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SOLVENT AND TEMPERATURE DEPENDENCE OF THE NMR SPECTRA OF N-FORMYL AND N-THIOACETYLINDOLINES*

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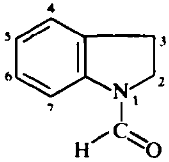
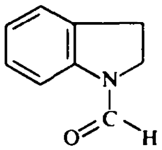
Abstract—The solvent and temperature dependence of the NMR spectra of N-formyl and N-thioacetylindolines has been studied.

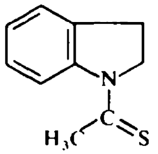
IN A previous paper,[1] the preferred configuration of the amide bond in N-acylindolines and N-acyltetrahydroquinolines was discussed. It was noted that in the case of N-formylindoline (I) and N-thioacetylindoline (II), the solution spectra showed that both configurations A and B were present. This communication deals with detailed studies on the NMR spectra of these derivatives.



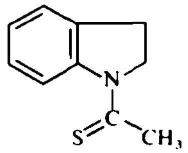
IA



IB



IIA



IIB

N-*Formylindoline.* The NMR spectrum[2] of N-formylindoline in $CDCl_3$ (20% soln) at 41° (probe temp) is reproduced in Fig. 1. The methylene protons at C-3 and the ones at C-2 appear as broad triplets at 3·07 and 4·02 ppm respectively. Two singlets (8·47, 8·88 ppm, total 1H) are from the formyl hydrogen. In configuration IA this would experience a deshielding effect due to the ring current of the benzene ring and hence would have a greater chemical shift. The relative intensities of the two signals indicate that about 74% of form A and 26% of form B are present in the $CDCl_3$ soln of N-formylindoline. The broad doublet at 8·05 ppm ($\sim\frac{1}{4}$ H) arises from the C-7 hydrogen in IB under the deshielding influence of the carbonyl group and supports the earlier deduction of the relative proportions of IA and IB. There was little change in the NMR spectrum of I in $CDCl_3$ during the course of 4 hr indicating that equilibrium was established immediately.[3] The relative proportions of IA and IB did

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[1] K. Nagarajan, M. D. Nair and P. M. Pillai, *Tetrahedron* **23**, 1683 (1967).

[2] Spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are in ppm from TMS as internal standard.

[3] A. Mannschreck, *Tetrahedron Letters* 1341 (1965).

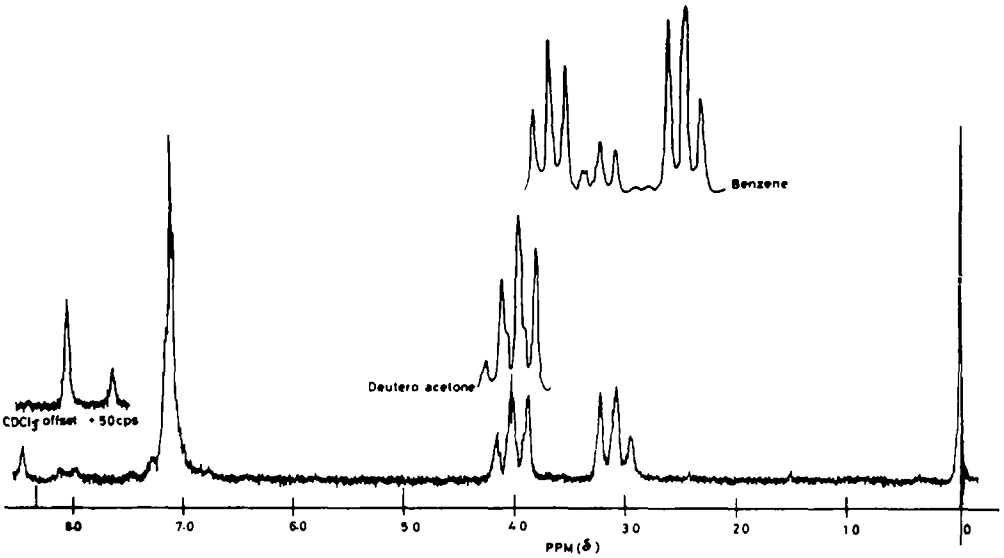

FIG. 1. NMR Spectrum of N-formylindoline (I) in $CDCl_3$.

not change significantly, nor did the chemical shifts of the formyl proton in a wide spectrum of solvents with varying dielectric constants (Table 1). The chemical shift (3·02 ± 0·05 ppm) and signal shape of the C-3 protons exhibited negligible solvent dependence. However, the signals of the C-2 protons appeared as a triplet in deuterochloroform and methylene chloride, but as a quartet in carbon tetrachloride, carbon disulphide, dioxan, methanol, d-acetone and d-DMSO. In the d-acetone spectrum, for example, the quartet (Fig. 1) can be recognized as two overlapping triplets at 4·07 and 3·93 ppm. The slightly larger chemical shift of the former would help its assignment to the C-2 protons of IA (carbonyl field effect). The benzene spectrum of I shows in this region (Fig. 1 inset), a major (3·66 ppm) and a minor (3·20 ppm) triplet.

TABLE 1. SOLVENT DEPENDENCE OF NMR SPECTRUM OF N-FORMYLINDOLINE[a]

Solvent	Dielectric constant ε	IA		IB	
		%	Chemical shift (ppm) of formyl H	%	Chemical shift (ppm) of formyl H
Dioxan	2·21	75	8·90	25	8·43
Benzene	2·28		8·78		Not recognizable
CCl_4	2·24	76	8·83	24	8·42
CS_2	2·64	72	8·82	28	8·32
$CDCl_3$	4·81[b]	74	8·88	26	8·47
CH_2Cl_2	9·08	74	8·88	26	8·47
d-Acetone	20·7[b]	71	8·97	29	8·50
Methanol	32·6	73	8·90	27	8·45
DMSO-d^6[c]	47[b]	69	8·98	31	8·45

[a] Probe temperature 41°.

[b] Values for nondeuterated solvents.

[c] At 37°.

The C-2 proton of IB, being *trans* to the carbonyl group would be expected to show a larger shift to high field in this solvent, compared with the same protons in IA.[4] In addition, the triplet of the C-3 protons is now centred at 2·43 ppm. One can visualize, extending the earlier postulate,[3] an alignment of benzene molecules in IA and IB in such a way that the C-3 protons are shielded equally in both cases, while those at C-2 are more shielded in IB than in IA.

The temperature dependence of the NMR spectrum (Fig. 2) of I was studied in d-DMSO. The signals due to the formyl proton from structures IA and IB respectively appear as sharp singlets 33 c/s apart. As the temperature is raised, they broaden and at 100° become a broad singlet at 8·87 ppm (Fig. 2 insets). Using the relative integrated intensities of the two signals at 37°, 57° and 77°, *approximate* equilibrium constants and thence the free energy differences between the forms IA and IB[5] were calculated. For the equilibrium IA $\rightleftharpoons$ IB, ΔS was found to be about $-2·75$ entropy units and ΔH about $-1·35$ kcal/mole.

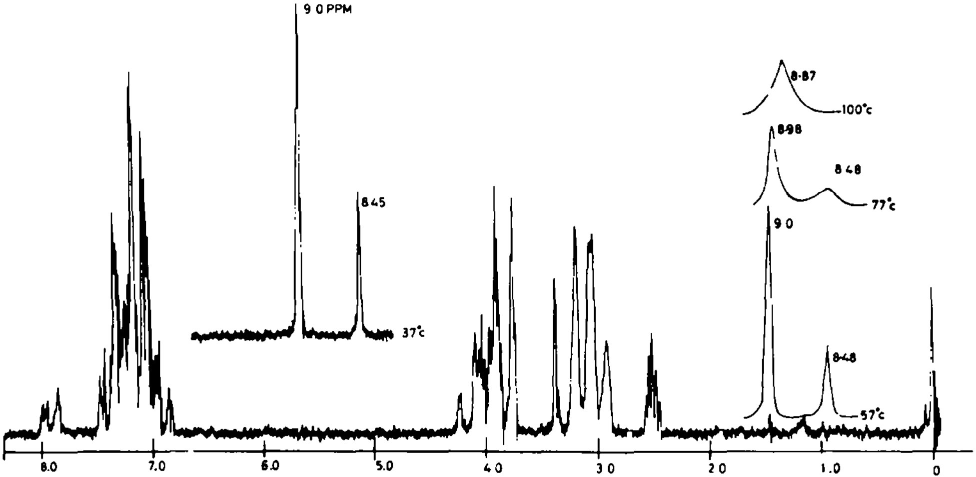

FIG. 2. NMR Spectrum of N-formylindoline (I) in DMSO-d_6.

N-*Thioacetylindoline*. The NMR spectrum of N-thioacetylindoline (II) in $CDCl_3$ at 41° (probe temp) (Fig. 3) shows the Me group as a small singlet at 2·77 ppm and a larger one at 2·98 ppm, the latter riding above the broad triplet from the C-3 methylene protons, centred around 3·08 ppm. The singlet at 2·98 ppm is assigned to the Me group in IIA which is deshielded because of the ring current of the benzene ring. The intensity of the singlet at 2·77 ppm from the Me group in IIB allows one to estimate that about 28% of this form is present in the solution of II. The methylene protons at C-2 are seen as overlapping triplets at 4·23 and 4·55 ppm respectively. The former is significantly less intense than the latter, and should arise from the C-2 protons of IIB, supporting the earlier conclusion regarding the relative proportions of IIA and IIB.

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[4] L. A. LaPlanche and M. T. Rogers, *J. Am. Chem. Soc.* **85**, 3728 (1963); N. S. Bhacca and D. H. Williams, *Tetrahedron Letters* 3127 (1964).

[5] B. Rickborn and F. R. Jensen, *J. Org. Chem.* **27**, 4606 (1962).

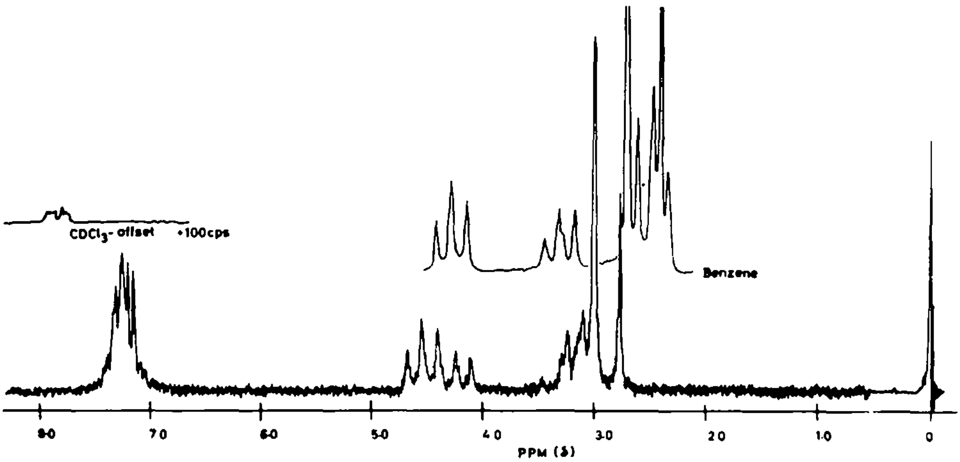

FIG. 3. NMR Spectrum of N-thioacetylindoline (II) in CDCl$_3$.

The larger chemical shift of the more intense triplet is to be expected for the C-2 protons of IIA as they are in the thiocarbonyl field. Consistent with the above deductions is the appearance of a broad doublet (C-7 proton iin IIB) at about 9·50 ppm (~) 1/3 H). The position of this doublet is shifted by about 75 c/s downfield compared with the C-7 hydrogen of N-acetylindoline,[1] which is in agreement with several authors[6] who reported larger field effects of the thiocarbonyl group.

The NMR spectrum of N-thioacetylindoline in CDCl$_3$ did not show any measurable time dependence at room temperature indicating that equilibrium was established immediately.[3] Increasing the concentration of II in CDCl$_3$ from 9 to 18 to 27% (w/w) changed the percentage of IIB from 27 to 28 to 30%. Significant changes in the relative proportions of IIA and IIB were however observed in various solvents (Table 2). Chemical shifts were generally unaffected except in the case of benzene. It is interesting to note that as the dielectric constant of the solvent increases, the percentage of IIB also increases; in d-acetone, there are approximately equal amounts of IIA and IIB, whereas in DMSO IIB is actually present to a larger extent than IIA. It is conceivable that in this solvent, considerable solvation of the thiocarbonyl group occurs; increased interaction in IIA of the solvated thiocarbonyl species with the C-2 protons may render IIB more favoured than IIA. Benzene appears to destabilize IIA in favour of IIB; further, it produces striking changes in the chemical shifts of some protons; the C-7 proton is shifted downfield by about 25 c/s; more interesting is that while the triplet due to the C-2 methylene protons of IIA shifts to 4·27 ppm that from IIB moves up to 3·28 ppm (see Fig. 3 inset). This is explicable in terms of the earlier argument.[4] The C-3 protons move from their location at 3·08 ppm in CDCl$_3$ to 2·45 ppm, while the Me groups of IIA and IIB exhibit smaller upfield shifts.

The temperature dependence of the NMR spectrum of N-thioacetyl-indoline was studied both in d-chloroform and in d-DMSO, as these solvents had opposite effects on the preferred configuration. In CDCl$_3$, the variation of the concentrations of IIA

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[6] R. H. Martin, N. Defay, F. Gearts-Evrard, P. H. Given, J. R. Jones and R. W. Wedel, *Tetrahedron*, 21, 1833 (1965); R. Greenhalgh and M. A. Weinberger, *Can. J. Chem.*, 43, 3340 (1965); P. L. Southwick, J. A. Fitzgerald and G. E. Milliman, *Tetrahedron Letters*, 1247 (1965).

and IIB was studied in the temperature range of $-7°$ to $57°$. Approximate equilibrium constants were calculated as before for IIA $\rightleftharpoons$ IIB, using the integrated intensities of the Me signals at 2·98 and 2·77 ppm respectively. Values of about $-4·7$ entropy units for ΔS and $-2·1$ kcal/mole for ΔH were derived.

The temperature dependence of the relative intensities of signals due to the Me protons of IIA and IIB in d-DMSO allowed the calculation of similar parameters for the equilibrium IIA $\rightleftharpoons$ IIB[7,8] in this solvent; values of about 5·1 entropy units for ΔS and about 1·82 kcal/mole for ΔH were found. At 100°, the two methyl signals had coalesced to a broad singlet at 2·83 ppm, which became considerably sharper at 120°.

TABLE 2. SOLVENT DEPENDENCE OF NMR SPECTRUM OF N-THIOACETYLINDOLINE[a,b]

Solvent	Di-electric Constant ε	IIA			IIB			
		%	Chemical shift (ppm) of		%	Chemical shift (ppm) of		
			protons at C-2	CH_3		proton at C-7	protons at C-2	CH_3
CCl_4[c]	2·24	79	4·50	2·93	21	9·45	4·22	2·70
Benzene	2·28	54	4·27	2·67	46	9·88	3·28	2·39
CS_2[c]	2·64	75	4·44	2·88	25	9·40	4·20	2·62
$CDCl_3$	4·81[d]	72	4·55	2·98	28	9·50	4·23	2·77
CH_2Cl_2	9·08	61	4·52	3·00	39	9·50	4·27	2·77
Pyridine	12·03	64	4·48	2·98	36		4·00	2·72
d-Acetone	20·7[d]	50	4·50	2·95	50	9·55	4·40	2·79
DMSO-d_6	47[d]	43	4·40	2·95	57	9·45	4·26	2·72

[a] About 18% w/w solutions were used.
[b] Probe temperature 41°.
[c] Not soluble to 18%; saturated solns were used.
[d] Values for nondeuterated liquids.

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[7] Due to partial overlapping of the Me signals by other peaks, the computation of their relative intensities was rendered difficult. The results are therefore less accurate than the others reported in this paper.

[8] Alternately, the intensity of the signal due to the C-7 proton in IIB could have been used. But as this is only a small fraction of *one* proton, no advantage could be gained.