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A ^{1}H Nuclear Magnetic Resonance Spectroscopic Study of Hindered Rotation about the Amide Bond in Some *N*-Formyl-2-indolinols

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The ^{1}H nuclear magnetic resonance spectra of a series of *N*-formyl-2-indolinols (I) and of two of their open-chain tautomers (II) are presented and discussed. Conclusive evidence for the existence of restricted rotation about the amide bond in the cyclic tautomers has been found. When both of the torsional single bond isomers are present in solution, the ratio of the two forms shows a large solvent dependency. For *N*-formyl-2-indolinol (Ia) the energy of the rotational barrier and other thermodynamic parameters have been calculated from the temperature dependence of the spectrum.

As part of our previous structure determination of *N*-acyl-2-indolinols (I) and their open-chain tautomers (II) [1–3] we employed ^{1}H nuclear magnetic resonance spectroscopy. It was found that these compounds preferentially existed as the cyclic tautomers (I) when X^2=H and as the open-chain tautomers (II) in other cases. It was furthermore shown that *N*-acetyl-3-methyl-2-indolinol (Ij) [1] and its *N*-benzoyl homolog (Ik) [2] existed as mixtures of their ring diastereoisomers in solution, thus indicating the presence of an equilibrium between the cyclic tautomers I and the open-chain tautomers II when X^2=H. No signals due to the open-chain tautomers have been found in any cases where X^2=H, just as no signals due to the cyclic tautomers have been

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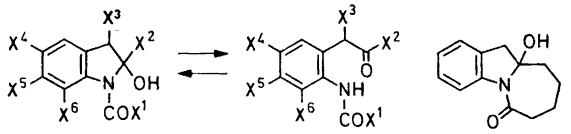


I II III

	X^1	X^2	X^3	X^4	X^5	X^6
a	H	H	H	H	H	H
b	H	H	H	CH_3	H	H
c	H	H	H	F	H	H
d	H	H	H	Br	H	H
e	H	H	H	CH_3O	H	H
f	H	H	H	H	Cl	H
g	H	H	H	H	H	CH_3
h	H	C_2H_5	H	H	H	H
i	H	C_6H_5	H	H	H	H
j	CH_3	H	CH_3	H	H	H
k	C_6H_5	H	CH_3	H	H	H

found where $X^2 \neq H$.* It should be noted, however, that mass spectrometric evidence has been recently published [5] which indicates a predominance of the open-chain tautomers in the gas phase even when $X^2 = H$.

In our preliminary communication [3] it was mentioned that the NMR spectra of the indolinols Ia, b, e recorded in DMSO-d_6 showed an extra pattern whose intensity was approximately 10 % of that of the major pattern.** Shortly after our preliminary communication,[3] Streith, Darrah and Weil [6] reported the photoinduced formation of *N*-formyl-2-indolinol (Ia). On the basis of NMR spectroscopic evidence these authors proposed that Ia was in equilibrium with measurable amounts of its open-chain tautomer IIa, and that the ring tautomer Ia existed as a mixture of two rotamers (*i.e.* restricted rotation about the amide bond gave rise to distinguishable *cis* and *trans* forms).

From an examination of the NMR spectra of a series of previously [3,7] described *N*-formyl-2-indolinols (Ia—g) which exist primarily as the ring tautomers I, we have reached the following conclusions.

All of these *N*-formyl-2-indolinols (I), with one exception (Ig), exist as mixtures of torsional single bond isomers *** arising because of restricted rotation about the amide bond (for a recent report of a closely related phenomenon see Ref. 9). The ratio of the two forms shows a remarkable solvent dependence. The spectrum of *N*-formyl-2-indolinol (Ia) was examined in a

* It is of interest to note that there is one report in the literature [4] of a preferred cyclic tautomer with $X^2 = H$, namely compound III. However, very little detail was given about the NMR spectrum of this compound.

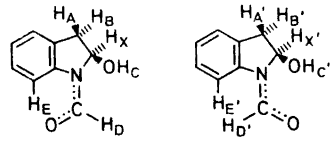
** Some less abundant signals observed earlier [3] have since been shown to be due to impurities in the solvent.

*** This nomenclature is as suggested in Ref. 8, p. 70—76.

series of solvents of varying polarity; the spectra of the other *N*-formyl-2-indolinols (Ib—g) were recorded in $CDCl_3$ and DMSO-d_6. The temperature dependence of the spectrum of Ia was also examined. No evidence for the presence of measurable amounts of the open-chain tautomers was found in any of these cases.

DISCUSSION OF SPECTRA

The frequency-swept ^1H 100 Mc/s NMR spectrum of *N*-formyl-2-indolinol (Ia) in DMSO-d_6 (Fig. 1, Table 1) shows the occurrence of two singlets, 1.29 τ and 0.90 τ, in the ratio of *ca.* 8:1, which must be due to the two formamido protons, H_D and $H_{D'}$. When the spectrum was recorded in $CDCl_3$ (Fig. 2, Table 1) there was a striking change in the intensity of these two signals and



s-trans-Ia s-cis-Ia

a small change in the chemical shifts. The higher frequency signal at 1.42 τ was less intense than the lower frequency signal at 1.18 τ, the ratio now being *ca.* 1:1.6. It has been shown (see below) that in both solvents the s-*trans* proton (H_D) occurs at higher frequency than the s-*cis* proton ($H_{D'}$), which means that the s-*trans*:s-*cis* ratio has been altered by a factor of *ca.* 13 by changing the solvent from DMSO-d_6 to $CDCl_3$. The s-*trans* isomer is the predominant one in DMSO-d_6 and the s-*cis* isomer is the predominant one in deuteriochloroform.

Since the equilibrium composition (relative amounts of s-*cis* and s-*trans* forms) of the *N*-formyl-2-indolinols (Ia—f) depends on the nature of the solvent (see Table 1), the NMR spectrum of *N*-formyl-2-indolinol (Ia) was recorded in a series of solvents with varying dielectric constants (Table 2).

Nagarajan and Nair [9] have recently shown that the preferred conformation of the amide group of *N*-formylindoline is that corresponding to s-*cis* Ia. The equilibrium ratio of the two forms showed very little solvent dependency. It can readily be seen (Table 2) that the equilibrium ratio (and thus the free energy difference) of the two forms of *N*-formyl-2-indolinol (Ia) is, however, very dependent on the nature of the solvent. In CH_2Cl_2 and $CDCl_3$ the predominant isomer is the s-*cis* form and this result is consistent with the results for *N*-formylindoline.[9] Thus, the introduction of a hydroxyl substituent at the 2-position of the indoline nucleus does not greatly affect the position of the equilibrium in these solvents. One might expect the greater steric size of the hydroxyl group (relative to a hydrogen atom) to shift the position of equilibrium to favor the s-*trans* form; it is possible, however, that the increased steric effect is offset by intramolecular hydrogen bonding of the hydroxyl group with the amide carbonyl group in the s-*cis* form. In solvents which can act as bases in hydrogen bond formation, the s-*trans* form is predominant

Table 1. NMR spectra of *N*-formyl-2-

Compound	Solvent	Form[b]	$H_D - H_{D'}$	Aromatic protons
Ia	$CDCl_3$[c]	s-*cis*(61) s-*trans*(39)	1.18,s 1.42,s	2.06,d[f], $J=8$; 2.6–3.2,m
	DMSO-d_6[d]	s-*cis*(11) s-*trans*(89)	0.90,s 1.30,s	2.04,d, $J=8$; 2.5–3.0,m
Ib	$CDCl_3$[c]	s-*cis*(80) s-*trans*(20)	1.14,s 1.37,s	2.12,d, $J=8$; 2.9–3.1,m
	DMSO-d_6[e]	s-*cis*(23) s-*trans*(77)	1.00,s 1.40,s	2.22,d, $J=8$; 2.7–3.1,m
Ic	$CDCl_3$[c]	s-*cis*(55) s-*trans*(45)	1.19,s 1.40,s	2.0–2.2,m; 2.7–3.4,m
	DMSO-d_6[c]	s-*cis*(19) s-*trans*(81)	1.03,s 1.42,s	2.13,dd, $J_1=8$, $J_2=9$; 2.6–3.2,m
Id	$CDCl_3$[c]	s-*cis*(72) s-*trans*(28)	1.06,s 1.29,s	2.05,d, $J=8$; 2.5–2.8,m
	DMSO-d_6[c]	s-*cis*(14) s-*trans*(86)	1.01,s 1.41,s	2.20,d, $J=8$; 2.5–2.8,m
Ie	$CDCl_3$[c]	s-*cis*(70) s-*trans*(30)	1.16,s 1.38,s	2.06,d, $J=8$[n]; 2.9–3.4,m
	DMSO-d_6[c]	s-*cis*(14) s-*trans*(86)	1.09,s 1.47,s	2.22,d, $J=9$; 3.0–3.5,m
If	$CDCl_3$[e]	s-*cis*(75) s-*trans*(25)	1.28,s 1.50,s	—[p]
	DMSO-d_6[c]	s-*cis*(20) s-*trans*(80)	0.98,s 1.39,s	2.12,d, $J=2$; 2.4–3.1,m
Ig	$CDCl_3$[e] DMSO-d_6[e]	s-*cis*(100) s-*cis*(100)	0.94,s 1.04,s	2.8–3.3,m 2.7–3.1,m
	Solvent	NH	N–CHO	Arom.
IIh	$CDCl_3$[e]	2.3[f]	1.75[f,l]	2.7–3.1,m
IIi	$CDCl_3$[e]	1.70[f,l]	1.70[f,l]	2.0–3.0,m

[a] Chemical shifts are reported in τ values; coupling constants are reported in cps; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets.

[b] The s-*cis* and s-*trans* nomenclature corresponds to that shown for Ia. The equilibrium percentage is given in parentheses.

[c] Frequency-swept 100 Mc/s spectrum with TMS as internal reference.

[d] Frequency-swept 100 Mc/s spectrum with TMS as external reference.

[e] Field-swept 60 Mc/s spectrum with TMS as internal reference.

[f] Broad signal.

[g] This multiplet can be resolved into 2 overlapping doublets of doublets.

[h] The signal from hydroxyl groups and water present in the solvent appeared as a broad singlet.

indolinols (I) and chain tautomers (II).[a]

$OH_C-OH_{C'}$	$H_X-H_{X'}$	$H_B-H_{B'}$	$H_A-H_{A'}$
5.4,s[f] 5.1,s[f]	3.91,dd, $J_1=7$, $J_2=3$ 4.28,d[f], $J=7$	6.45–6.85,m[g]	7.08,d, $J=17$ 7.11,d, $J=17$
6.03,s[h]	4.0,d[i] 4.05,dd, $J_1=7$, $J_2=2$	—[j] 6.54,dd, $J_1=17$, $J_2=7$	7.15,d, $J=17$ 7.03,d, $J=17$
5.84,s[h]	3.86,dd, $J_1=7$, $J_2=3$[k] 4.26,s[f]	6.68,dd, $J_1=17$, $J_2=8$ —[j]	7.07,d, $J=17$ 7.10,d, $J=18$
5.9[f]	—[j] 4.15,dd, $J_1=7$, $J_2=1.5$	—[j] 6.60,dd, $J_1=17$, $J_2=7$	—[j] 7.20,d, $J=17$
5.6[f]	3.84,dd, $J_1=7$, $J_2=3$ 4.18,d, $J=6.5$	6.3–6.9,m[g]	7.02,d, $J=17$
3.3[f]	4.22,m	—[j] 6.63,dd, $J_1=17$, $J_2=7$	7.28,d, $J=17$ 7.16,d, $J=17$
2.98,d[l], $J=8$	3.80d[l], $J\cong 7$	6.3–6.8,m[g]	6.93,d, $J=17$
3.4,m[f] 3.25,d, $J=6$	4.16,m[m]	—[j] 6.65,dd, $J_1=17$, $J_2=7$	7.27,d, $J=17$ 7.18,d, $J=17$
5.92,d, $J=3$	3.80[l] 4.25[l]	6.35–6.85,m[g]	7.07,d, $J=17$ 7.09,d, $J=17$
—[o]	4.18,m[l]	—[j] 6.68,dd, $J_1=17$, $J_2=7$	7.30,d, $J=17$ 7.20,d, $J=17$
—[p]	—[p]	—[p]	—[p]
3.43,d, $J=6$ 3.21,d, $J=6$	4.12,m[l]	—[j] 6.70,dd, $J_1=17$, $J_2=7$	7.30,d, $J=17$ 7.20,d, $J=17$
5.28,s[f] 3.57,d, $J=5$	3.79,d, $J=7$ 4.00,m[l]	6.68,dd, $J_1=17$, $J_2=7$ 6.68,dd, $J_1=17$, $J_2=6$	7.10,dd[l], $J_1=17$, $J_2=2$ 7.30,d, $J=17$
Aliphatic protons			
6.33,d[l]; 7.45,q; 8.99,t 5.78,d[l]			

[i] Partly obscured by signal centered at 4.05 τ. Coupling constant estimated *ca.* 7 cps.

[j] Obscured by corresponding signal from the s-*trans* (or s-*cis*) form.

[k] This signal sharpened remarkably by spin decoupling at 5.84 τ.

[l] Poorly resolved.

[m] This signal was changed to a sharp doublet of doublets ($J_1=7$, $J_2=1$), overlapping a poorly resolved weaker signal (from the *cis* compound), by spin decoupling at 3.25 τ, whereas spin decoupling at 6.65 τ sharpened this signal to a poorly resolved doublet, $J=ca.$ 6).

[n] Spin decoupling at 3.2 τ caused this signal to collapse to a singlet.

[o] Overlapped by other signals.

[p] Because of poor solubility in $CDCl_3$ no attempt was made to analyze the rest of the spectrum.

Table 2. Solvent dependence of the NMR spectrum[a] of *N*-formyl-2-indolinol (Ia).

Solvent	Dielectric constant	$H_{D'}$[b]	H_D[b]	% s-*trans*[c]	$-\Delta G_{39}$[d]
Dioxane	2.21	1.05	1.37	51	0.02
$CDCl_3$	4.81[e]	1.22	1.42	38	−0.30
Ethyl acetate	6.02	1.05	1.37	63	0.33
CH_2Cl_2	9.08	1.10	1.35	29	−0.56
Pyridine-d_5	12.3[e]	0.75	0.93	64	0.36
Acetone-d_6	20.7[e]	0.98	1.30	70	0.53
Methanol	33.6	1.03	1.38	70	0.53
DMSO-d_6	47.0[e]	0.90	1.30	89	1.30

[a] Field-swept 60 Mc/s spectra. All solutions were *ca.* 10 % w/v.
[b] Chemical shifts reported in τ values relative to tetramethylsilane as internal standard.
[c] Calculated from the relative intensities of $H_{D'}$ and H_D.
[d] Standard free energy difference between the s-*cis* and the s-*trans* form in kcal/mole. Evaluated from the equation: $\Delta G = -2.303\ RT \log K$ at the probe temperature, 39°.
[e] This value is for the corresponding non-deuterated solvent.

and the relative amount of this form increases with increasing polarity of the solvent. In these solvents the effective steric size of the hydroxyl group is much larger (due to hydrogen bonding with the solvent) than in CH_2Cl_2 and $CDCl_3$ and the steric factor is the major one determining the position of the equilibrium.

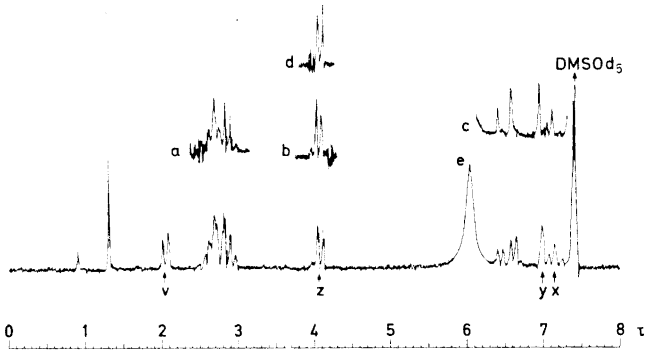


Fig. 1 100 Mc/s frequency-swept NMR spectrum of *N*-formyl-2-indolinol (Ia) in DMSO-d_6 with TMS as external reference. a. Double resonance at V; b. Double resonance at X; c. Double resonance at Z; d. Double resonance at Y; e. This signal is partly due to O*H* and partly due to water present in the solvent.

The equilibrium ratio of the two forms of *N*-formyl-2-indolinol (Ia) in $CDCl_3$ was also concentration dependent. Thus, as the concentration of Ia was varied from 10.2 to 2.1 % (w/v) the relative amount of the s-*cis* form increased from 67 % to 83 %. This suggests that the degree of association of the *N*-formyl-2-indolinols plays a significant role in determining the position of the equilibrium in non-basic solvents.

The assignment of configuration to the two isomers was made by considering the doublet centered at 2.06 τ in the spectra (Figs. 1—2, Table 1). We believe that this signal arises from the proton in the 7-position of the s-*trans* form, H_E in s-*trans*-Ia. The relative intensity of this signal in both solvents is the same as that of the signal due to H_D and corresponds to a value less than

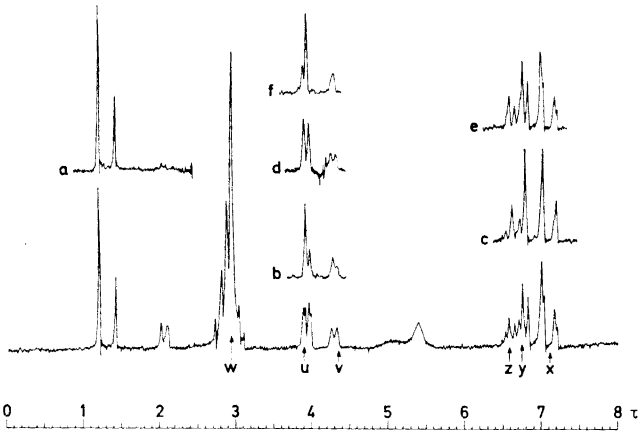


Fig. 2. 100 Mc/s frequency-swept NMR spectrum of *N*-formyl-2-indolinol (Ia) in $CDCl_3$ with TMS as external reference. a. Double resonance at W; b. Double resonance at Y; c. Double resonance at U; d. Double resonance at X; e. Double resonance at V; f. Double resonance at Z.

one proton. In the s-*trans* isomer the proximity of the amide carbonyl group and the proton in the 7-position (H_E) allows the carbonyl group to exert its influence thereby deshielding H_E. Thus, the signal due to H_E occurs at appreciably lower frequency than those from the other aromatic protons. A similar observation and conclusion was reported previously for *N*-formylindoline,[9] and it has recently been noted [10] that the signals due to the *ortho* protons in a series of *N*-phenyl amides appeared at lower field than those due to the other aromatic protons. In s-*cis*-*N*-formyl-2-indolinol (s-*cis*-Ia) the signal due to proton in the 7-position ($H_{E'}$) occurs at approximately the same field as those due to the other aromatic protons and is not readily identifiable.* That the signal at 2.06 τ in Figs. 1 and 2 is due to one of the aromatic protons and not

* By examining the previously reported NMR spectra of *N*-acetyl-[1] and *N*-benzoyl-2-indolinols [2] it is concluded that the conformation of these compounds in DMSO-d_6 is s-*trans* and not s-*cis* as previously indicated in the formulas in Refs. 1 and 2 (see also Ref. 11).

to the aldehydic proton of the chain tautomer IIa, as suggested by other workers,[6] was confirmed by double resonance (see Fig. 1, a).

The other aromatic protons in the two spectra (Figs. 1 and 2, Table 1) give rise to multiplets between 2.5 and 3.1 τ. In DMSO-d_6 the hydroxyl protons (H_C and $H_{C'}$) sometimes gave rise to two well-resolved doublets because of coupling with the corresponding methine protons (H_X and $H_{X'}$), but as a rule these signals appeared as in Fig. 1, e. In deuteriochloroform the signals due to these protons generally appeared as broad signals (see Fig. 2, 4.8—5.5 τ). In DMSO-d_6, in the absence of coupling with the hydroxyl protons, and in $CDCl_3$, the aliphatic ring protons gave rise to two overlapping ABX systems (see Figs. 1 and 2 and Table 1). These assignments were confirmed by the various spin decouplings shown on Figs. 1 and 2 and reported in Table 1. It is noteworthy that whereas the AB parts of the ABX systems in Figs. 1 and 2 have almost the same chemical shifts, Streith, Darrah and Weil [6] reported a difference in chemical shift of *ca.* 1 τ for the two doublets of doublets arising from the H_A and $H_{A'}$ protons.* In the cases where coupling occurred between the hydroxyl protons and the methine protons, the latter gave rise to doublets of doublets or triplets. Analogously to the previously discussed *N*-acetyl-2-indolinols,[1] the numerical value of the *cis* coupling constant between vicinal protons in the five-membered ring is *ca.* 7 cps, whereas that of the *trans* coupling constant is 0—3 cps.**

The temperature dependence of the low frequency region of the NMR spectrum of *N*-formyl-2-indolinol (Ia) in dioxane was investigated over the temperature range 40—90° (see Fig. 3 and discussion below). Dioxane was used as solvent for this study because it allowed a rather wide range of temperature to be investigated and because the equilibrium mixture of Ia near room temperature consists of approximately equal amounts of the s-*cis* and the s-*trans* forms in this solvent (see Table 2). At 40° the signals due to the formamido protons ($H_{D'}$ and H_D) appear as two singlets at 1.05 and 1.37 τ, respectively; the signal due to H_E (see above) appears as a broad doublet centered at 1.95 τ. As the temperature is increased the signals due to $H_{D'}$ and H_D broaden and coalesce at approximately 70°. As the temperature is increased still further, and the rate of rotation about the amide bond increases, the broad signal sharpens and appears as a singlet at 1.27 τ at 90°. As expected the doublet due to H_E also coalesces and broadens as the temperature is increased; at 90° this signal has shifted to higher frequency and is not separable from the signals due to the other aromatic protons. These facts offer conclusive proof for restricted rotation about the amide bond in *N*-formyl-2-indolinol (Ia) and substantiate our conclusion concerning restricted rotation in the *N*-formyl-2-indolinols (Ib—f).

* It seems apparent that this discrepancy arises because of a misprint in the values given in Ref. 6.

** Theoretical ABX spectra for *N*-acetyl-2-indolinol were generated by computer methods. The values used for the chemical shifts of the A, B, and X protons (270, 320, and 572 cps) and the values of J_{AB} and J_{AX} (17.0 and 7.0 cps) were taken from the observed spectrum. By varying the value of J_{BX} from 0.0—2.5 cps in the calculation, it was estimated that the actual coupling constant J_{BX} must be less than 1.0 cps. In our previous papers the value of J_{BX} was reported as 0 cps.

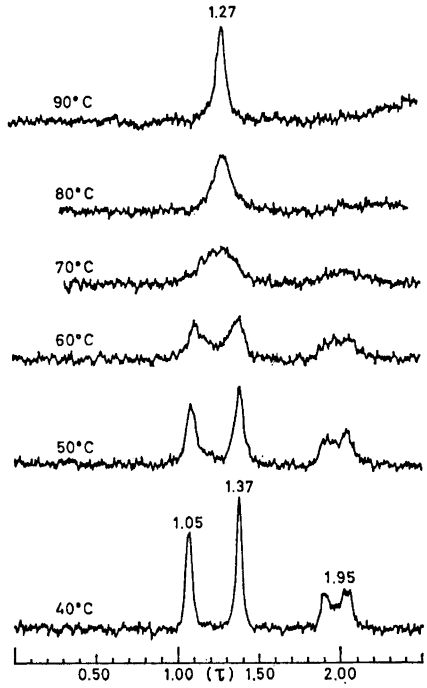


Fig. 3. Temperature dependence of low field region in the NMR spectrum of Ia.

The NMR spectra of the 5-substituted *N*-formyl-2-indolinols (Ib—e) and the 6-chloro derivative (If) were very similar to that of the unsubstituted compound (see Table 1). It is significant that in the spectrum of 5-fluoro-*N*-formyl-2-indolinol (Ic) the signal due to the proton in the 7-position appears as a doublet of doublets because of the long range F—H coupling in addition to the normal *ortho* coupling.

7-Methyl-*N*-formyl-2-indolinol (Ig), which *a priori* could be expected to exist solely in the less strained s-*cis* conformation, exhibited an NMR spectrum which was consistent with the presence of only one torsional isomer in both $CDCl_3$ and DMSO-d_6. By comparison with the spectra of the other compounds, it is concluded that this compound exists solely in the expected s-*cis* conformation (Table 1).

The two compounds with $X^2 \neq H$ gave NMR spectra (Table 1) which corresponded to the open-chain tautomers, that is 1-(2-formamidophenyl)-2-butanone (IIh) and 2-formamidophenylacetophenone (IIi), respectively. It is interesting that in the spectra of both of these compounds, the signal from the benzylic methylene protons appeared as poorly resolved doublets. This indicates a magnetic nonequivalence of these two protons, a phenomenon which was not found in the corresponding *N*-acetyl-[1] and *N*-benzoyl-[2] derivatives.

DETERMINATION OF ROTATIONAL BARRIER IN *N*-FORMYL-2-INDOLINOL

For *N*-formyl-2-indolinol (Ia) the activation energy for rotation about the C—N amide bond was calculated by two methods: the peak separation method of Gutowsky and Holm [12] and the intensity ratio method of Rogers and Woodbrey.[13] The temperature dependence of the signal(s) due to the two formamido protons (H_D and $H_{D'}$) was studied over the temperature range of 40—90°. Representative spectra (low field region only) are shown in Fig. 3; spectra were recorded at much closer temperature intervals than shown in Fig. 3 (*e.g.* 13 different temperatures in the range 50—70°). Either of the methods utilized for calculation of the rotational barrier is valid for the general two-site case; however, the mathematical treatment is much simpler when the two sites (H_D and $H_{D'}$ in the present case) are equally populated. Therefore, dioxane was used as the solvent in the present work because the s-*cis*:s-*trans* ratio for *N*-formyl-2-indolinol (Ia) is *ca.* 1 (see Table 2) and thus the relative populations (P_{H_D} and $P_{H_{D'}}$) and lifetimes (τ_{H_D} and $\tau_{H_{D'}}$) are approximately equal at the two sites.

The Gutowsky and Holm method [12] relates the experimentally observed ratio $(\delta\omega_e/\delta\omega)$ to the reorientation rate constant $(1/2\tau)$. The value $\delta\omega_e$ is the observed peak separation of the two signals and $\delta\omega$ is the chemical shift difference between the two resonances in the absence of rotational averaging ($\delta\omega$ in the present case was evaluated at 17.5° and found to be 19.5 cps). The value of $1/(T_2\,\delta\omega)$ used in the present calculations (see pertinent equations and the discussion in Ref. 12), where T_2 is related to the natural line width, was found to be *ca.* 0.05 and thus the overlap of the two signals under consideration is negligible. By fitting the rate constants to the Arrhenius equation,* utilizing a regression analysis,** values of the activation energy (E_a) and the frequency factor (A) were obtained (Table 3).

The Rogers and Woodbrey method [13] allows the determination of reaction rates from the ratio (r) of the intensities of the peaks to the intensity midway between the peaks. From the ratio r and the $\delta\omega$ value (defined as above) values of the rate of rotation can be determined as a function of temperature. The observed data were fitted to the Arrhenius equation by regression analysis ** to obtain the values for E_a and A which are given in Table 3.

Both of the above methods suffer the disadvantage that there is a very narrow range of temperatures (and thus reaction rates) for which the necessary experimental parameters can be determined. In both cases these parameters can be obtained only below the coalescence temperature (T_c) and become increasingly difficult to measure as the coalescence temperature is approached.***

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* For a recent review of analysis of chemical rate processes by NMR see Ref. 14.

** For the regression analysis the value of T (and thus $1/T$) at each temperature was assumed to be invariant and equal to the temperature as determined by the method indicated in the experimental section.

*** For a recent discussion of these problems and a comparison of the two methods, see Ref. 12b.

Table 3. Thermodynamic parameters and coalescence temperature (T_c) for *N*-formyl-2-indolinol (Ia).

Method	E_a (kcal/mole) [a]	log A [a]	$\Delta G^{\ddagger}$ (kcal/mole) [b]	$\Delta H^{\ddagger}$ (kcal/mole) [b]	$\Delta S^{\ddagger}$ (e.u.) [b]	T_c (°K)
Gutowsky and Holm	13.52 ± 0.50	10.29 ± 0.32	15.5 ± 0.50	12.84 ± 0.50	−7.8 ± 2.9	342
Rogers and Woodbrey	14.87 ± 1.28	11.04 ± 0.83	15.5 ± 1.28	14.19 ± 1.28	−3.8 ± 7.5	342

[a] The values and errors given are based upon 90 % confidence limits determined from the regression analysis.[20]

[b] The errors in $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ are assumed to be the same as in E_a. The error given for $\Delta S^{\ddagger}$ is twice the error in E_a dividided by T_c.

As a check on the validity of the above treatments in the present case, the theoretical line shapes were calculated [15] at selected temperatures (17.5, 50.0, 54.0, 59.0, 60.0, 63.5, 67.0, 70.0, 80.0, and 90.0°) below, near, and above the coalescence temperature (T_c). In each case the theoretical spectrum agreed very well with the experimental spectrum.

CALCULATION OF OTHER THERMODYNAMIC PARAMETERS

The free energy of activation ($\Delta G^{\ddagger}$) for the rotation process was evaluated by the Eyring equation (1), and the enthalpy and entropy of activation were evaluated by eqns. (2) and (3), respectively. In all cases, these equations were evaluated at the coalescence temperature (T_c). The results are shown in Table 3.

$$\Delta G^{\ddagger} = -2.303\ RT_c \log \frac{hk_r}{kT_c} \quad (1)$$

$$\Delta H^{\ddagger} = E_a - RT_c \quad (2)$$

$$\Delta S^{\ddagger} = \frac{\Delta H^{\ddagger} - \Delta G^{\ddagger}}{T_c} \quad (3)$$

DISCUSSION OF ROTATIONAL BARRIER

The NMR method has previously been widely used (see for example Refs. 12, 13, 16—18) to study hindered rotation. In *N*-formyl-2-indolinol (Ia) the energy of the rotational barrier has been found to be 14.3 kcal/mole (Table 3). Since a compound will exist as isolable rotational isomers only if the barrier to rotation is greater than *ca.* 20 kcal/mole [19] it is not surprising

that *N*-formyl-2-indolinol (Ia) could not be separated into its torsional single bond isomers by usual chemical methods. The value reported here (*ca.* 14 kcal/mole) is qualitatively of the same order of magnitude as that for the rotational barrier of a wide range of *N*,*N*-dimethylamides.[12,13,18]

Though rotational barriers have not been calculated for the other *N*-formyl-2-indolinols (Ib—g) it is reasonable to assume that these values will be similar to that of *N*-formyl-2-indolinol (Ia).

EXPERIMENTAL

Materials. The *N*-formyl-2-indolinols (I) and the open-chain tautomers (II) were prepared by previously described methods.,

Room temperature NMR spectra. The 60 Mc/s NMR spectra were recorded on a Varian A60A spectrometer and the 100 Mc/s spectra on a Varian HA 100 spectrometer. All 60 Mc/s spectra were recorded using field sweep whereas all 100 Mc/s spectra were recorded using frequency sweep. Unless noted otherwise, tetramethylsilane was used as internal reference and the temperature was 39°.

Other NMR spectra. The temperature of the sample was obtained from the chemical shift difference between the CH and OH signals of ethylene glycol. The spectra were recorded on a Varian A60A spectrometer equipped with a Varian V-6040 variable temperature probe and temperature controller. The spectra were recorded with a sweep width of 5.0 cps/cm at a rate of 0.5 cps/sec. The radiofrequency field was kept well below the saturation level. At each temperature 4 spectra were recorded, 2 with the recorder moving upfield and 2 with it moving downfield. Tetramethylsilane was used as internal standard.

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REFERENCES

1. Buchardt, O., Becher, J. and Lohse, C. *Acta Chem. Scand.* **20** (1966) 2467.
2. Buchardt, O., Jensen, B. and Kjøller Larsen, I. *Acta Chem. Scand.* **21** (1967) 1841.
3. Buchardt, O. and Lohse, C. *Tetrahedron Letters* **1966** 4355.
4. Kaneko, C., Yamada, S., Yokoe, I. and Ishikawa, M. *Tetrahedron Letters* **1967** 1873.
5. Buchardt, O., Duffield, A. M. and Djerassi, C. *Acta Chem. Scand.* **22** (1968) 2329.
6. Streith, J., Darrah, H. K. and Weil, M. *Tetrahedron Letters* **1966** 5555.
7. Buchardt, O., Kumler, P. L. and Lohse, C. *Acta Chem. Scand.* **23** (1969) 159.
8. Mislow, K. *Introduction to Stereochemistry*, W. A. Benjamin Inc., New York 1966.
9. Nagarajan, K. and Nair, M. D. *Tetrahedron* **23** (1967) 4493.
10. Ribera, A. and Rico, M. *Tetrahedron Letters* **1968** 535.
11. Nagarajan, K., Nair, M. D. and Pillai, P. M. *Tetrahedron* **23** (1967) 1683.
12. (a) Gutowsky, H. S. and Holm, C. H. *J. Chem. Phys.* **25** (1956) 1228; (b) Allerhand, A., Gutowsky, H. S., Jonas, J. and Meinzer, R. A. *J. Am. Chem. Soc.* **88** (1966) 3185.
13. Rogers, M. T. and Woodbrey, J. C. *J. Phys. Chem.* **66** (1962) 540.
14. Waugh, J. S., (Ed.), *Advances in Magnetic Resonance*, Academic, New York 1965, Vol. 1, pp. 33—102.

15. *Tables of Exchange Broadened NMR Multiplets*, Technical Note No. 2, Contract No. AF 61(052)—03, between the U.S. Air Force and the Weizmann Institute of Science, Rehovoth, Israel 1958; Astia No. AD-213 032.
16. Piette, L. H. and Anderson, W. A. *J. Chem. Phys.* **30** (1959) 899.
17. Looney, C. E., Phillips, W. D. and Reilly, E. L. *J. Am. Chem. Soc.* **79** (1957) 6136.
18. Isaksson, G. and Sandström, J. *Acta Chem. Scand.* **21** (1967) 1605.
19. Kistiakowsky, G. B. and Smith, W. R. *J. Am. Chem. Soc.* **58** (1936) 1043.
20. Bennet, C. A. and Franklin, N. L. *Statistical Analysis in Chemistry and the Chemical Industry*, Wiley, New York 1954, pp. 223—243.

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