

Conformational Studies by Dynamic Nuclear Magnetic Resonance. Part 4.¹ Rotational Isomers and Torsional Barriers of Pyridinecarbaldehydes

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Conformational isomers due to the restricted rotation of the formyl group have been detected in some pyridine-carbaldehydes and non-equivalence has been observed in the symmetric pyridine-4-carbaldehyde, by means of ¹H and ¹³C n.m.r. spectroscopy at low temperature. Assignment of the preferred conformers in pyridine-3-carbaldehyde has been achieved mainly by means of lanthanide shift effects. It has been shown that the carbonyl group shifts the ¹³C resonance of the *syn-ortho*-carbon upfield. This can be used as a general method for identifying rotational isomers in analogous derivatives. Barriers to internal rotation have been measured for all the derivatives examined by total line shape analysis of ¹H or ¹³C spectral patterns. In one case both measurements were carried out and substantial agreement was obtained.

EVIDENCE of rotational isomers in aromatic aldehydes neat or in solution have been collected by means of dipole moment measurement,²⁻⁴ interpretation of long range spin-spin couplings,⁵⁻⁷ molar Kerr constant investigations,⁸ ultrasonic relaxation studies,⁹ and, more recently, by analysing n.m.r. spectra in liquid crystalline solvents.^{9b,10}

All these methods are based upon the fact that the experimental data are the result of averaging of the properties of two (or more) individual conformers. On the contrary low temperature studies using n.m.r. (or e.s.r. when radicals are concerned¹¹) spectroscopy allow direct evidence of the phenomenon to be obtained, in that separate signals for different rotamers can be identified.

When no individual conformers are expected, owing to the symmetry of the molecule investigated, these techniques still give different signals for non-equivalent atoms: the term topomer has been suggested to identify

the two chemically equivalent species involved in the equilibrium process.

As far as aromatic aldehydes are concerned, the first investigation leading to direct evidence of topomers was published by Anet and Amahad¹² for benzaldehyde and some of its 4-substituted derivatives. Forsén and his co-workers detected two rotational isomers of furan-2-carbaldehyde.¹³ Since then many examples have been reported of direct detection of rotamers in aromatic aldehydes.^{1,14} The advent of ¹³C n.m.r. spectroscopy helped in obtaining more accurate results for torsional barriers.^{15,16}

Line shape analysis of the ¹³C signals of benzaldehyde gave all the thermodynamic parameters involved in the torsional process of the formyl group.¹⁶

These studies also introduced a new problem as they showed that the ¹³C chemical shifts of the *ortho*-carbons are more separated than would be expected on the basis of charge density distribution.¹⁶ This large difference

¹ Part 3, L. Lunazzi, D. Macciantelli, G. Spunta, and A. Ticca, *J.C.S. Perkin II*, 1976, 1121.

² C. Pigenet, J. P. Morizur, Y. Pascal, and H. Lumbroso, *Bull. Soc. chim. France*, 1969, 361; H. Lumbroso and P. Pastour, *Compt. rend.*, 1965, **261**, 1279; H. Lumbroso, D. M. Bertin, M. Robbe, and B. Roques, *ibid.*, 1966, **262**, 36; H. Lumbroso, D. M. Bertin, and P. Cagniant, *Bull. Soc. chim. France*, 1970, 1720.

³ J. Barassin, G. Quenquinez, and H. Lumbroso, *Bull. Soc. chim. France*, 1967, 4707.

⁴ Chun Lai Chen and G. L. D. Ritchie, *J.C.S. Perkin II*, 1973, 1461.

⁵ B. Roques, S. Cambrisson, C. Riche, and C. Pascard Billy, *Tetrahedron*, 1970, **26**, 3555; B. Roques and M. C. Fournie-Zaluski, *Org. Magnetic Resonance*, 1971, **3**, 305; *Tetrahedron Letters*, 1971, 145; R. J. Abraham and T. M. Siverns, *Tetrahedron*, 1972, **28**, 3015; M. C. Fournie-Zaluski, C. Jaureguiberry, and B. Roques, *Tetrahedron Letters*, 1973, 4177; C. Jaureguiberry, M. C. Fournie-Zaluski, and B. Roques, *Org. Magnetic Resonance*, 1973, **5**, 165; D. J. Chadwick, *Tetrahedron Letters*, 1975, 679.

⁶ G. J. Karabatsos and F. M. Vane, *J. Amer. Chem. Soc.*, 1963, **85**, 3886.

⁷ W. Danchura, T. Schaeffer, J. R. Rowbotham, and D. J. Wood, *Canad. J. Chem.*, 1974, **52**, 3986.

⁸ R. J. W. Le Fèvre and P. J. Stiles, *J. Chem. Soc. (B)*, 420, 1966.

⁹ (a) R. A. Pethrick and E. Wyn Jones, *J. Chem. Soc. (A)*, 1969, 713; (b) G. Conti, E. Matteoli, C. Petrolongolo, C. A. Veracini, and M. Longeri, *J.C.S. Perkin II*, 1975, 1673.

¹⁰ P. L. Barili, L. Lunazzi, and C. A. Veracini, *Mol. Phys.*, 1972, **24**, 673; L. Lunazzi, G. F. Pedulli, M. Tiecco, and C. A. Veracini, *J.C.S. Perkin II*, 1972, 755; L. Lunazzi and C. A. Veracini, *ibid.*, 1973, 1739; P. L. Barili, M. Longeri, and C. A. Veracini, *Mol. Phys.*, 1974, **28**, 1101.

¹¹ A. Hudson and J. W. E. Lewis, *Tetrahedron*, 1970, **26**, 4413; L. Lunazzi, G. F. Pedulli, M. Tiecco, C. Vincenzi, and C. A. Veracini, *J.C.S. Perkin II*, 1972, 751.

¹² F. A. L. Anet and M. Ahmad, *J. Amer. Chem. Soc.*, 1964, **86**, 119.

¹³ K. I. Dahlqvist and S. Forsén, *J. Phys. Chem.*, 1965, **69**, 4062.

¹⁴ L. Arlinger, K. I. Dahlqvist, and S. Forsén, *Acta Chem. Scand.*, 1970, **24**, 662, 672; D. J. Chadwick, G. D. Meakins, and E. E. Richards, *Tetrahedron Letters*, 1974, 3183; R. Jost, P. Rimmelin, and J. M. Sommer, *ibid.*, 1971, 3005; T. Drakenberg, S. Forsén, and J. M. Sommer, *J.C.S. Perkin II*, 1974, 520; R. Jost, J. M. Sommer, and T. Drakenberg, *Org. Magnetic Resonance*, 1975, **7**, 351.

¹⁵ T. Drakenberg, R. Jost, and J. Sommer, *J.C.S. Chem. Comm.*, 1974, 1011; *J.C.S. Perkin II*, 1975, 1682.

¹⁶ L. Lunazzi, D. Macciantelli, and A. C. Boicelli, *Tetrahedron Letters*, 1975, 1205.

could be used to assign unambiguously rotational isomers in carbonyl derivatives: one has however to prove first whether the carbonyl group shifts up- or down-field the ^{13}C signal of the *ortho*-carbon on the same side of the carbonyl function.

In order to solve this problem ^1H and ^{13}C n.m.r. studies of pyridinecarbaldehydes have been undertaken. In particular pyridine-3-carbaldehyde (1) turned out to be highly suited for this purpose.

RESULTS AND DISCUSSION

(a) *Assignment of Rotamers.*—Both the ^1H (100 MHz; CHF_2Cl) and ^{13}C spectra (25.15 MHz; Me_2O) allowed the detection of separate signals for the two isomeric forms of pyridine-3-carbaldehyde (1).*

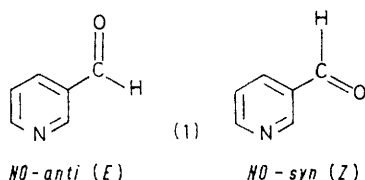


Figure 1 shows the ^{13}C spectrum at various temperatures: the assignment of the carbon atoms is known from previous work^{17,18} (Table I). It can be seen that

TABLE I

^{13}C Chemical shifts (p.p.m. downfield from Me_4Si) of pyridinecarbaldehydes (1)–(4)										
Compound	Solvent	$t/^\circ\text{C}$		C-2	C-3	C-4	C-5	C-6	CHO	CH_2
(1)	Me_2O	-143	{ <i>NO-anti</i> (80%) <i>NO-syn</i> (20%) }	152.2	129.1	130.3	121.7	152.2	189.0	
(2)	CHF_2Cl	-150	{ <i>NO-anti</i> (80%) <i>NO-syn</i> (20%) }	144.6	128.7	138.0	121.7	151.8	189.9	22.1
(3)	$\text{CCl}_2\text{F}_2\text{-CHFCl}_2$	-150		151.6 *	119.7	141.1	127.3	152.5 *	195.5	
(4)	$\text{CCl}_2\text{F}_2\text{-CHFCl}_2$	-130	<i>NO-anti</i> (93%)	152.3	122.3	138.3	129.3	150.8	195.3	18.3

* Assignments may be reversed.

C-2 and -4 resonances broaden on lowering the temperature and eventually become separate at -140°C . Non-equivalent signals can also be detected for C-3, CHO, and C-6; the ratio was approximately the same (80 : 20) for every pair of peaks. The chemical shift difference is much larger for C-2 and -4 than for the others: this can also be taken as additional evidence that the assignment of the corresponding signals (*i.e.* *ortho* to the formyl group) is correct. Also, the effect of carbonyl on C-4 is opposite to that on C-2, in that the intense peak of C-2 is shifted downfield whereas that of C-4 moves upfield with respect to the corresponding averaged values detectable at temperatures $> -100^\circ\text{C}$.

Therefore, if it is possible to determine which is the preferred conformer, one can ascertain the effect of the carbonyl group and use it subsequently as a probe for assigning conformational isomers.

In the case under discussion, if *NO-anti* is the more

* For Me_2O , ^{13}C exchange can be stopped but this does not happen with ^1H spectra. On the other hand the lower boiling CHF_2Cl is suitable for ^1H spectra (since the 2- and 6-H peaks are not obscured) but not for ^{13}C (the C-2 and -4 peaks are obscured).

¹⁷ H. L. Retckofsky and R. A. Friedel, *J. Phys. Chem.*, 1967, **71**, 3592 and 1968, **72**, 290, 2619.

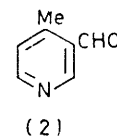
stable conformer, then the carbonyl group would displace upfield the *ortho*-carbon on the same side (C-4 in the *E*- and C-2 in the *Z*-form), whereas the opposite situation would apply (*i.e.* upfield C-2 in the *E*- and C-4 in the *Z*-form) if *NO-syn* is the more stable conformer.

The interpretation of dipole moments⁴ and of long range couplings^{6,7} indicates that the first hypothesis (*NO-anti* more stable) is correct; the same conclusion is supported by theoretical calculations.^{7,19} Other independent evidence confirms this assignment.

(i) The 2-H signal at -140°C (Figure 2) shows that the shift of the less abundant rotamer (*ca.* 27%) is downfield with respect to that of the more intense (73%). Independent of the assignment it is proved that the effect of formyl on a proton is opposite to that on carbon. Since in six-membered aromatic derivatives it has been recognized that carbonyl shifts the vicinal *ortho*-protons downfield²⁰ (*i.e.* 2-H in the *Z*-form), the conclusion that the *NO-syn*-form is the less abundant conformer is supported.

(ii) The ^1H and ^{13}C spectra of 4-methylpyridine-3-carbaldehyde (2) below -140°C also show the existence of the two conformers in an 80 : 20 ratio. The less intense 2-H signal is still downfield, thus indicating that the proportion of the two rotamers (whatever the

assignment) has not been reversed with respect to (2). The more intense ^{13}C signal of the formyl group in (2) is at lower field (195.8 p.p.m.) with respect to the less intense (193.5 p.p.m.), a situation opposite to that for unsubstituted pyridine-3-carbaldehyde (see Table 1).



Furthermore, the difference in the shift of the rotamers is larger [2.3 instead of the 0.9 p.p.m. of (1)]. Whereas in (1) the small difference in the carbonyl shift between the two conformers is mainly due to a slight variation in the electronic distribution, in (2) a substantial contribution must also come from steric hindrance. It is well known that the more hindered aromatic carbonyl

¹⁸ J. B. Stothers, 'C-13 N.M.R. Spectroscopy,' Academic Press, New York, 1972.

¹⁹ V. Galasso, *Mol. Phys.*, 1973, **26**, 81.

²⁰ G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. Fenoglio, *J. Amer. Chem. Soc.*, 1967, **89**, 5067; J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1967, **23**, 2339.

derivatives have the ^{13}C shifts at lower field with respect to those of less hindered analogous molecules, the effect having been interpreted as due to a loss of conjugation between CO and the ring, with a consequent shift of the carbonyl signal toward the region of aliphatic carbonyl compounds.^{18,21} If so, the more hindered

of the *NO-syn*-form. Since experimentally the downfield signal is the more intense, *NO-anti* appears to be the more stable conformer.

(iii) An alternative method for analysing this conformational problem requires the use of lanthanide shift reagents.^{22,23} The method can be used for stereochemical purposes and also for identifying the relative amount of two conformers at equilibrium.²⁴

In the case of (1) the effects of two such reagents, $\text{Eu}(\text{fod})_3$ and $\text{Yb}(\text{dpm})_3$, have been studied. The first point to be ascertained is the site of complexation, *i.e.* the carbonyl group or the nitrogen atom. The latter is known to have the greater ability of associating lanthanides.²³ In the present case this can be further proved by examining pyridine-4-carbaldehyde (III). The measured l.i.s. with $\text{Yb}(\text{dpm})_3$ are 57.9 for 2- and 6-H, 21.8 for 3- and 5-H, and 12.3 p.p.m. for HCO: it is evident that the opposite trend would have been observed if the complexation site had been on the carbonyl group. Furthermore inspection of Table 2 shows that the l.i.s. effects are equal, within the error, for 2- and 6-H in (1), an expected result if the site is nitrogen but not if it is the carbonyl.

Following a method similar to that reported in ref. 24 the l.i.s. values were calculated assuming the basic geometry of the two isomers and an N-Ln distance of 3 Å.^{23,24} Inspection of the system of equations obtained in this way²⁴ shows that there are four unknowns and five experimental data (l.i.s.). The problem is thus overdetermined.

TABLE 2

Experimental and computed ^1H lanthanide induced shift (l.i.s.) in p.p.m. at 100 MHz for pyridine-3-carbaldehyde (1) with two lanthanide complexes in CDCl_3 . The l.i.s. values are the slope of the straight line relating the shift with the molar ratio lanthanide : pyridine-3-carbaldehyde. For the meaning of the angles ω and ϕ and of the constant K see ref. 24

	L.i.s. with $\text{Yb}(\text{dpm})_3$		L.i.s. with $\text{Eu}(\text{fod})_3$	
	Observed	Computed	Observed	Computed
CHO	10.4 ± 0.5	10.4	2.45 ± 0.11	2.45
H-2	49.4 ± 0.5	49.7	10.88 ± 0.55	10.97
H-4	15.0 ± 0.6	14.1	3.61 ± 0.14	3.21
H-5	18.1 ± 0.9	17.2	4.02 ± 0.21	3.95
H-6	48.0 ± 1.6	48.3	11.25 ± 0.54	11.30
R.m.s. deviation	0.6		0.2	
<i>NO-trans</i>	$90\% \pm 10$		$91\% \pm 10$	
ϕ	85°		85°	
ω	90°		50°	
K	2 338		532	

The results given in Table 2 confirm again that the *E*-form (*NO-anti*) is the preferred rotamer, although from a quantitative point of view the result is not so satisfactory (at room temperature the *E*-form is expected to be present in 60–65% from extrapolation of low temperature data).

²³ A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, 1973, **73**, 553.

²⁴ G. Montaudo, S. Caccamese, V. Librando, and P. Maravigna, *Tetrahedron*, 1973, **29**, 3915; *J. Amer. Chem. Soc.*, 1973, **95**, 6365; P. Finocchiaro, A. Recca, P. Maravigna, and G. Montaudo, *Tetrahedron*, 1974, **30**, 4159.

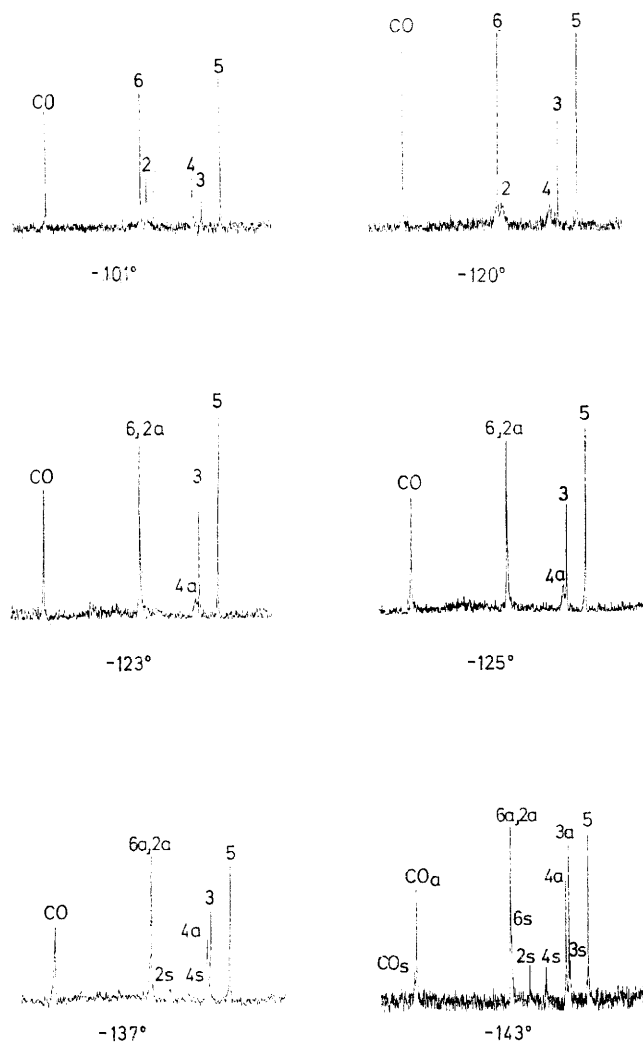


FIGURE 1 ^{13}C N.m.r. spectrum of pyridine-3-carbaldehyde (1) in dimethyl ether as a function of the temperature. The C-2 and -4 signals which are still averaged at -101 and -120° separate into two signals at -123 and -125° ; owing to the extreme broadening only the signals of the more intense *NO-anti*-rotamer (labelled 2a and 4a) are visible; At -137 and -143° the signals of the *NO-syn* (2s and 4s) are sharp enough to be detected. At -143° separate signals are also visible for C-3, -6, and CHO

rotamer (*NO-anti*) is expected to have a downfield carbonyl shift in the ^{13}C spectrum with respect to that

²¹ K. S. Dhimi and J. B. Stothers, *Tetrahedron Letters*, 1964, 631; *Canad. J. Chem.*, 1965, **43**, 479; B. F. Bonini, L. Lunazzi, G. Maccagnani, and G. Mazzanti, *J.C.S. Perkin I*, 1973, 2314; G. W. Buchanan, G. Montaudo, and P. Finocchiaro, *Canad. J. Chem.*, 1973, **51**, 1053.

²² R. Von Ammon and R. D. Fischer, *Angew. Chem. Internat. Edn.*, 1972, **11**, 675; M. R. Peterson, jun. and G. H. Wahl, jun., *J. Chem. Educ.*, 1972, **49**, 790; I. Ya. Slonim and A. Kh. Bulai, *Russ. Chem. Rev.*, 1973, **42**, 904.

We may therefore conclude that our additional evidences fully confirms the previous studies,^{4,6,7} thus indicating *NO-anti* as the more stable conformer; as a consequence the ¹³C shifts of the *ortho*-carbons are upfield when *syn* to the carbonyl group and downfield when *anti*.

(b) *Torsional Barriers*.—Line shape analysis of the low temperature n.m.r. spectra also allowed us to determine the torsional barriers of the formyl group.

In the case of (1) the process could be followed either from ¹H signals in CHF₂Cl (Figure 2) or from ¹³C signals in dimethyl ether. In both cases a number of small approximations are involved: since they are different in nature it is possible that slightly different ΔG^\ddagger values are obtained. In Figure 2 the 2- and 6-H signals are

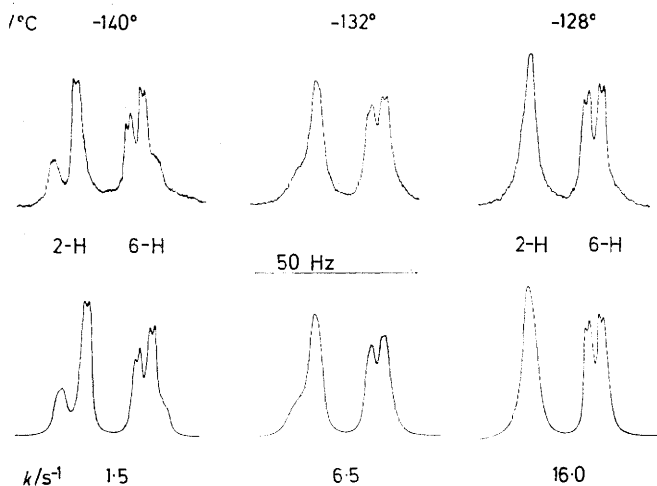


FIGURE 2 Experimental (top) and computer simulated 100 MHz ¹H n.m.r. signals for 2-H (downfield) and 6-H (upfield) of pyridine-3-carbaldehyde (1) in CHF₂Cl

displayed. The remaining aromatic signals are under the solvent peak, whereas the formyl signal is not split. Although only this part of the spectrum was used, the system had to be treated as a four spin group. The shifts of 5- and 6-H were taken from spectra in a different solvent at room temperature.²⁵ Since the spectrum is close to first order, errors in the shifts do not affect the shape of the 2- and 6-H signals. The observed J_{HH} values were equal for both conformers; accordingly the values taken from spectra at room temperature²⁵ were assumed equal for both conformers. Furthermore, owing to the broad linewidth at low temperature (*ca.* 1.5 Hz) long range couplings with formyl were neglected. The thermodynamic parameters obtained in the range -146 to -126 °C are given in Table 3; as observed in analogous cases^{1,16} ΔS^\ddagger was negligible so ΔG^\ddagger instead of ΔH^\ddagger is used throughout. A parallel analysis carried out on the ¹³C spectra was not so accurate as to allow a meaningful determination of all the thermodynamic parameters. This mainly depends upon deviations from the Lorentzian line shape in the Fourier transform method, difficulties in determining conformer ratios owing to nuclear Overhauser effects, and temperature

gradients in the large samples required for ¹³C spectra. The ΔG^\ddagger value obtained from the ¹³C spectra ($7.1_5 \pm 0.2$ kcal mol⁻¹) differs slightly from that determined from ¹H spectra (7.53 ± 0.02 kcal mol⁻¹) (see Table 4). Owing to the different sources of error for the two methods it is likely that a more meaningful value is the average, *i.e.* 7.3_5 kcal mol⁻¹.

In the case of derivative (2) line shape analysis was carried out on the ¹H spectra only, in CHF₂Cl as solvent. In this case, the signals of the formyl protons, which

TABLE 3

Thermodynamic parameters for the interconversion *NO-anti* (73%) to *NO-syn* (27%) determined for pyridine-3-carbaldehyde (1) by line shape analysis of the 100 MHz spectrum in the interval -146 to -126 ° using CHF₂Cl as solvent. The chemical shift differences between the signal of the two rotamers are 9.0 for 2-H and 5.0 Hz for 6-H (see Figure 1). The J_{HH} values were taken from ref. 25

E_a kcal mol ⁻¹	log A	ΔH^\ddagger kcal mol ⁻¹	ΔS^\ddagger cal K ⁻¹ mol ⁻¹
$7.9_5 \pm 0.19$	$13.1_5 \pm 0.29$	$7.6_8 \pm 0.20$	1.1 ± 1.4

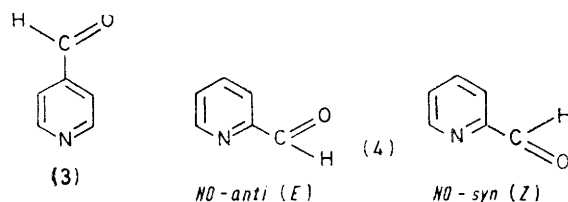
TABLE 4

Free energies of activation (kcal mol⁻¹) of pyridinecarbaldehydes (1)–(4) averaged over a range of temperatures. They refer to the forward *NO-anti* → *NO-syn* equilibrium

Compound	ΔG^\ddagger_{av}	<i>anti</i> : <i>syn</i>	Method	Solvent
(1)	7.53 ± 0.02	73 : 27	¹ H	CHF ₂ Cl
	$7.1_5 \pm 0.2$	80 : 20	¹³ C	Me ₂ O
(2)	6.59 ± 0.02	79 : 21	¹ H	CHF ₂ Cl
(3)	6.3 ± 0.2	50 : 50	¹³ C	CCl ₂ F ₂ -CHFCl ₂
(4)	7.7 ± 0.2	93 : 7	¹³ C	CCl ₂ F ₂ -CHFCl ₂

give two lines (80 : 20 intensity ratio) separated by 40 Hz at -150 °C, could be analysed. A ΔG^\ddagger value of 6.60 ± 0.03 kcal mol⁻¹ was obtained; a decrease in the barrier with respect to (1) agrees with the results for *ortho*-substituted benzaldehydes.¹ The planar ground state is slightly distorted by hindrance by CH₃ and its energy raised, whereas the perpendicular transition state is almost unaffected; as a consequence the energy difference is reduced in the more hindered 4-methylpyridine-3-carbaldehyde.

The barriers of pyridine-4- (3) and -2-carbaldehyde (4) could be better studied by ¹³C n.m.r. (Table 4). In the spectrum of (3) two lines for C-3, and -5 and two for C-2 and -6 were detected at -150 °C (see Table 1).



For the first pair the upfield signal was assigned to C-3 and the downfield to C-5 according to the previously

²⁵ V. J. Kowalewski and D. G. Kowalewski, *J. Chem. Phys.*, 1962, **36**, 266.

reported arguments; on the other hand the difference between C-2 and -6 is so small as to make any assignment pointless.

In the case of (4) no separate signals for two conformers were detected, however the C-3 signal is broadened considerably below -80°C and sharpens again below -130°C . Furthermore (see Figure 3) the

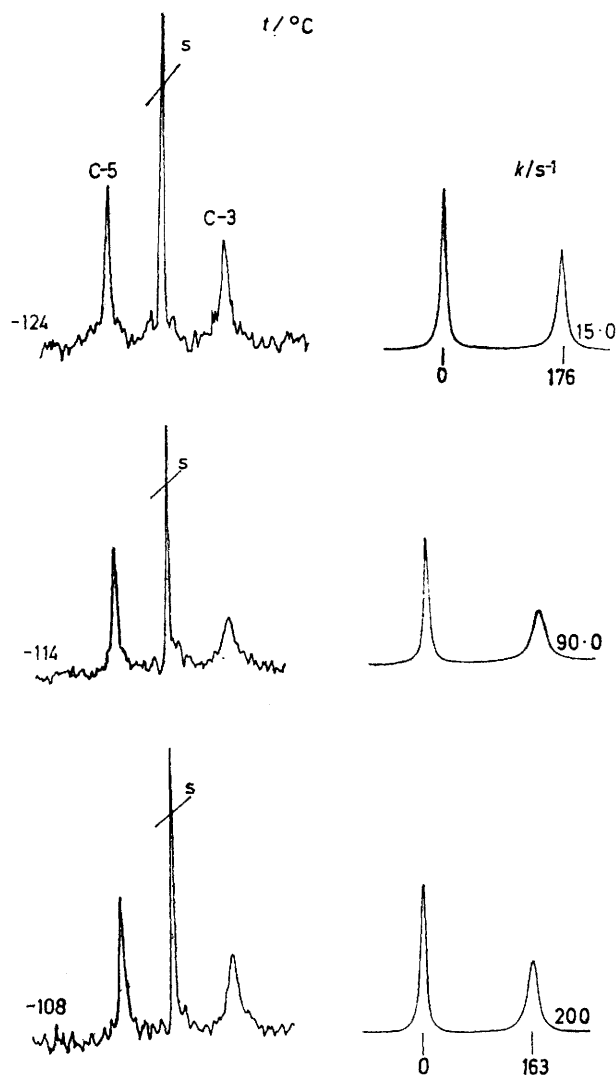


FIGURE 3 Experimental (left) and computer simulated ^{13}C lines of C-3 and -5 of pyridine-2-carbaldehyde (4) in CCl_2F_2 - CHFCl_2 as solvent (line S is the triplet of CCl_2F_2). Below -130° and above -80° the two peaks have essentially the same line width and height; the broadening of C-3 as well as the variation of the relative shift (from 176 to 163 Hz) indicate that there is a small amount (ca. 7%) of the *NO-cis*-rotamer whose C-3 signal is undetectable either because it is hidden by that of C-5, or because the signal-to-noise ratio is too small

C-3 signal is 176 Hz from that of C-5 at -124°C and 163 Hz at -108°C . This is not a temperature dependent shift as there is no variation below -130 and above -100°C , but rather indicates that there is an exchange

²⁶ F. A. Miller, W. G. Fateley, and R. E. Witkowski, *Spectrochim. Acta*, 1967, **23A**, 89.

process between two rotamers. One of these, however, either has its signal hidden by that of C-5 or the signal-to-noise ratio is too small.

The shift of the visible signal is much closer to that of C-3 than to that of C-5 in derivative (3); accordingly *NO-anti* is the preferred conformation (Table 1).

In order to calculate the barrier we assumed that the C-3 chemical shift difference between the two rotamers is the same as observed for similar *ortho*-carbons in other aldehydes (7.6 p.p.m. or 191 Hz). If so, the shift of 13 Hz (*i.e.* 176—163) for the intense signal of C-3 could indicate that the hidden isomer is present in 7% (*i.e.* 13/191). Moreover, various amounts of the less intense conformer have been assumed and a complete range of the rate constants, tested for each ratio by computer simulation (Figure 3). The amount of the less intense species was found to lie in the range 5—10%; the computed matched best the experimental spectra at 7%, in good agreement with the indications obtained from the relative displacement. The *anti-syn*-interconversion barrier turned out to be $7.7 \pm 0.2 \text{ kcal mol}^{-1}$ (Table 4). It should also be pointed out that whereas for values $<5\%$ or $>10\%$, no agreement is possible between computed and experimental spectra; variations of ± 1.0 p.p.m. in the assumed shifts do not appreciably affect the computed patterns. A further indication that the phenomenon is due to exchange is the absence of the broadening in Me_2O . As observed in the case of (1), dimethyl ether reduces the amount of the less stable isomer by a few percent: in the case of (4) this is enough to reduce the line broadening effect beyond the possibility of experimental observation.

It is worthwhile mentioning that the presence of a small amount of the *NO-syn*-rotamer had been also inferred^{9b} from n.m.r. spectra in liquid crystalline solvents. The same method also yielded the torsional barrier ($5.3 \text{ kcal mol}^{-1}$) as did *ab initio* calculations^{9b} ($4.9 \text{ kcal mol}^{-1}$) and ultrasonic relaxation measurements^{9b} ($\Delta G_{300}^\ddagger 6.0$, $\Delta G_{120}^\ddagger 5.1 \text{ kcal mol}^{-1}$). These data refer to the *syn* \rightarrow *anti* equilibrium and should thus be compared with $\Delta G^\ddagger 6.9$ for the present work. However, owing to the different estimate of ΔG° , if the *anti* to *syn* data are calculated from ref. 9b (*i.e.* 7.5 for liquid crystals and 7.1 for *ab initio* computations) the comparison with $7.7 \text{ kcal mol}^{-1}$ of this work is satisfactory. The barriers in gas, as determined by i.r. spectra,²⁶ are smaller than ours for the three isomeric pyridinecarbaldehydes.

To summarize the results we may consider that the trend of the torsional barriers is pyridine-2- > -3- > -4-carbaldehyde [*i.e.* (4) > (1) > (3)]. Whereas a ΔG^\ddagger value for (1) larger than for (3) is expected, since the effect of the *para*-nitrogen is likely to reduce conjugation between the ring and the formyl group, the largest value observed for (4) is not so easy to understand. Its conjugative behaviour should be much closer to that of (3) than of (1). A possible explanation is the reduced steric repulsion in (4), because of the presence of only one ring-hydrogen near the formyl group instead of the two present in (3) and (1). As a consequence the planar ground

state would be stabilized whereas the perpendicular transition state is probably unaffected.

This interpretation is in line with the smaller ΔG^\ddagger values observed in the more hindered derivatives [*e.g.* (2) with respect to (1) and *ortho*-substituted benzaldehydes with respect to the benzaldehyde¹]. A second possible explanation takes into account the electrostatic repulsion between negatively charged oxygen and nitrogen. This enhances the energy of the transition state of pyridine-2-carbaldehyde with respect to those of the 3- and 4-isomers, owing to the shorter distance involved. This would also account for the large amount of the *E*-rotamer. Both hypotheses could be true as they do not exclude each other.

EXPERIMENTAL

Spectral Measurements.—(a) ¹³C Spectra were taken in the Fourier transform mode at 25.15 MHz on a JEOL PS 100 instrument using 10 mm tubes sealed in a vacuum line. Typical set parameters were: spectral width 2 500 Hz, acquisition time 2 s, pulse width 17 μ s (corresponding flip angle 70°), 250 or 500 transients collected. A small amount of deuterioacetone was added to provide the deuterium lock.

(b) 100 MHz ¹H Spectra of (1) and (3) were taken in the continuous wave mode in vacuum sealed 3 mm tubes. Calibration of temperature for both (a) and (b) was made

²⁷ G. Binsch, *J. Amer. Chem. Soc.*, 1969, **91**, 1304 (obtained through the QCPE, Indiana University).

by placing a thermocouple in a dummy tube after the spectrum was taken.

The computation of the line shape was made with the d.n.m.r. program developed by Binsch.²⁷

Materials.—Derivatives (1), (3), and (4) were commercially available and were distilled before use. 4-Methylpyridine-3-carbaldehyde (2) was prepared as follows.²⁸ Cyanoacetamide and ethyl acetoacetate were condensed to give 3-cyano-2,6-dihydroxy-4-methylpyridine with potassium hydroxide. This was allowed to react with phosphoryl chloride in an autoclave to give 2,6-dichloro-3-cyano-4-methylpyridine which was reduced with hydrogen on palladium chloride to 3-cyano-4-methylpyridine which was subsequently refluxed with Amberlite and water to yield 4-methylpyridine-3-carboxamide. The amide then gave ethyl 4-methylpyridine-3-carboxylate by reaction with H₂SO₄ and EtOH. A subsequent reaction with aqueous hydrazine yielded the corresponding hydrazide which was finally converted into 4-methylpyridine-2-carbaldehyde (2) with ammonium hydroxide, sodium metaperiodate, and barium acetate.

To avoid oxidation of (2) to the corresponding carboxylic acid the reaction was carried out and the final product kept under nitrogen, b.p. 110–112° at 12 mmHg,²⁸ *m/e* 121 (*M*⁺).

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²⁸ J. M. Bobbitt and D. A. Scola, *J. Org. Chem.*, 1960, **25**, 560.
²⁹ T. Drakenberg, *J.C.S. Perkin II*, 1976, 147.