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Activation Parameters for Inversion of 1-(1-Naphthyl)-isoquinoline. I. Synthesis and Optical Resolution of 1-(1-Naphthyl)-isoquinoline

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1-(1-Naphthyl)-isoquinoline has been synthesized and resolved by a second-order asymmetric transformation of the 1-(1-naphthyl)-isoquinolinium α-bromocamphor-π-sulfonate, which mutarotates in solution. The half-life for mutarotation of the bromocamphor sulfonate varies with the acidity of the solvent. This has been interpreted as evidence that the compound racemizes partly as the free base in equilibrium with the conjugate acid.

(−)-1-(1-Naphthyl)-isoquinolinium chloride was obtained in methanolic hydrochloric acid by ion exchange on an anion exchange resin at −15°C, $[\alpha]_{436}^{-15} = -161°$ ($c = 0.29$ g/100 ml).

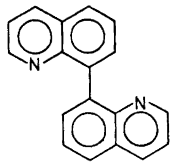
The free base (−)-1-(1-naphthyl)-isoquinoline was liberated optically active in methanol at −20° by neutralization of the α-bromocamphor-π-sulfonate salt with anion exchange resin in the OH^- form and subsequent filtration; $[\alpha]_{436}^{-20} = -140°$ ($c = 0.1$ g/100 ml MeOH). The half-life for racemization is 13 min at −20°, corresponding to a $\Delta\Delta G^{\ddagger}$ for inversion of 18.6 kcal mol^{-1}.

Atropisomerism is well known in the biphenyl and the binaphthyl series and has been observed in a number of heterocyclic series such as the biquinolyls [1] and the biisoquinolyls.[2] The optical stability in these series is usually lower than for the corresponding carbocycles especially when nitrogen occupies a "blocking" position. For example the 8,8′-biquinolyl *1* has been reported to be unresolvable,[3] and the 1,1′-biisoquinolyl *2* has been found to exhibit evidence of mutarotation of its basic hydrogen tartrate.[2]

The optical stability of these compounds, with the free electron pair on nitrogen in a blocking position, relative to the optical stability of 1,1′-binaphthyl can be used as a criterion of the steric requirements of the lone pair compared to hydrogen.

The limited data available suggest that the steric requirements of the lone electron pair in these compounds are negligible. They do not explain, however,

why these compounds are not easily resclvable as the conjugate acids. The latter should be appreciably more stable than the bases and to a first approximation be comparable in stability to 1,1'-binaphthyl which is fairly stable at room temperature ($t_{1/2}$ = 14.5 min at 50°).[4]



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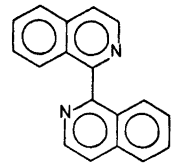

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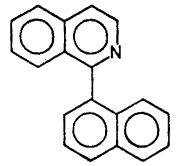

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One reason for the apparent low optical stability of the conjugate acids of *1* and *2* may be the rather low basicity of the corresponding bases. The conjugate acids of *1* and *2* would be expected to be in equilibrium with appreciable quantities of monoprotonated base and free base in solution, offering a lower energy path for racemization.

To test this hypothesis and perhaps gain some insight into the steric requirements of the free electron pair, it was decided to synthesize 1-(1-naphthyl)-isoquinoline *3* and to obtain it in optically active form by means of some suitable optically active acid.

It was thought that the barrier to inversion in this compound should be reasonably high; the choice was influenced by the report on mutarotation in solution of the basic hydrogen tartrate of *2*.[2]

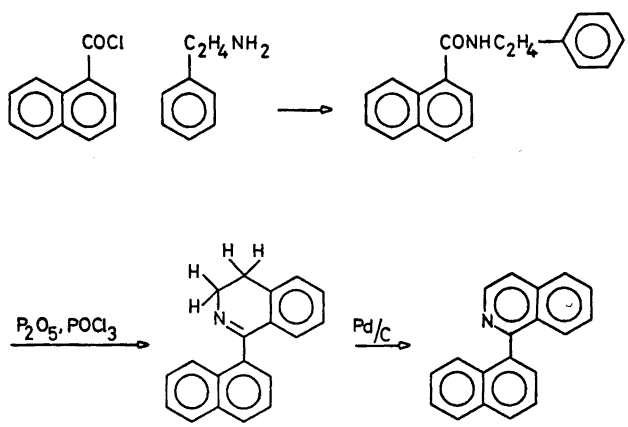
1-(1-Naphthyl)-isoquinoline was synthesized by the Bischler-Napieralski method from 1-naphthoyl chloride and β-phenethylamine,[5,6] with subsequent dehydrogenation of the resulting 2,3-dihydroisoquinoline using palladium on carbon catalyst in boiling mesitylene,[7,8] Scheme 1.

The resolution was complicated by the low basicity of the base *3*, $pK_a = 3.8$ in 50 % aqueous methanol, compared to $pK_a = 5.4$ for unsubstituted isoquinoline.[9]

The usual acid resolving agents, tartaric, malic, mandelic, quinic, and 10-camphorsulfonic acids, yielded only oils with *3* in organic solvents, and even with 10-camphorsulfonic acid the free base crystallized out from aqueous solutions.

Resolution was finally accomplished with (+)-α-bromocamphor-π-sulfonic

SCHEME 1



acid in a xylene, chloroform, and acetone mixture, v/v 50:10:5, that was slowly evaporated with agitation at room temperature over a fortnight.

The resulting diastereomeric salt mutarotated in methanol solution with a half-life of 1.7 min at 23.6°C. In 1 N methanolic hydrogen chloride the rate of mutarotation was considerably slowed down; the half-life was then 23 min at 25°C. The difference in rate suggests that the conjugate acid of 1-(1-naphthyl)-isoquinoline is in equilibrium with appreciable quantities of free base in the less acidic solution.

RESULTS AND DISCUSSION

(−)-1-(1-Naphthyl)-isoquinolinium chloride was obtained in 1 N methanolic HCl solution by ion exchange on a column of anion exchange resin at −20°C, and the product was shown to be free of residual traces of the optically active anion. Attempts to obtain active material in crystalline form failed because of the tendency of the compound to form supersaturated solutions, the residue on freeze-drying being a glass which, due to the time lag in removing the last hydrochloric acid, was racemized before any measurements could be attempted.

Racemization of the chloride was followed in 1 N methanolic HCl solution with an initial specific rotation of $[\alpha]_{436}^{15} = -161°$, the half-life at this temperature being 165 min corresponding to a $\Delta G^{\ddagger}$ for *inversion* of 23 kcal mol^{-1}, or $\Delta G^{\ddagger}$ for racemization of 22 kcal mol^{-1} (rounded off to two significant figures). This should be compared to $\Delta G^{\ddagger}$ for racemization of binaphthyl, which can be calculated from the activation parameters given in Refs. 4 and 10 to be 23.4 and 23.79 kcal mol^{-1}, respectively, both measured in dimethyl-

formamide solution. The assumption that the conjugate acid of *3* should to a first approximation have the same optical stability as 1,1′-binaphthyl seems to be valid.

The data are unsuitable for any quantitative comparison, however, as the 1-(1-naphthyl)-isoquinolinium chloride has a charged center near the pivot bond and presumably racemizes as the ion pair. It has been shown [11–13] that salt effects are important in racemization of charged biphenyls, and thus specific racemization rates should be extrapolated to infinite dilution to obtain better defined activation parameters. In this case, besides, the observed rate is a composite of the rate of inversion of the free base and the rate of inversion of the conjugate acid. These two rates can probably be separated by measuring the rate of racemization in solutions of different H_0, and this will be the subject of a future paper.

(−)-1-(1-Naphthyl)-isoquinoline was obtained in solution by neutralization of its salt with (+)-α-bromocamphor-π-sulfonic acid in methanol with an excess amount of anion exchange resin in the OH^- form at −20°. The solution was shown to be free of any contaminating optically active acid and had an initial specific rotation of $[\alpha]_{436}^{-20} = -140°$. The solution racemized at −20° with a half-life of 13 min which corresponds to a $\Delta G^{\ddagger}$ for *inversion* of 18.6 kcal mol^{-1}.

The relatively low optical stability of the free base compared to 1,1′-binaphthyl [4,10] with $\Delta\Delta G^{\ddagger} \sim 5$ kcal mol^{-1} at −20°, suggests that the steric requirements of the lone electron pair are indeed much less than those for hydrogen but not negligible. Unfortunately the available data are insufficient for anything but qualitative interpretation, but even with precise experimental values of the activation parameters, it would not be possible to make quantitative comparisons of the van der Waals potentials of the electron pair and hydrogen, as the transition state for inversion of *3* is unsymmetric.

Besides that, there is one further complication, that the dimensions of the isoquinoline moiety are not equal to the dimensions of naphthalene. To a *first* approximation, however, one may assume that the two ring systems are equal in size.[1,2] Detailed analyses of the bond lengths and angles of the rings in the monoazanaphthalenes have not yet been published. It seems probable, however, that the carbocyclic rings of *1*, *2*, and *3* will show similarities to naphthalene. For example, there is evidence of bond fixation in isoquinoline

Table 1.

Isoquinoline *6*		Naphthalene *7*	
Bond	Bond order	Bond order	Bond length, Å
A	0.554	0.60	1.418
B	0.530	0.50	1.421
C	0.742	0.78	1.373
D	0.586	0.54	1.423
E	0.741	0.78	1.373
F	0.536	0.50	1.421

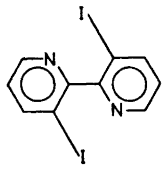
similar to naphthalene, and the reactivities of different positions are roughly parallel in the two systems.[14] SCF molecular orbital calculations for isoquinoline [15] and for naphthalene [16] give bond orders of comparable magnitude for similar bonds in the two ring systems. Formulas *6* and *7*, together with Table 1, show values of bond orders for isoquinoline and naphthalene,[15,16] and bond lengths for naphthalene.[17] While these values can only be approximately valid for the concatenated counterparts, one would not expect the differences to be large.

The results suggest that *1* and *2* may also be obtained optically active as the dihydrochlorides in very acid solution. The free bases, on the other hand, would probably be too easily racemized for accurate measurements, although $\Delta\Delta G^{\ddagger}$ relative to 1,1′-binaphthyl would not be expected to be twice $\Delta\Delta G^{\ddagger}$ for *3* relative to 1,1′-binaphthyl, as in *3* the 2′-hydrogen interaction with the 8-hydrogen might be largely relieved by bending of the 1,1′-bond in the transition state.

It would obviously be very interesting if precise activation parameters for inversion of the free bases of *1*, *2*, and *3* could be obtained and compared. But although the transition states of the free bases may be considered comparatively simple, as no bonds are broken or formed, the precise geometries are completely unknown. Even in 1,1′-binaphthyl, where the racemization may be considered relatively thoroughly studied,[4,10] the exact path of inversion is still under debate. Thus one cannot hope to extract the van der Waals potential for the repulsion of the electron pair and hydrogen from such limited data.

It would be possible, however, to get qualitative information giving the order of "effective" steric size. The "effective" steric size of the electron pair would, for instance, be expected to differ in *1* and *2* because of the directional nature of the lone pair.

The only other case which might perhaps yield a more clear-cut example of restricted rotation caused by the steric volume of the free electron pair would be 3,3′-diiodo-2,2′-bipyridyl *4*. The results of Brydowna,[18] who on



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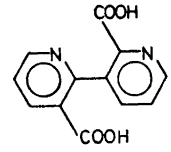

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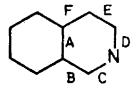

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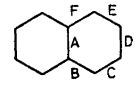

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attempted optical activation of 3,2′-dicarboxyl-2,3′-bipyridyl *5*, obtained two salts with different rotations both with strychnine and quinine, suggest that the barrier for inversion of *4* might be high enough to make resolution possible. Compound *4* would have the further advantage that it could easily be fitted into Westheimer's [19–21] classical model for inversion of biphenyls. Some information concerning the van der Waals potential for the electron pair *versus* iodine, could then be gained from the experimental value of the barrier to inversion, by the method suggested by Hill.[22]

EXPERIMENTAL

The melting points were determined with a Kofler hot-stage microscope. The infrared spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer. The UV spectra were obtained on a Cary 15 spectrophotometer. The NMR spectra were obtained with a Varian model A-60 spectrometer with tetramethylsilane used as internal reference. Kinetic runs were made on a Perkin-Elmer 141 polarimeter; the error in each reading was assumed to be 0.002°. The test solutions were contained in a 10 cm jacketed tube, and the temperature of the circulating medium was kept at ±0.1° with a Haake FT thermostat for the runs over 0°C, and at ±0.5°C with a Lauda Ultra-Kryostat for runs below 0°C.

N(β-Phenethyl)-1-naphthoamide. To a solution of β-phenethylamine (12.1 g, 0.1 mol) and 25 ml of pyridine in 100 ml of chloroform, contained in a 500 ml three-necked flask equipped with a dropping funnel, reflux condenser and teflon stirrer, was added 1-naphthoyl chloride (14.1 g, 0.074 mol) dissolved in 50 ml of dry chloroform. The temperature rose to boiling during the addition, and the solution refluxed briefly. The mixture was left overnight at room temperature with stirring. The solvent was then evaporated on a Rotavapor and the residue, a light brown oil, was treated with 200 ml of water. The precipitated crystals, light tan in color, were filtered from the mother liquor, washed with water and dried. After recrystallization from ethanol cream colored crystals were obtained. The yield of *N*-(β-phenethyl)-1-naphthoamide was 18.2 g (90 %), with m.p. 112 – 114°. The IR spectrum of the product has bands at 3250 cm^{-1} (NH stretching amide), and at 1640, 1545, and 1310 cm^{-1} (amide I, II, and III). The NMR spectrum in chloroform-*d* consists of a triplet at δ 2.9 (CH_2), a quartet at δ 3.6 (CH_2), a broad band at δ 6.2 (amide proton), and a multiplet at δ 7.0 – 8.3 (aromatic protons), with a ratio of intensities of 2 : 2 : 1 : 12. The quartet at δ 3.6 became a triplet in a double resonance experiment by decoupling the amide proton at δ 6.2.

1-(1-Naphthyl)-3,4-dihydro-isoquinoline. To a solution of *N*-(β-phenethyl)-1-naphthoamide (16 g, 0.057 mol) and 500 ml of dry distilled xylene in a round-bottomed three-necked flask, equipped with reflux condenser and teflon stirrer, P_2O_5 (50 g, 0.35 mol) and 50 ml of $POCl_3$ were added. The mixture was kept at a gentle reflux overnight. After cooling the mixture was poured onto ice and neutralized with 5 N NaOH solution. The xylene layer was separated, treated with active carbon, dried over Na_2SO_4 and evaporated on a Rotavapor. The dark brown residue was recrystallized repeatedly from ethanol yielding pure 1-(1-naphthyl)-3,4-dihydro-isoquinoline, 10 g (60 %) with a melting point of 141 – 142°. Its NMR spectrum in chloroform-*d* consists of a quartet at δ 2.9 (CH_2), a quartet at δ 4.0 (CH_2) and a multiplet at δ 6.7 – 8.0 (aromatic protons), with a ratio of intensities of 2:2:11.

1-(1-Naphthyl)-isoquinoline. In a 100 ml three-necked flask fitted with reflux condenser, teflon stirrer, and gas-inlet tube 1-(1-naphthyl)-3,4-dihydro-isoquinoline (6 g, 0.0233 mol) and 0.5 g of palladium-on-carbon catalyst were suspended in 50 ml of distilled mesitylene. The mixture was refluxed for 30 h with a slow stream of CO_2 passed through the suspension during the reflux period. The mixture was filtered hot and the solution was evaporated to dryness on a Rotavapor. The product was recrystallized three times from dilute ethanol, yielding 3.6 g of pure 1-(1-naphthyl)-isoquinoline (60 %), melting at 102 – 103°. The NMR spectrum in chloroform-*d* consists of a multiplet centered at δ 7.8 and contains no signal from methylene protons of possible starting material. The UV spectrum is similar to the spectra of 1,1′-, 4,4′-, 5,5′-, and 8,8′-biisoquinolyls,[2] ε_{222} =

1.1×10^5, $\varepsilon_{282} = 1.0 \times 10^4$, $\varepsilon_{324} = 6.0 \times 10^3$. The IR spectrum has bands at 3030 cm^{-1} (aromatic CH stretching), at 1620, 1585, 1560, and 1500 cm^{-1} (C=C stretching and C=N stretching in rings). A high-resolution mass spectrum contained a weak parent peak with $m/e = 255.1054 \pm 0.0025$; calc. for $C_{19}H_{13}N$ $m/e = 255.1048$. The mass of the $P-1$ peak was $m/e = 254.0984 \pm 0.0025$; calc. for $C_{19}H_{12}N$ $m/e = 254.0970$.

1-(1-Naphthyl)-isoquinolinium chloride. 1-(1-Naphthyl)-isoquinoline (5 g, 0.0196 mol) was dissolved in 100 ml of dry ether, the solution was cooled in an ice bath and saturated with hydrogen chloride. The solution was left for 30 min and the precipitated crystals were filtered, washed with dry ether and dried in a desiccator. Yield 5.5 g of pure 1-(1-naphthyl)-isoquinolinium chloride, m.p. 156–158°. The IR spectrum was similar to that of the free base but contained in addition two broad absorption bands at 2400–2200 and 2100–2000 cm^{-1}, "ammonium bands". The UV spectrum in 5 N HCl was similar to that of the base, $\varepsilon_{221} = 1.15 \times 10^5$, $\varepsilon_{282} = 1.0 \times 10^4$, $\varepsilon_{323} = 6.4 \times 10^3$.

(−)-1-(1-Naphthyl)-isoquinolinium α-bromocamphor-π-sulfonate. 1-(1-Naphthyl)-isoquinolinium chloride (0.2915 g, 0.001 mol) and (+)-α-bromocamphor-π-sulfonic acid ammonium salt (Aldrich) (0.312 g, 0.001 mol) were dissolved in 25 ml of 5 N sulfuric acid, and the solution was extracted repeatedly with 10 ml portions of chloroform. After each extraction the rotatory power of the sulfuric acid solution was measured. Extraction was continued until the measured rotation was $0.000 \pm 0.002°$ (6 extractions). The chloroform solution was dried over Na_2SO_4, evaporated to a volume of 10 ml and added to 50 ml of dry distilled xylene. The solution was left at room temperature with magnetic stirring in an open flask in the fume hood. After three days an oil separated on the walls of the flask. The oil was washed down into the solution with 5 ml of acetone, and after one day crystals began to precipitate. After a total time of two weeks 5 ml of solution and a mass of crystals remained. The crystals were filtered off and dried in a desiccator over solid paraffin. The yield was 0.498 g (90 %), m.p. 113–115°. A sample of 0.0121 g of the salt was dissolved in 2 ml of 1 N methanolic HCl at 25°C. $\alpha_{initial} = -0.004°$. The solution mutarotated to a value of $\alpha = +0.546°$ in 82 min; the subsequent change in rotation was very slow. The half-life was calculated to be 23 min by fitting the experimental data to the equation for a first-order reaction, using the method of least squares. The solution was made alkaline with 5 ml of 2 N NaOH solution and extracted with 5 ml of chloroform. The IR spectrum obtained after evaporation of the chloroform was identical with the spectrum of racemic 1-(1-naphthyl)-isoquinoline.

The mutarotation was also followed in methanol solution at 0.5°C and at 23.6°C, the half-lives being 8.4 min and 1.7 min, respectively. The strong dependence of the rate of mutarotation on solvent acidity suggests that the compound racemizes partly as free base in equilibrium with the conjugate acid.

Racemization of (−)-1-(1-naphthyl)-isoquinolinium chloride. (−)-(1-Naphthyl)-isoquinolinium α-bromocamphor-π-sulfonate (0.030 g, 5×10^{-5} mol) was dissolved in 2 ml of 1 N methanolic HCl at −10°C. The solution was ion-exchanged on a jacketed ion-exchange column (25 g of Amberlite IRA 400) in the chloride form. The temperature of the column was kept at −10°C by circulating cooling liquid from a cryostat through the jacket of the column. The fractions were cooled to dry-ice temperature immediately after leaving the column. The optically active fraction had a specific rotation of $[\alpha]_{436}^{15} = -161 \pm 6°$. The concentration was determined in the following way: 1 ml of the solution was pipetted into a tared 5 ml round-bottomed flask and evaporated to dryness on a Rotavapor; the residue weighed 0.0029 ± 0.0001 g. The solution racemized at 15.0 ± 0.1°C with a half-life of 165 min. This corresponds to a $\Delta G^{\ddagger}$ for inversion of 23 kcal mol^{-1}. The racemization was followed to $0.000 \pm 0.002°$ and the solution was left at room temperature overnight to check for residual rotation. The rotation remained 0° within the limits of experimental error.

A 10 mg sample was ion-exchanged at a somewhat lower temperature and the optically active fraction was freeze-dried in vacuum at −20° (50 h). Due to the tendency of 1-(1-naphthyl)-isoquinolinium chloride to form supersaturated solutions, only a glass was formed. When dissolved in methanol the product showed no optical activity. The IR spectrum of the glass was identical with the spectrum of racemic 1-(1-naphthyl)-isoquinolinium chloride.

Racemization of (−)-1-(1-naphthyl)-isoquinoline. (−)-1-(1-Naphthyl)-isoquinolinium α-bromocamphor-π-sulfonate (5 mg, 9×10^{-6} mol) was dissolved in a slurry of 2 g of Amberlite IRA 400 ion exchange resin in the OH-form and 2 ml of methanol in a 5 ml

test tube. The test tube was inserted in the cooling medium of a cryostat kept at $-20 \pm 0.5°$ and the salt dissolved very slowly. After 5 min stirring with a spatula the solution was filtered into the cooled polarimeter tube. The initial rotation was measured 8 min after wetting of the crystals, $\alpha_{436} = -0.139°$. The racemization was folllowed at $-20 \pm 0.5°$ to $\alpha_{436} = 0.000 \pm 0.002°$ and the rate constant $k_{rac} = 8.7 \pm 0.3 \times 10^{-4}$ s^{-1} was calculated by the least squares method. The corresponding half-life is 13.2 min. This corresponds to a $\Delta G^{\ddagger}$ of 18.6 kcal mol^{-1}. The solution was left at room temperature overnight to check on any residual rotation, but α remained 0° within the experimental error. A sample of 1 ml of the solution was pipetted into a tared 5 ml round-bottomed flask and evaporated to dryness on a Rotavapor. The residue weighed 1.0 ± 0.1 mg. From this the initial specific rotation was calculated to $[\alpha]_{436}^{-20} = -139 \pm 14°$. The IR spectrum of the residue was identical to the spectrum of the racemic base.

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