

## STEREODYNAMICS AND CONFORMATION OF FURAN-3-ALDEHYDE AND OF ITS CORRESPONDING FUROYL $\sigma$ -RADICAL.<sup>1</sup>

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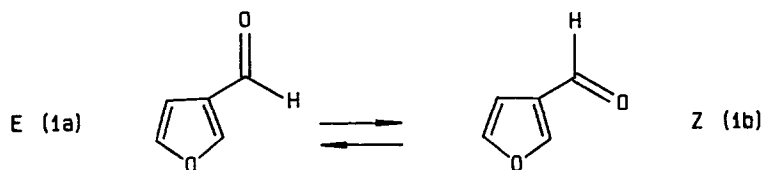
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*Key Words:*

Rotational barrier; Dynamic NMR; NOE effect; MM-2 calculations; ESR spectra

**Abstract.** NOE measurements, combined with MM-2 calculations, predict that the proportion of the Z conformer in the title compound is high enough (14% at room temperature) as to give line broadening effects due to E,Z exchange. Line shape analysis of the dynamic C-13 NMR signals at variable temperature yielded a free energy of activation of 8.3 Kcal/mol. One of the lines of the spectrum of the Z conformer was also directly observed (0.8% at -140°C, corresponding to 11% at room temperature if the entropy difference is assumed zero). ESR spectra and INDO calculations show that also the  $\sigma$ -radical (obtained by H-abstraction from the HCO moiety of the title compound) essentially adopts the E conformation.

Barriers to rotation about the Ar-CHO bond have been determined, by dynamic NMR experiments, for the isomeric aldehydes containing the furan<sup>2,3</sup> or the thiophen<sup>4</sup> ring, except furan-3-aldehyde (1). This lack is a consequence of the indications of a number of NMR studies that conformer E (1a) is the only species present<sup>5</sup> at the equilibrium.



Four reports (based either on stereospecific H,H couplings<sup>6,7</sup> or on Lanthanide Induced Shifts effects<sup>8,9</sup>) agreed that 1a is present in a 96-100% proportion, in CHCl<sub>3</sub> at room

temperature. A recent, independent investigation, using long range C,H couplings, confirmed<sup>10</sup> that the population of 1a is 97±1%, in the same conditions. At the low temperature required to slow the E,Z interconversion on the NMR timescale (about -140°), the minor conformer is thus predicted to have a population lower than 0.1%. With such a small amount of the minor conformer at the equilibrium, one cannot observe the line broadening effect that is required to experimentally determine the exchange rate constant, hence the  $\Delta G^*$  value.

## Results and Discussion

We have reinvestigated the conformational behavior of furan-3-aldehyde 1 by the differential Nuclear Overhauser Enhancement (NOE) technique: our conclusions, although qualitatively in agreement with the previous reports,<sup>5-10</sup> outlined an important difference concerning the amount of the minor conformer present at the equilibrium.

Saturation of the H-2 and H-4 signals of 1 in CDCl<sub>3</sub> at room temperature resulted in the enhancements of the signals corresponding to the HCO group, conversely saturation of the HCO signal enhanced those of H-2 and H-4. The ratio of the two NOE effects ( $\eta$ ) observed for the HCO group can be considered approximately equal to the ratio of the cross relaxation rates, that depend upon the inverse 6th power of the ratio of the average H-2, HCO and H-4, HCO interproton distances. When HCO is saturated, the ratio of the NOE values observed for H-2 and H-4 is essentially equal to the one observed in the previous experiment, as the  $T_1$  values of the protons involved are equal<sup>11,12</sup> (Table 1).

Table 1. Relaxation times ( $T_1$ , estimated error  $\pm 0.3$  s) relative to the CHO, H-2 and H-4 protons of Furan-3-aldehyde (1) and Thiophen-3-aldehyde (2) measured in the same sample where the NOE values ( $\eta$ , column 5) were also obtained irradiating the signals of column 4.

Compound	$T_1$ (s)	observed signal	irradiated signal	$\eta$ (%)
1	10.0	CHO	H-2	12.0 $\pm$ 0.7
	10.0	CHO	H-4	2.4 $\pm$ 0.2
	9.9	H-2	CHO	10.8 $\pm$ 0.5
	9.9	H-4	CHO	2.2 $\pm$ 0.2
2	4.3	CHO	H-2	15.6 $\pm$ 0.8
	4.3	CHO	H-4	5.8 $\pm$ 0.4
	5.6	H-2	CHO	11.6 $\pm$ 0.6
	5.1	H-4	CHO	3.6 $\pm$ 0.3

The same average distance H-2,CHO and H-4,CHO will thus be obtained by using two

different NOE experiments, giving additional confidence on the internal consistency of the method. In conditions of fast exchange these average interproton distances are, of course, related to the relative proportion of the pair of conformers 1a, 1b. In order to estimate the distances within each conformer, molecular mechanics calculations<sup>13</sup> were carried out. The four distances ( $r$ , in Å)<sup>14</sup> obtained in this way were then related to the NOE values according to the relationship:<sup>12</sup>

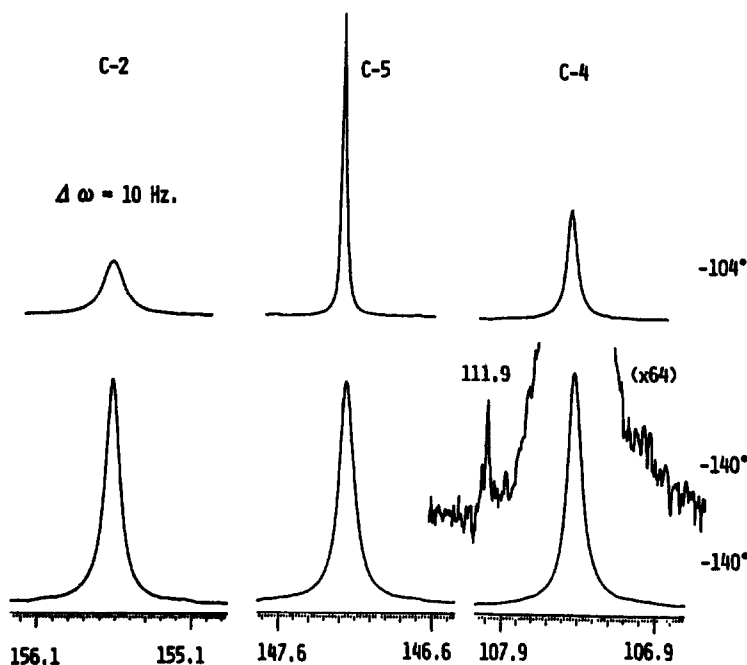
$$\frac{{}^{\text{H}2}\eta(\text{CHO}) / {}^{\text{H}4}\eta(\text{CHO})}{5.0 \pm .7} = \frac{x(r_2^{\text{E}})^{-6} + (1-x)(r_2^{\text{Z}})^{-6}}{x(r_4^{\text{E}})^{-6} + (1-x)(r_4^{\text{Z}})^{-6}}$$

where  $\eta(\text{CHO})$  is the observed NOE on the aldehyde when H-2 or H-4 are irradiated (Table 1), the unknown ( $x$ ) is the amount of the E conformer 1a,  $r_2$  is the H-2,CHO distance and  $r_4$  the H-4,CHO distance in the conformer E or Z, as indicated. Solution of this equation yields  $x = 86 \pm 3\%$ . According to this result the proportion of the minor conformer 1b at low temperature should be at least ten times larger than previously predicted.<sup>15</sup> Detection of line broadening effects should be thus quite evident, at least in the C-13 spectra where large shift differences are expected. In the analogous case of thiophen-3-aldehyde (2)<sup>4</sup>, in fact, the C-2 signal of the minor conformer Z is about 9 ppm upfield and the C-4 about 5 ppm downfield<sup>16</sup> with respect to the corresponding signal of the major conformer E.

The reliability of this approach to conformational analysis was checked in the case of thiophen-3-aldehyde (2) where low temperature NMR spectra had shown<sup>4</sup> that the Z conformer (2b) was about 3% at  $-140^\circ\text{C}$ . This value corresponds to about 18% at room temperature (if the entropy difference is assumed zero), in agreement with the conclusions (2b=20%) reached by other NMR investigations at room temperature.<sup>8,9,17</sup> The NOE values obtained for 2 are also reported in Table 1. By introducing the ratio<sup>18</sup> of the observed NOE values (2.7) and the appropriate distances<sup>19</sup> in the same equation used for 1, the proportions of conformer Z (2b) turns out to be 20%, in excellent agreement with the known values.<sup>4,8,9,17</sup>

On the basis of these results, the C-13 spectrum of 1 was thus examined as function of temperature in dimethyl ether: this solvent was selected having a dielectric constant similar to that of chloroform. As predicted by our analysis of the NOE results, line broadening was actually observed: the lines of C-2 and C-4, that were as sharp as the other three lines down to  $-70^\circ$ , broadened substantially between  $-95^\circ$  and  $-115^\circ$  and sharpened again on further lowering the temperature. As shown in Figure 1, the line

widths of C-2 and C-4 are wider than that of C-5 at  $-104^\circ$  but have the same width at  $-140^\circ$ . The maximum broadening is observed for the line of C-2 ( $\Delta\omega = 10$  Hz), since it has a larger shift separation than the line of C-4 for the E and Z conformers.<sup>4</sup> Using the appropriate equation<sup>20</sup> relating the maximum width to the rate constant, a  $\Delta G^*$  of 8.3 Kcal/mol is obtained for the rotational process.



**Figure 1.** C-13 (75.5 MHz) lines of C-2, C-5 and C-4 of 1 in Me<sub>2</sub>O at  $-104^\circ$  (upper) and at  $-140^\circ$  (lower). The inset (right hand side) displays the C-4 line (at  $-140^\circ$ ) vertically expanded 64 times and with an horizontal scale reduced by a factor of 8. Downfield to the intense signal of the major conformer E (107.4 ppm) it is then visible the C-4 signal (111.9 ppm) of the minor conformer Z ( $0.8 \pm 0.2\%$ ).

As observed in the case of the two isomeric thiophen aldehydes, the  $\Delta G^*$  of the furan-3-aldehyde (1) is also lower than that of the furan-2-aldehyde: the difference is 2.6 Kcal/mol (i.e.  $10.9 - 8.3$ ), indicating a much lower conjugative ability of the CHO group with the furan ring substituted in position 3 than in position 2. On the other hand, whereas the rotational barrier of furan-2-aldehyde ( $10.9$  Kcal/mol)<sup>2,3</sup> is definitely larger than that of thiophen-2-aldehyde ( $10.1$  kcal/mol)<sup>4</sup> that of furan-3-aldehyde is equal, within the errors, to that of thiophen-3-aldehyde ( $8.5$  Kcal/mol).<sup>4</sup> This seems to suggest that the two rings have a different conjugation ability in position 2 but an almost equal one in position 3.

Since the observed line broadening offered an unambiguous proof of the existence of

a not negligible amount of the minor conformer 1b, we carefully looked for a direct detection of the corresponding signal. Whereas the region upfield to the C-2 line (where the C-2 signal of 1b is expected<sup>4</sup> to be found) is obscured by the intense line of C-5, the region downfield to the C-4 line is free from any other signals.<sup>21</sup> When a signal to noise ratio larger than 500:1 was obtained at  $-140^\circ$ , a small line ( $0.8 \pm 0.2\%$  with respect to that of the major one) was actually observed at 4.45 ppm downfield with respect to the C-4 line of 1a (Figure 1). This small signal disappears at temperatures higher than  $-120^\circ$ , as expected owing to the exchange with its intense companion. On the basis of this measurement the signal of the conformer 1a ( $99.2 \pm 0.2\%$  at  $-140^\circ$ ) should become  $89 \pm 1\%$  at ambient temperature, in good agreement with the results of the NOE experiment ( $86 \pm 3\%$ ).<sup>22</sup>

The knowledge of the shift difference and of the relative amount of the two conformers also allowed us to carry on a complete line shape analysis for the line of C-4: the  $\Delta G^*$  obtained in this way ( $8.15 \pm 0.15$  Kcal/mol) matches, within the uncertainty, the value previously obtained from the C-2 line using the formula of ref. 20.

It has been recognized that the  $\sigma$ -radicals produced by H-abstraction from aromatic aldehydes have conformations that can be related to those of the parent molecule<sup>23</sup> and it has been shown that the Ar- $\dot{C}O$  rotational barriers of these radicals are approximately 5 Kcal/mol lower than the Ar-CHO barriers of the parent aldehydes.<sup>24</sup> In the present case the  $\sigma$ -radical (3) derived from 1 is thus expected to have a barrier of about 3.0 - 3.5 Kcal/mol: this is a fast enough process as to allow the radical to reach its own thermodynamic equilibrium, between 3a and 3b, before decaying.<sup>23,25</sup>



As a consequence, the conformational preference of 3 might be, in principle, different from the one of its parent aldehyde 1.

The ESR spectrum of 3 (Figure 2) displays four lines due to the h.f.s. constants of two of the three ring hydrogens (2.0 and 0.7 G. respectively), the constant due to the third one being zero. Even at the lowest attainable temperature ( $-135^\circ$ ) no selective line broadening effect was observed. Since in the ESR spectroscopy it is possible to observe such an effect when motions with barriers larger than 2.5 Kcal/mol are involved,<sup>25,26,27</sup> the absence of any line broadening suggests that either only one conformer is present or

that the 3a, 3b equilibrium is so biased toward one of them as to make this feature negligible. Like the parent molecule, radical 3 seems therefore to be present mainly in a single conformation. From the ESR data it is also possible to assess which of the 3a, 3b conformers is the preferred one.

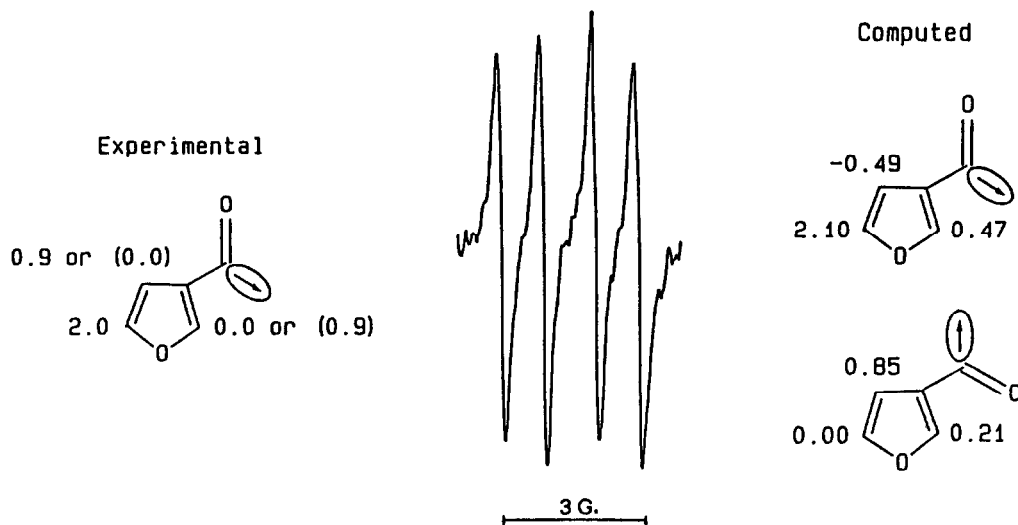


Figure 2. ESR spectrum of radical 3 in cyclopropane at  $-110^\circ$ . The INDO computed  $a_H$  values are reported, for both the E (3a) and Z (3b) conformers, on the right hand side and the experimental  $a_H$  values on the left hand side.

It has been shown, in fact, that in aryl  $\sigma$ -radicals the  $a_H$  splittings of the ortho- and para-like positions are very small and not stereospecific, whereas the meta-like positions have  $a_H$  values depending on the stereochemical arrangement.<sup>26,28</sup> In particular, the meta-like splitting of an hydrogen bonded to a carbon located at the end of a W pathway, having the  $sp^2$  orbital of the unpaired electron at the other extreme, is relatively large (2-3 G.): on the contrary if such a W pathway cannot be followed, this  $a_H$  value is zero. The only hydrogen in radical 3 that can give a large meta-like splitting is the one bonded to C-5 in conformer 3a. In conformer 3b, on the contrary, there is not any hydrogen that fulfills the requirements for such a splitting. INDO calculations carried out on 3 confirm this prediction, in that the only large splitting is the one predicted for H-5 in conformer 3a (Figure 2). It can be therefore concluded that both the molecule 1 and its corresponding  $\sigma$ -radical 3 have, essentially, the same conformational preferences. The reason has probably to be found in the lower level of energy available

to a situation where the C=O double bond is trans to the C-2,C-3 double bond: in both the molecule (1) and the radical (3) steric or dipolar repulsions are too small to substantially modify this arrangement.

### Experimental

The differential NOE experiments were carried out in nitrogen saturated  $\text{CDCl}_3$  solutions of 1 at 200 MHz (Varian, Gemini 200). The signals were presaturated for a time equal to about  $5T_1$  before acquiring the spectrum with the decoupler turned off. The irradiation was carried out by setting the decoupler at the frequencies of the various lines of the multiplet to be saturated and cycling it over these lines<sup>11</sup> (about 60 cycles). A program that accumulates the difference between two FID's (the one corresponding to the preirradiated spectrum and the one where the irradiation is kept away from any signal) was employed. A control spectrum, with half the number of scans, was subsequently obtained in the same conditions and the NOE values determined by comparing the line intensities of the two spectra. The samples for the low temperature measurements were prepared by condensing dimethylether into NMR tubes, containing the aldehyde 1 and some deuterio acetone for the lock. The temperatures were determined by introducing in the spectrometer (Varian, Gemini 300 operating at 75.5 MHz) a sample containing methanol, methanol-d<sub>4</sub> and  $\text{CHF}_2\text{Cl}$ : the temperature dependence of the chemical shifts having been previously calibrated with thermocouples and thermistors in the same physical sample. To detect the very small signal of the minor conformer, 10 mm tubes had to be used, owing to the low solubility of 1 near  $-140^\circ\text{C}$  (Bruker, CXP 300, 75.5 MHz).

The samples for the ESR investigation were prepared by condensing the gaseous solvent (cyclopropane) into a suprasil quartz tube containing aldehyde 1 and some di-tert-butyl peroxide ( $\text{Bu}^t\text{-OO-Bu}^t$ ). The sealed samples were then introduced in the cooled cavity of the ESR spectrometer (Varian E-3) and photolyzed using an high-pressure Hg lamp (500 W), keeping the temperature in the range  $-70^\circ$ ,  $-135^\circ$ .

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15. If the amount of the minor conformer Z (1b) is 14±3% at room temperature, an amount of about 1.7±0.8% is expected at -140°, assuming that  $\Delta G^\circ$  is temperature independent.
16. As observed in 2, the other lines of 1 are expected<sup>4</sup> to have shift differences, in the two conformers, too small to produce noticeable line broadening.
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18. The ratio of the NOE's obtained when observing two different nuclei (here H-2 and H-4) irradiating a third one (here HCO) is even better approximated to the ratio of the cross relaxation rates, if it is divided by the ratio of the two corresponding  $T_1$ 's (see ref. 11,12). For instance in 2 the ratio of the NOE's observed for H-2, H-4 (i.e. 11.6/3.6 = 3.2) is slightly different from the NOE ratio observed for HCO when irradiating H-2, H-4 (i.e. 15.6/5.8 = 2.7). If however 3.2 is divided by the ratio of the corresponding  $T_1$ 's (i.e. 5.6/5.1) the two ratio becomes almost identical.
19. In 2 the computed  $r_2$  distances are 2.54 and 3.91 Å and the  $r_4$  distances 3.84 and 2.47 Å for the E and Z conformers respectively.
20. The equation is  $k = 2 \pi \Delta \omega$ , where  $\Delta \omega$  is the maximum broadening (in Hz) due solely to the exchange process and  $k$  ( $s^{-1}$ ) is the rate constant. See for instance: Anet, F.A.L.; Yavari, I.; Ferguson, I.J.; Katritzky, A.R.; Moreno-Manas, R.; Robinson, M.J.T. J.Chem.Soc., Chem.Commun., 1976, 399.  
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21. At -140° the C-13 chemical shifts (ppm from TMS) of the conformer 1a in Me<sub>2</sub>O are; C-2= 155.65; C-3= 130.05; C-4= 107.4; C-5= 147.15; CHO= 186.9.
22. It is interesting to observe that this amount corresponds to the one computed by ab-initio calculations for 1 in CHCl<sub>3</sub> as solvent. See: Benassi, R.; Folli, U.; Schenetti, L.; Taddei, F. J.Chem.Soc. Perkin Trans. 2, 1988, 1501.
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