The Nuclear Magnetic Resonance Spectra of 2-Formylaminopyridine and 2-Formylamino-γ-picoline

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The NMR spectra of 2-formylaminopyridine and 2-formylamino-γ-picoline have been recorded under various conditions. At low temperatures, these compounds were found to exist in two forms. In these two forms, the chemical shifts of the ring proton-3 differ much from each other because of the difference in the orientation of the formylamino group, which has a large magnetic anisotropy. The difference in the chemical shifts of the formyl protons in the two forms are too large to be explained by the anisotropic shielding effect of the pyridine-ring currents. At higher temperatures, the signal coalescence of these protons in two forms have been observed. The molecular structures of these compounds have been concluded to be planar.

A large magnetic anisotropy is associated with the amide group. The acetylation effect on the *ortho* proton chemical shifts was studied for a number of anilines, and it was shown that pronounced downfield shifts of the protons at the 6-position were observed when the molecules had substituents at the 2-position capable of forming intramolecular hydrogen bonds with the amide proton.[1-5]

This kind of intramolecular hydrogen bonding would be rather easily disrupted in polar solvents, such as dimethyl sulfoxide, which is well known as an agent for interacting with amide protons.[6] The free rotation around the C_{ring}–N bond thus induced by the disruption of the intramolecular hydrogen bond is reflected in the upfield shifts of the proton-6 in 2,4-dichloroacetanilide[2] or of 2,4-dinitroacetoanilide[2,7] in dimethyl sulfoxide, for example, as compared to the signals observed in chloroform.

In acetylaminopyridines, the conjugation interaction between the substituent and the pyridine ring is dependent upon the position of substitution. A remarkable deshielding shift of the proton-3 of 2-acetylaminopyridine was considered to be indicative of the planarity of the molecule, probably in the *endo* form.

It has been reported that acetanilide exists in the *endo* form,[8] whereas formanilide in solution coexists in both forms, *endo* and *exo*.[2,9]

In this paper we will present the NMR spectra of 2-formylaminopyridines under various conditions and make it clear that the large deshielding shift of the proton-3 is associated with molecules in the *endo* form.

Experimental

2-Aminopyridine was refluxed with excess formic acid for 5 hr. The water produced and the excess formic acid were distilled off under reduced pressures. The 2-formylaminopyridine was distilled out last. This fraction was submitted to redistillation and finally to recrystallization from benzene; mp 71°C.

Found: C, 59.17; H, 5.17; N, 22.77%. Calcd for $C_6H_6N_2O$: C, 59.01; H, 4.95; N, 22.94%.

2-Formylamino-γ-picoline was prepared in a similar way; mp 89°C.

Found: C, 62.01; H, 6.06; N, 20.63%. Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58%.

Reasonable mass spectra were obtained for these two compounds.

The NMR spectra were recorded on a Varian A-60D spectrometer under various conditions. Temperatures could be controlled within ±2°C at higher temperatures, but only within ±4°C at lower temperatures. The concentration dependence of the chemical shifts was found to be negligible for any protons but amide protons. The figures reported in this paper were read from the spectra of solutions with a concentration of 10 w/v%.

Results and Discussion

Assignment. The low-field part of the spectrum of 2-formylamino-γ-picoline in di-*n*-propyl ketone is shown in Fig. 1. It is clear that there are two molecular species in solution at low temperatures. Following the general concept that $J_{trans} > J_{cis}$, the sharp doublet with a coupling constant of 11 Hz at 9.50 ppm was assigned to the formyl proton in the *exo* form. Another doublet with a smaller splitting, 2 Hz, at 8.63 ppm was ascribed to the formyl proton in the *endo* form. The lower-field resonance of the formyl proton in the *exo* form could be attributed to its closer proximity to the pyridine ring than the same proton in the *endo* form. This chemical-shift difference is much larger than that observed for formanilide.[9]

Bourn *et al.* estimated the chemical-shift difference of the formyl protons of formanilide at the *exo* and *endo* positions as about 0.25 ppm, using reasonable values for the bond lengths and assuming that all bond angles are 120° and that the moleclule is planar.[9]

1) T. H. Siddall, III and W. E. Stewart, *J. Mol. Spectrosc.*, **24**, 290 (1967).
2) R. F. C. Brown, L. Radom, S. Sternhell, and I. D. Rae, *Can. J. Chem.*, **46**, 2577 (1968). B. D. Andrews, I. D. Rae, and B. E. Reichert, *Tetrahedron Lett.*, **1969**, 1859.
3) J. R. Bartels-Keith and R. F. H. Cieciuch, *Can. J. Chem.*, **46**, 2593 (1968).
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6) a) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 337 (1964). b) R. H. Barker and G. J. Boudreaux, *Spectrochim. Acta*, **A23**, 727 (1967).
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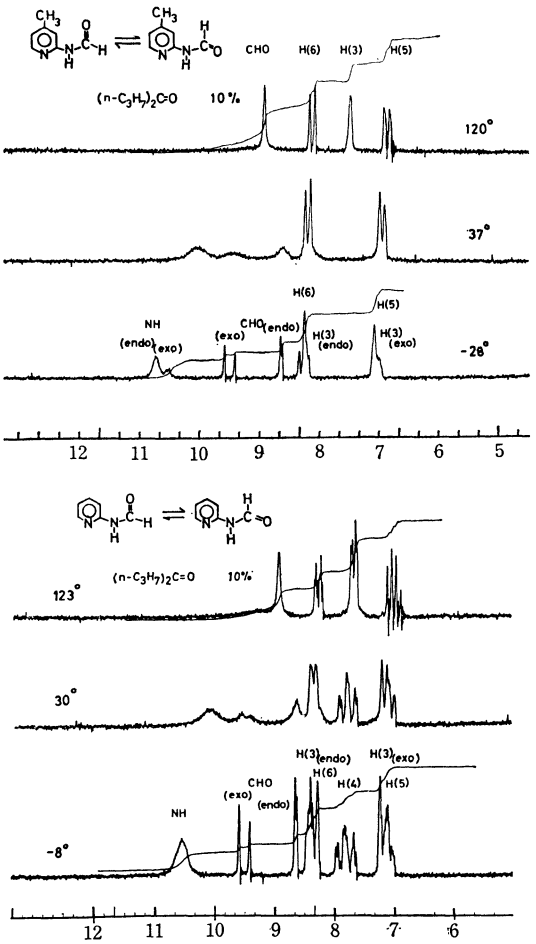


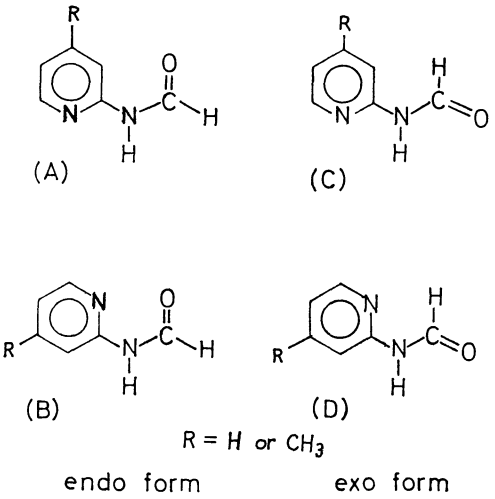
Fig. 1. The lowfield region of the NMR spectra of 2-formylamino-γ-picoline and 2-formylaminopyridine in di-*n*-propyl ketone at different temperatures.

The difference of 0.87 ppm observed in the present case is too large to be explained by the anisotropic effect of the pyridine ring, because the latter is similar in size to that of the benzene ring. The formyl proton in the *exo* form might be subjected to a strong deshielding effect due to the lone-pair electrons on the ring nitrogen in the D configuration, because the flip-rotation about the C_{ring}–N_{amide} bond, C⇌D, seems to be very probable.

There are two other signals, at 10.73 and 10.62 ppm, which are easily assigned to the amide protons in the *exo* and *endo* forms respectively on the basis of their temperature dependence. The amide-proton signal shifts to higher fields on an increase in the temperature of the solution; this shift is due to diminished intermolecular interactions through the amide group.[9] The signal then undergoes a pronounced broadening due primarily to the intermolecular exchange of the amide protons.

Roughly speaking, there are two multiplets, at 7.0 and 8.2 ppm, and each multiplet has an intensity corresponding to more than one proton. The multiplet at lower fields is attributable to the ring proton-6 and the proton-3 in the *endo* form. The other multiplet signal arises from the proton-5 and the proton-3 in the *exo* form. These assignments of the proton-5 and -6 are consistent with the NMR parameters of unsubstituted pyridine.[10] The assignment of the signals of the proton-3 is based on the signal intensity.

At elevated temperatures, the signal for the proton-3 coalesces and appears at 7.53 ppm as a singlet with a



somewhat unresolved structure. A considerable rapid rotation around the amide bond, CO–NH, is responsible for this coalescence.[11] This rotation also causes the coalescence of the formyl proton signal with a linewidth comparable with that of the proton-3 signal.

From these observations, it is quite certain that the proton-3 experiences quite a different magnetic environment depending upon whether the molecules are in the *exo* form or in the *endo* form. On the other hand, the proton-5 or -6 has nearly the same value for the chemical shift in either form. Similarly, the signals of the methyl protons at the 4 position in the two rotamers almost overlap each other. These observation reflect a sharp distance-dependence of the anisotropy effect.

Arguments almost the same as those above are certainly applicable to the NMR spectrum of 2-formylaminopyridine at various temperatures, except for the fact that the ring-proton spectrum is somewhat complicated because of the presence of the proton-4.

Table 1 summarizes the results obtained under various conditions.

Chemical Shifts of Ring-proton-3 in the endo *and* exo *Forms.* In chloroform, acetone, and di-*n*-propyl ketone, the chemical shifts of the proton-3 in the two rotamers are nearly the same, suggesting that the molecular structures are also very similar in these solvents. In toluene, however, the chemical shift for the *exo* form is shifted to a field higher by about 0.6 ppm, whereas the *endo* form signal is shifted little with respect to those in chloroform solutions. This observation is also indicative of the reasonableness of the assumption that the lower-field signal of the proton-3 is associated with the *endo* form, for it is well known that the protons *trans* to the carbonyl oxygen with respect to the amide bond are more shielded than those in the *cis* position

10) S. Castellano, C. Sun, and R. Kostelnik, *J. Chem. Phys.*, **46**, 327 (1967).

11) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York (1959), p. 365.

TABLE 1. CHEMICAL SHIFTS OF RING PROTON-3, FORMYL PROTON AND AMIDE PROTON

Solvent	Temp.	CHO		NH		H(3)	
		endo	*exo*	*endo*	*exo*	*endo*	*exo*
2-Formylaminopyridine							
$CDCl_3$	−40°C	8.62	9.38	11.3	11.4	8.4	7.1
	37	8.63	9.87	10.1		8.3	7.1
Acetone-d_6	−31	8.62	9.47	10.3		8.3	7.1
	37	8.60	9.47	9.9		8.3	7.1
$(n\text{-}C_3H_7)_2CO$	− 8	8.70	9.52	10.6		8.4	7.2
	37	8.60	9.50	10.0		8.2	7.2
	123	8.92		9.3		7.7	
Toluene-d_8	12	8.28	9.30	10.5	11.7	8.4	6.4
	37		9.30	9.9	10.5	8.4	6.4
	103	8.67		8.9		7.33	
DMSO-d_6	37	8.33	9.23	10.5		7.8	7.0
	150	8.93		9.8		7.5	
2-Formylamino-γ-picoline							
$CDCl_3$	−41	8.63	9.37	11.70		8.22	6.88
	37	8.56	9.33	10.4		8.17	6.78
Acetone-d_6	−21	8.53	9.38	10.30		8.13	6.92
	37	8.53	9.37	9.35		8.07	6.87
$(n\text{-}C_3H_7)_2CO$	−28	8.63	9.50	11.15	11.03	8.20	7.00
	37	8.60	9.47	10.0		8.20	6.90
	117	8.97		8.9		7.53	
Toluene-d_8	13	8.33	9.30	10.65	11.10	8.25	6.33
	37	8.32	9.33	10.35	10.82	8.28	6.33
	100	8.67		9.00		7.25	
DMSO-d_6	37	8.37	9.25	10.47		7.97	6.93
	130	8.83		9.87		7.27	
DMSO-d_6–D_2O	−12	8.48	9.20			7.87	6.87
	37	8.50	9.20			7.83	6.97
	90	8.87				7.37	

when aromatic hydrocarbons are used as the solvents.[12] In a mixed solvent such as D_2O–DMSO-d_6, on the other hand, the chemical shift of the proton-3 in the *endo* form shows an upfield shift, probably due to a slight decrease in the deshielding effect of the amide group, which might be twisted slightly out of the plane of the pyridine ring, as has already been described in the introductory section for 2,4-dichloroacetanilide. This twisting could be attributed to the interactions of the amide group with the solvent molecules, water and dimethyl sulfoxide; both are representative solvents capable of interacting with solute molecules having polar groups through the formation of intermolecular hydrogen bonds.

Planarity of 2-Formylaminopyridine. The acetylation effect on the *ortho* protons is smaller in acetanilide than in 2-chloroacetanilide.[1] This difference is probably to be ascribed to the fact that the rotation around the C_{ring}–NH bond is free in the former, but is strongly restricted in the latter, which holds the molecule planar.

The chemical shift of the proton-3 of 2-formylaminopyridine in the *endo* form is about 8.2 ppm. Therefore, the "formylation" deshielding shift is about 1.85 ppm, because the chemical shift of the proton-3 in 2-aminopyridine is 6.35 ppm.[13] A similar value of 1.70 ppm has been reported as the "acetylation" shift for the proton-3 resonance of 2-aminopyridine.[2] Consistent with this, the proton-6 in 2,4-dichloroacetanilide, where the internal rotation around the C_{ring}–N_{amide} bond is strongly restricted by the intramolecular hydrogen bond, resonates at 8.32 ppm, lower by 1.66 ppm than the resonance of the corresponding proton in 2,4-dichloroaniline. The excellent agreement of these values seems to indicate a restricted rotation around the C_{ring}–N_{amide} in 2-formylaminopyridines.[14]

This is also supported by the fact that the chemical shifts of the 2 and 6 protons in *p*-formyltoluidide in chloroform are 7.37 and 7.11 ppm for the molecules in the *endo* and *exo* forms.[1] It is quite certain that this small difference in the chemical shifts for the two rotamers is attributable to the free rotation around the C_{ring}–N bond.

The downfield shift of the proton-3 in 2-acetylaminopyridine has been reported to be very large, suggesting that molecules have a planar structure. The

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13) W. B. Smith and J. L. Roark, *J. Phys. Chem.*, **73**, 1049 (1969).

14) The authors have no idea about the flip-rotation about the C_{ring}–N_{amide} bond, A⇌B.

molecular planarity of this compound is reflected in other evidence wherein a weak, long-range coupling is observed between the amide proton and the proton-4.[15] Unfortunately, in the case of 2-formylaminopyridine, however, the corresponding long-range coupling could not be identified because of the superposition of the two signals corresponding to the two rotamers where the chemical shifts of the proton-4 are very similar to each other.

The large difference in the chemical shifts of the formyl protons in the *endo* and *exo* forms, already described, also strongly suggests the planarity of 2-formylaminopyridines.

From these facts, it seems very probable that 2-formylaminopyridines have planar structures near room temperature. The dipole interaction between the amide group at the position 2 and the pyridine ring is considered to be a main factor in keeping the molecule planar.[1] A similar situation occurs with α-dipyridyl, which has been determined to be planar and *trans* in chloroform.[16]

endo-exo *Equilibrium.* The *endo-exo* equilibrium can be evaluated only at low temperatures. Table 2 gives the *endo-exo* equilibrium constant, $R=I(endo)/I(exo)$, where $I(endo)$ and $I(exo)$ stand for the intensities of the signals from molecules in the *endo* and *exo* forms respectively. It is very interesting to note that the R value changes slightly with the change in solvent from chloroform to a mixed solvent of dimethyl sulfoxide and water (1:1). In the cases of thioacetanilide[17,18] and thioacetonaphthalide,[19] the corresponding R values are strongly dependent upon the polarity of solvents. In the case of formanilide, the addition of dimethyl sulfoxide to a chloroform solution caused an intensification of the *endo*-signal.[20] This trend is contrary to the present results.

Table 2. Population ratio of *endo/exo* in different solvents

Solvent	Temperature	Ratio (*endo/exo*)
Chloroform	−28 (°C)	1.4
Acetone	−28	1.3
Di-*n*-propyl ketone	−28	1.2
DMSO-water (1:1)	−12	0.93

In a chloroform solution of 2-chloro-*p*-formyltoluidide,[3] the proton-6 chemical shifts were found to be 7.0 and 8.13 ppm in the *exo* and *endo* form respectively, at 10°C and with the R value of 0.5. At 40°C, however, a partial coalescence occurred and the proton-6 signal appeared at 8.10 ppm, lower than the value estimated directly from the two chemical shifts and the R value at 10°C given above. This suggests that the equilibrium was shifted to the *endo* form with an increase in the temperature. In the present case, however, the resonance positions of the formyl protons and of the proton-3 at higher temperatures are almost the same as those evaluated from the R values and the chemical shifts of these protons obtained from the NMR spectra at low temperatures. This suggests a temperature independence of the population ratio of the two rotational isomers.

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16) S. Castellano, H. Gunter, and S. Ebersole, *J. Phys. Chem.*, **69**, 4166 (1965).
17) I. Suzuki, M. Tsuboi, T. Shimanouchi, and S. Mizushima, *Spectrochim. Acta*, **16**, 471 (1960).
18) M. Kondo, unpublished data.
19) M. Kondo, unpublished data.
20) T. Nishiyama and F. Yamada, *Nippon Kagaku Zasshi*, **89**, 979 (1968).