# Nuclear Magnetic Resonance Conformational Studies of *C*-Substituted Pyrrolecarbaldehydes. Part II.[1] Barrier to Internal Rotation in 5-Substituted Pyrrole-2-carbaldehydes

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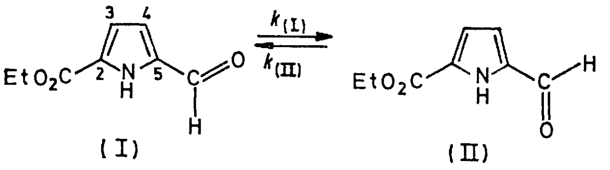
A study of the variations of the n.m.r. spectra of ethyl 5-formylpyrrole-2-carboxylate and pyrrole-2,5-dicarbaldehyde with temperature allowed a determination of the activation parameters by lineshape analysis of the formyl signals. The influence of the nature of the substituent on the spectrum is considered.

THE use of n.m.r. and complete lineshape analysis has allowed the determination of the barriers to internal rotation of aldehyde and ketone derivatives of five-membered heterocycles.[2-4] For the pyrrole series, the influence of the nature of an alkyl substituent on the nitrogen atom has also been established [5] by a study of the rotation barriers of the corresponding 2-aldehydes and a rotational barrier for *N*-t-butylpyrrole-3-carbaldehyde has recently been observed.[6] However these studies have been performed on a restricted number of carbonyl derivatives and no *C*-substituted heterocyclic aldehyde has to our knowledge been investigated.

Our results from studies of the stereospecific long-range coupling constants in several different *C*-substituted pyrrolecarbaldehydes [1,7] led us to believe that some of these molecules would allow an examination of the effect of substituents on the aldehyde torsional barrier. Low temperature n.m.r. results have however showed us that only some of the *C*-substituted pyrrole-2-carbaldehydes could be studied in this way and in this paper we report the results obtained for ethyl 5-formylpyrrole-2-carboxylate and pyrrole-2,5-dicarbaldehyde.

## RESULTS

*Ethyl 5-Formylpyrrole-2-carboxylate*.—The formyl group of this ester-aldehyde can exist in two conformations, NO-*trans* (I) and NO-*cis* (II). The n.m.r. spectrum of this



(1)

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[3] L. Arlinger, K.-I. Dahlqvist, and S. Forsén, *Acta Chem. Scand.*, 1970, **24**, 662.

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[5] C. Jaureguiberry, M. C. Fournie-Zaluski, B. Roques, and S. Combrisson, *Org. Magnetic Resonance*, 1973, **5**, 165.

[6] M. C. Fournie-Zaluski, C. Jaureguiberry, and B. Roques, *Tetrahedron Letters*, 1973, 4177.

[7] M. Farnier and T. Drakenberg, *Tetrahedron Letters*, **1973**, 429.

compound at room temperature is reported in Part I.[1] At low temperature only analysis of the formyl proton has been performed to determine activation parameters. In fact the 3- and 4-H are coupled with the imine proton and because of this the analysis of the 4-H signal is difficult.

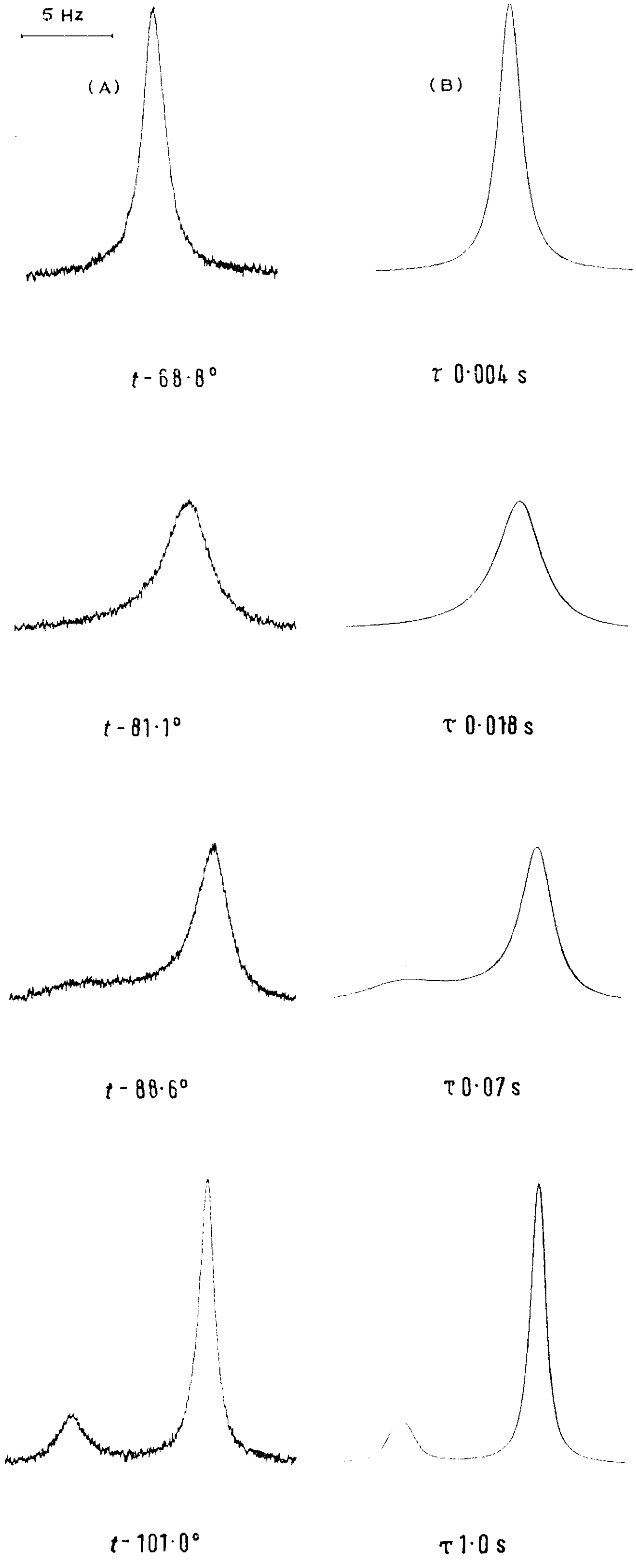


FIGURE 1 Experimental (A) and simulated (B) n.m.r. spectra of the formyl proton of ethyl 5-formylpyrrole-2-carboxylate

At low temperature (−110°) the formyl proton spectrum consists of two signals due to the two conformers. At *ca.* −80° these two signals coalesce to a single broad line. Some examples of this spectrum at different temperatures are given in Figure 1. The assignment of the signals to the two conformers has been made by using as a model the anisotropic effect of the carbonyl group proposed by ApSimon *et al.*[8] (that of Jackman[9] would lead, and has led,[2-4] to the reverse attribution). According to this model the least deshielded and least intense 4-H signal is attributed to the NO-*trans*-conformer and therefore the least intense and more deshielded formyl signal must be attributed to the *trans*-conformer. This result is analogous to those observed for furfural[2] and *N*-methylpyrrole-2-carbaldehyde.[4] It should be noted that this is also in agreement with the results obtained from the stereospecificities of the $^5J$ and $^4J$ couplings.

At temperatures where the formyl proton signal is temperature-dependent, the rate constants $k_{(\mathrm{I})}$ and $k_{(\mathrm{II})}$ can be obtained from lineshape analysis of the spectrum. The equation describing the lineshape was derived from the method used by McConnell,[10] and is, in the present case, a function of the spin–spin relaxation times $T_{2(\mathrm{I})}$ and $T_{2(\mathrm{II})}$, the chemical shift difference $\delta\nu$ between the exchanging protons, the lifetime $\tau\,[= 1/k_{(\mathrm{I})}]$ of the formyl proton in the *trans*-conformation and the population $p$ of the *trans*-conformer. The equation also takes account of the three coupling constants $^5J_{\mathrm{CHO-H(3)}}$ and $^4J_{\mathrm{CHO-H(4)}}$ for the NO-*trans*-conformer and $^4J_{\mathrm{CHO-NH}}$ for the NO-*cis*-conformer, with the values 0·7, 0·4, and 0·3 Hz respectively. Variations in $T_2$ and $\delta\nu$ with temperature have been estimated by methods described previously.[11]

At temperatures from −68·8 to −91·8°, it was possible to determine the lifetime $\tau$ with an estimated accuracy of ±10% (see Table). The free energy of activation was calculated using the Eyring equation (2) where it is assumed

$$k = \frac{1}{\tau} = \frac{\kappa k_{\mathrm{b}} T}{h} \exp\left(-\Delta F^{\ddagger}/RT\right) \qquad (2)$$

that $\kappa = 1$, and the enthalpy and entropy of activation are deduced from a plot of log $(\tau T)$ *versus* $1/T$ as shown in Figure 2. The following values are thus obtained: $\Delta F^{\ddagger}_{T_c(\mathrm{I})} = 9{\cdot}55 \pm 0{\cdot}05$ kcal mol$^{-1}$, $\Delta H^{\ddagger}_{(\mathrm{I})} = 10{\cdot}0 \pm 0{\cdot}5$ kcal mol$^{-1}$, and $\Delta S^{\ddagger}_{(\mathrm{I})} = 2 \pm 3$ cal mol$^{-1}$ K$^{-1}$.

Lifetimes and activation parameters for ethyl 5-formylpyrrole-2-carboxylate

| $t$/°C | $\tau$/s | $\Delta F^{\ddagger}_{(\mathrm{I})}$/kcal mol$^{-1}$ |
|---|---|---|
| −91·8 | 0·1 | 9·60 |
| −88·6 | 0·07 | 9·64 |
| −85·4 | 0·04 | 9·61 |
| −81·1 | 0·018 | 9·52 |
| −77·7 | 0·012 | 9·55 |
| −72·3 | 0·006 | 9·55 |
| −68·8 | 0·004 | 9·56 |

[8] J. W. ApSimon, P. V. Demarco, D. W. Mathieson, W. G. Craig, A. Karim, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1970, **26**, 119.

[9] L. M. Jackman and S. Sternhell, ' Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1959, p. 124.

[10] H. M. McConnell, *J. Chem. Phys.*, 1958, **28**, 430.

[11] T. Drakenberg, K.-I. Dahlqvist, and S. Forsén, *Acta Chem. Scand.*, 1970, **24**, 694.

The value of the equilibrium constant $K$ [$= k_{(I)}/k_{(II)}$] is easily determined from $K = (1 - p)/p$. At the temperature of coalescence $T_c$, there is 25% *trans*-conformer (I) ($p = 0{\cdot}25$). The free energy $\Delta F^\circ$ corresponding to equilibrium (1) is deduced from $K$ and thus at $T_c$ we find $\Delta F^\circ_{T_c} = -0{\cdot}42$ kcal mol$^{-1}$ [and $\Delta F^\ddagger_{T_c(II)} = 9{\cdot}97$ kcal mol$^{-1}$].

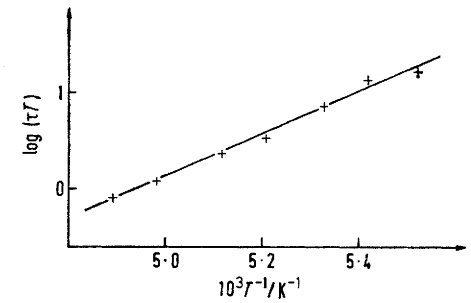
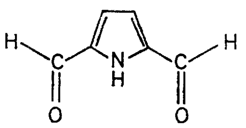
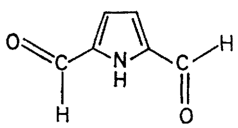


FIGURE 2 Plot of log ($\tau T$) against $T^{-1}$ for ethyl 5-formylpyrrole-2-carboxylate

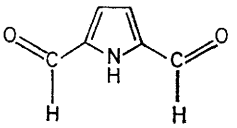
*Pyrrole*-2,5-*dicarbaldehyde*.—This compound can in theory exist as three conformers, NO-*cis-cis*, NO-*trans-trans*, and NO-*cis-trans* (or *trans-cis*) [*cc*, *tt*, and *ct* (or *tc*) respectively] using the notation for the thiophen isostere.[12]



*cc*



*ct*, *tc*



*tt*

The n.m.r. spectra were recorded between room temperature and −120°. At room temperature no coupling can be detected as observed [1] for this compound under other solvent and concentration conditions. With a progressive decrease in the temperature the signals of the two formyl protons broaden and coalescence is reached at *ca.* −95°. At lower temperature three signals are observed, the most intense appearing in the middle (typical spectra are shown in Figure 3). No spin couplings could be resolved; however the same coupling constants were assumed as those used in the 2,5-ester-aldehyde study.

The signals observed at −117·6° have been assigned by reference on the one hand to the carbonyl anisotropic model of ApSimon *et al.*[8] and on the other to the respective chemical shifts of the formyl group in the *cis*- and *trans*-forms obtained for the 2,5-ester-aldehyde. Thus the middle signal (the most intense) is attributed to the NO-*cis-cis*-conformer. The other two signals are due to the formyl protons of the NO-*cis-trans*-conformer. For this conformer the most deshielded signal is that of the *trans*-formyl proton and the most shielded that of the *cis*-formyl proton. The two extreme signals thus correspond to the same *ct*-conformer. It should be noted that the most deshielded signal is broader than that attributable to the *cis*-formyl proton: this is due to the fact that the *trans*-formyl proton is coupled twice (with 3- and 4-H) while the *cis*-proton is coupled only once (with the imine proton).

The third conformer, *tt*, if it exists, has a population too low to give a detectable signal, in agreement with observations for the thiophen isostere by n.m.r. in a nematic mesophase [12] and by e.s.r.[13]

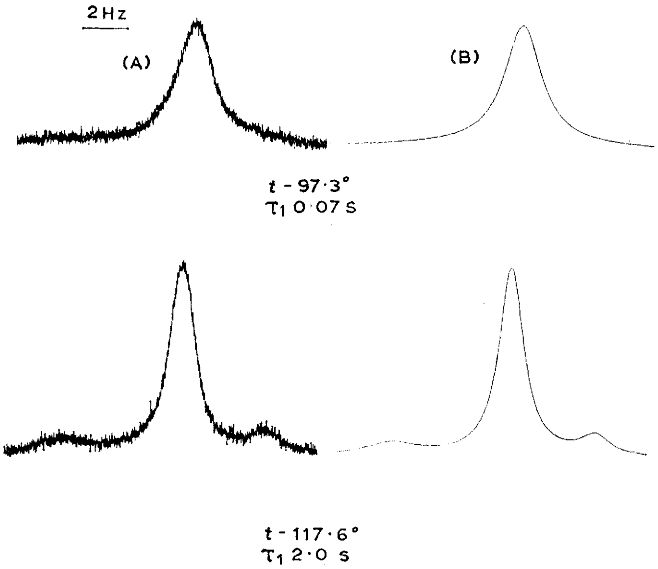


FIGURE 3 Experimental (A) and simulated (B) n.m.r. spectra of the formyl protons of pyrrole-2,5-dicarbaldehyde

In spite of the fact that conformer *tt* could not be detected, a study of the rate of rotation was carried out assuming an exchange among the four forms. The equation

$$\begin{tikzcd} ct \arrow[r, shift left, "k_1"] \arrow[d, shift left] & cc \arrow[l, shift left] \arrow[d, shift left] \\ tt \arrow[u, shift left, "k_4"] \arrow[r, shift left] & tc \arrow[l, shift left, "k_3"] \arrow[u, shift left, "k_2"'] \end{tikzcd}$$

used to calculate the shape of the signals due to an exchange among the four forms was derived in the same way as for the two site exchange described above. This equation is a function of the four rate constants $k_1$—$k_4$ and the $T_2$ values, populations, and chemical shifts at each site. In the calculations the percentage of *tt*-conformer was assumed to be 1% ($p_{tt}$ 0·01). This value can however change significantly without affecting the lineshape noticeably. We have also set $p_{tc} = p_{ct}$. As knowledge of a single lifetime, taking account of populations, allows the determination of all the others we show only the lifetime $\tau_1 = 1/k_1$ in Figure 3.

For the experimental conditions used, the lifetimes can only be determined accurately at temperatures close to that of coalescence $T_c$ and thus only the free energy of activation can be obtained with an acceptable error. Application of equation (2) gives $\Delta F^\ddagger_{ct \longrightarrow cc} = 9{\cdot}26$ kcal mol$^{-1}$ at −93·1° and 9·16 kcal mol$^{-1}$ at −97·3°. The free energy of activation $\Delta F^\ddagger_{T_c}$ corresponding to the passage of

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[12] L. Lunazzi, G. F. Pedulli, M. Tiecco, and C. A. Veracini, *J.C.S. Perkin II*, 1972, 755.

[13] L. Lunazzi, G. F. Pedulli, M. Tiecco, C. Vincenzi, and C. A. Veracini, *J.C.S. Perkin II*, 1972, 751.

conformer *ct* to *cc* can, at the temperature of coalescence, be considered to be *ca.* 9·2 kcal mol$^{-1}$, with an error of *ca.* ±0·1 kcal mol$^{-1}$. At coalescence the conformer populations are: $p_{tc} = p_{ct} = 0{\cdot}10$, $p_{cc} = 0{\cdot}79$. Thus the 2,5-dialdehyde exists as *ca.* 80% *cc* and 20% *ct* or *tc*. The free energy $\Delta F^{\circ}_{T_c}$ for the equilibrium $ct \rightleftharpoons cc$ is then easily determined as $-0{\cdot}73$ kcal mol$^{-1}$ from which $\Delta F^{\ddagger}_{T_c(cc \rightarrow tc)} = \Delta F^{\ddagger}_{T_c(cc \rightarrow ct)} = 9{\cdot}9 \pm 0{\cdot}1$ kcal mol$^{-1}$.

## DISCUSSION

The population ratios obtained for the 2,5-ester-aldehyde and the 2,5-dialdehyde at low temperature are in good agreement with the conclusions drawn from a study[1] of the long-range coupling constants $^5J$ and $^4J$ for these compounds. We also note that the population ratio for pyrrole-2,5-dicarbaldehyde is similar to that found for thiophen-2,5-dicarbaldehyde.[12,13] The thiophen isostere can be assumed to be a suitable compound for comparison and better than the furan isostere,[14,15] especially because of the fact that the population ratio for furfuraldehyde[2,16] differs markedly from those of pyrrole- and thiophen-2-carbaldehydes. Additionally we note that a substituent with a $-M$ effect at C-5 appreciably influences the conformer proportions of pyrrole-2-carbaldehydes.

The nature of the substituent at C-5 influences the conformational rate parameters. Thus while the signals of the two conformers of pyrrole-2-carbaldehyde appear distinctly at −70°,[4] the temperature of coalescence is only reached at *ca.* −80° for the 2,5-ester-aldehyde and at −95° for the 2,5-dialdehyde. This will also be reflected in the free energy of activation for these compounds.

Arlinger *et al.*[4] have stated that pyrrole-2-carbaldehyde behaves analogously to its *N*-methyl derivative, and it has furthermore been shown that *N*-substitution has little effect on the free energy.[5] We will thus assume that the free energy of activation, $\Delta F^{\ddagger}_{(\mathrm{I})}$, for pyrrole-2-carbaldehyde is *ca.* 11 kcal mol$^{-1}$.

It appears that the presence of an ethoxycarbonyl or formyl group at C-5 causes a distinct decrease in the barrier to rotation which is in agreement with the expected effect from an electron-withdrawing substituent. This is also in agreement with some results that have been obtained for the benzene series:[17] *para*-substitution by a group with an electron donating mesomeric effect results in an increase in the rotational barrier. The 5-substituted pyrrole-2-carbaldehydes are structural analogues of *para*-substituted benzaldehydes and the presence of an electron-withdrawing substituent should thus normally mean a decrease in the rotation barrier, as found in this work.

From consideration of the $-M$ effect of a nitro-group (which is greater than that of $CO_2Et$ and CHO) it must be expected that the torsional barrier for the former is even lower than those observed here. The temperature of coalescence must thus be very low and it is therefore not surprising that we were not able to carry out studies of the nitro-aldehyde although at room temperature the conformer proportions[1] appeared particularly favourable.

## EXPERIMENTAL

*Ethyl 5-Formylpyrrole-2-carboxylate.*—This compound was prepared by the method given in the literature.[18] N.m.r. studies were carried out by dissolving the ester (15 mg) in [$^2H_6$]acetone (0·3 ml)–[$^2H_{10}$]diethyl ether (0·3 ml) containing tetramethylsilane as internal reference. The choice of solvents was dictated in part by solubility considerations and in part by the need to obtain temperatures $\leqslant -100°$. N.m.r. spectra were recorded at 60 MHz on a Varian A-60A spectrometer fitted with variable temperature accessories. For recording the spectra a scale expansion of 1 Hz cm$^{-1}$ was used and the sweep rate was 0·02 Hz s$^{-1}$. Chemical shifts were measured with the sideband technique using a Hewlett–Packard frequency counter model 5216A. The spectrometer resolution was adjusted so as to always obtain the same linewidth for the tetramethylsilane signal.

Temperatures were determined (±0·5°) by a method described previously[11] using a capillary containing dimethyl ether–methanol.

*Pyrrole-2,5-dicarbaldehyde.*—This was prepared by the method of Cresp *et al.*[19] Because of its very low solubility at low temperature and the need to work at below −100° experiments were carried out by dissolving the dialdehyde (10 mg) in [$^2H_6$]acetone (0·3 ml)–dimethyl ether (*ca.* 0·3 ml). The spectra were recorded at 100 MHz on a Varian XL 100 spectrometer with the following conditions: internal lock on the dimethyl ether signal; scale expansion 0·5 Hz cm$^{-1}$; sweep rate 0·05 Hz s$^{-1}$.

Temperatures were measured (±1°) directly using a precalibrated copper–constantan thermocouple.

*Rate Measurements.*—The rate of internal rotation of the formyl group was determined by comparison of the experimental and simulated spectra obtained on a Univac 1108 computer.[1]

This study was carried out in the laboratory of Professor S. Forsén, Lund. M. F. thanks Professor Forsén for his interest and hospitality.

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[16] M. L. Martin, J.-C. Roze, G. J. Martin, and P. Fournari, *Tetrahedron Letters*, 1970, 3407; B. Roques, S. Combrisson, C. Riche, and C. Pascard-Billy, *Tetrahedron*, 1970, **26**, 3555; B. Roques and S. Combrisson, *Canad. J. Chem.*, 1973, **51**, 573.

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