mean value of k_{rac} varies only within an interval of 20 %, and the reproducibility appears to be satisfactory. The large deviation at $H_0 = -0.6$ is mainly due to a single large deviation

from the mean; this is partially corrected for by a substantially larger number of measurements at this point.

The rate of racemization has been represented as a function of H_0 in the plot of Fig. 1. It can be seen that the rate of racemization goes through a shallow minimum at $k_{\text{rac}} = (1.0 \pm 0.1) \times 10^{-4} \text{ s}^{-1}$ and increases slightly at very low H_0 . The latter feature is similar to the behaviour of 2 which also shows a slight increase in the rate of racemization at very low H_0 . Crawford and Ingle² suggest that this effect may be due to further protonation of diprotonated 2 at one of the pivot-bond carbons, resulting in a tetrahedral intermediate which can undergo inversion readily *via* rotation about the pivot bond which is then a true single bond. Another explanation may be that salt effects become very important at low H_0 values with the inevitable high ionic strength. Berntson *et al.*⁷ found a linear relation between $\ln k$ and the ionic strength in the racemization of the 2,2'-diiodo-4,4'-dicarboxybiphenyl dianion. They did not follow the relation further than to approximately $J = 1.5$ and it is unlikely that the relation remains linear at ionic strengths greater than that. The observed increase in the rate of racemization at low H_0 values, however, is rather small suggesting that erratic salt effects may interfere.

While rates of racemization are the quantities observed, the quantity of interest in this investigation is the free energy of activation for

inversion. This was calculated using the equations:⁸

$$k_{\text{rac}} = 2k_{\text{inv}}$$

$$\Delta G^\ddagger = RT[\ln(k/h) - \ln(k_{\text{inv}}T)]$$

The limiting free energy of activation for inversion of protonated **1** is thus found to be 95.9 ± 0.3 kJ mol⁻¹, close to that for 1,1'-binaphthyl which has been measured by two independent research teams.^{6,9} From the data in Refs. 6 and 9 the barrier to inversion for 1,1'-binaphthyl in DMF solution at 293.16 K has been calculated to be 99.7 ± 1.5 kJ mol⁻¹, and 98.0 kJ mol⁻¹, respectively. Detailed analyses of bond lengths and angles in the rings of monoazanaphthalenes have not yet been published, but Crawford and Ingle⁸ have argued that the non-bonded distances of importance should be slightly greater in **2** than in 1,1'-binaphthyl. Similar arguments imply that the same non-bonded distances in protonated **1** should also be slightly greater than in 1,1'-binaphthyl. This would presumably explain why the barrier to inversion of protonated **1** is lower than that for 1,1'-binaphthyl. One cannot exclude, of course, the possibility that the small difference in $\Delta G^\ddagger$ for inversion is due to a difference in $\Delta S^\ddagger$ for inversion. The entropies of activation for inversion of biphenyls and biphenyl-like compounds are known to range between +36 and -68 J mol⁻¹ K⁻¹.¹⁰

The close similarity in molecular structure and barrier to inversion of protonated **1** and 1,1'-binaphthyl supports the reasonable assumption that the two systems undergo inversion through similar transition states. The suggestion that **1** and similar systems may be used to estimate the van der Waals volume of the lone electron pair in comparison to that of hydrogen¹ seems to be strongly supported by the present results.

A study of the temperature dependence of the limiting racemization rate was not undertaken for the following reason. The limiting racemization rate for protonated **1** has to be measured at high ionic strength in ethanol. Carter and Berntsson^{7,11,12} have unambiguously shown the necessity of eliminating salt effects from the Eyring plot by extrapolating the rate constants to infinite dilution. It would be possible, of course, to do a temperature variation of the racemization rate at a specific H_0 value, e.g. $H_0 = -0.8$. The change in H_0 with temperature

is probably not very large and the rates of racemization are not very sensitive to small changes in H_0 , as can be seen from Fig. 1. The results could undoubtedly yield some information about changes in solvation and similar intermolecular changes as the molecule passes into the transition state for inversion. In the present context, however, only intramolecular changes are of interest, and it seems impossible to determine activation parameters for these separately.

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