Conformational Studies by Dynamic Nuclear Magnetic Resonance. Part 26.[1] Interconversion Barriers between *syn*- and *anti*-Conformers of Isomeric Thiophenecarbaldehydes

Lodovico Lunazzi * and Giuseppe Placucci
Istituto di Chimica Organica, Università, Viale Risorgimento 4, Bologna, Italy
Chryssostomos Chatgilialoglu and Dante Macciantelli
Istituto CNR, Via Tolara di Sotto, Ozzano E., Italy

The low-temperature ^{13}C n.m.r. spectra (25.16 MHz) of thiophene-2- and -3-carbaldehyde [(1) and (2)] display line-broadening effects due to the exchange between their *S,O-syn*- and *S,O-anti*-conformers. In both cases the free energy of activation for rotation of the -CHO moiety was measured, the values being 10.15 and 8.5 kcal mol^{-1} for (1) and (2), respectively. In the case of thiophene-3-carbaldehyde (2) the signals of both conformers were detected, the ratios being 97 : 3 at −140 and 93 : 7 at −100 °C in favour of the *S,O-anti*-conformer. In thiophene-2-carbaldehyde (1) the minor conformer (*S,O-anti*) was present in too small an amount to be unambiguously detected by a conventional spectrometer, but spectra taken with a superconducting instrument (75.48 MHz) revealed *ca.* 1.5 % of this conformer at −100 °C.

The conformational preferences of formyl, acetyl, and other acyl derivatives of five-membered heterocyclics (furan, thiophene, pyrrole) have been investigated by a variety of n.m.r. techniques. In the case of furan-2-carbaldehyde,[2-5] 2-acetylfuran,[5-7] and *N*-alkylpyrrole-2-carbaldehydes,[8-10] the *syn*- and *anti*-conformers were detected directly at low temperature. The corresponding interconversion barriers could thus be determined.

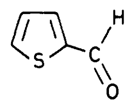
On the other hand, such conformers of the analogous thiophene derivatives have never been observed directly. In the case of thiophene-2-carbaldehyde (1), a number of studies at room temperature seemed to indicate that, essentially, only the *S,O-syn* conformer (1a) is present,[11-13] and this finding was substantiated by a structure determination in nematic solution [14] and by the structure of the 4-bromo derivative in the solid state.[11] This explained the apparent absence, at low temperature, of the n.m.r. signals corresponding to the second conformer (1b), and hence the impossibility of determining the rotational barrier *via* n.m.r. Recently, however, a reinterpretation of the long-range couplings of (1) suggested the existence of a small, but not negligible, amount of the *S,O-anti*-conformer.[15] This would explain the selective line-broadening effect reported, at low temperature, in the ^{13}C spectrum of thiophene-2-carbaldehyde.[4] With regard to thiophene-3-carbaldehyde (2), all the indications so far agree on the presence of both conformers in 4 : 1 ratio at room temperature, the *S,O-anti*-form (2b) being the more stable.[11,16,17]

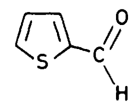
If these predictions are correct, both conformers should be detectable at low temperature and the rotational barrier could in principle be determined. This would be particularly desirable since a number of barrier heights are available for furans and pyrroles bonded to carbonyls,[2,6,7,9,10,18] whereas none has yet been measured for a thiophene derivative.

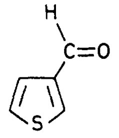
In the present work we have attempted to measure the interconversion barriers in thiophene-2- and -3-carbaldehydes by ^{13}C n.m.r. spectroscopy.

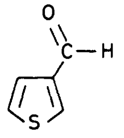
Results and Discussion

The ^{13}C spectrum (25.16 MHz) of thiophene-3-carbaldehyde (2) in $CHF_2Cl-CCl_2F_2$ at −140 °C shows two pairs of lines for C-2 and C-4, in the ratio 97 : 3. According to the Boltzmann distribution this corresponds, at +25 °C, to an 80 : 20 ratio, if the reasonable assumption is made that $\Delta S°$ is negligible.


(1a) *S,O-syn*

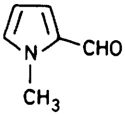
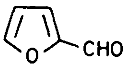
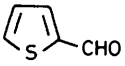
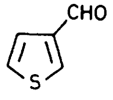
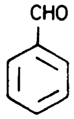

(1b) *S,O-anti*


(2a) *S,O-syn*


(2b) *S,O-anti*

Such a result confirms the predictions of studies based on averaged long-range couplings.[11,16] and on the averaged lanthanoid-induced shift.[17] The more intense signals of the pairs due to C-2 and C-4 are, respectively, at lower and higher field with respect to the corresponding weaker signals. Since it is known that the C=O moiety shifts upfield the signals of carbon atoms in a *syn* relationship,[6,19,20] the intense signals belong to the *S,O-anti*-conformer (2b). This assignment agrees with the previous ones,[11,16,17] based on different assumptions. Because of the very biased equilibrium between the two conformers of (2), line-shape simulation could be best carried out at temperatures where maximum line broadening occurs (*i.e.* −98 °C for C-2, linewidth 19 Hz, and −100 °C for C-4, linewidth 12 Hz). At higher temperatures (*e.g.* −75 °C) these lines are still broader than that of C-5. However, the broadening is too small to allow meaningful measurements: it is only noticeable since it makes the apparent intensity (or height of these lines) lower than that of C-5. On the other hand the integrated intensities of the C-2, C-4, and C-5 signals at −75 °C were equal, within the (large) experimental errors. By using the chemical shift differences measured at −140 °C (*i.e.* 222 Hz for C-2 and 137 Hz for C-4) the maximum broadening could be computer-simulated only by assuming a conformer ratio of 93 : 7. According to the Boltzmann distribution this is actually the expected ratio in the range −98 to −100 °C on the basis of the ratio observed at −140 °C. The rate constants best reproducing the linewidth (95 s^{-1} for C-2 and 70 s^{-1} for C-4) yield the free energy

Table 1. Free energies of activation ($\Delta G^\ddagger$/kcal mol^{-1}) for the conversion of the more stable into the less stable conformer (note that the *syn–anti* assignment reported in ref. 2 should be reversed; see refs. 6 and 7*b*)

Compound	$\Delta G^\ddagger$	Solvent	*T*/°C	Ref.
	11.2	$CDCl_3$	−51	9
	10.9	Me_2O	−81, −57	2
	10.1_5	CD_2Cl_2	−75	This work
	8.5	$CHFCl_2$–CF_2Cl_2	−100, −98	This work
	7.7	Me_2O	−125, −104	19

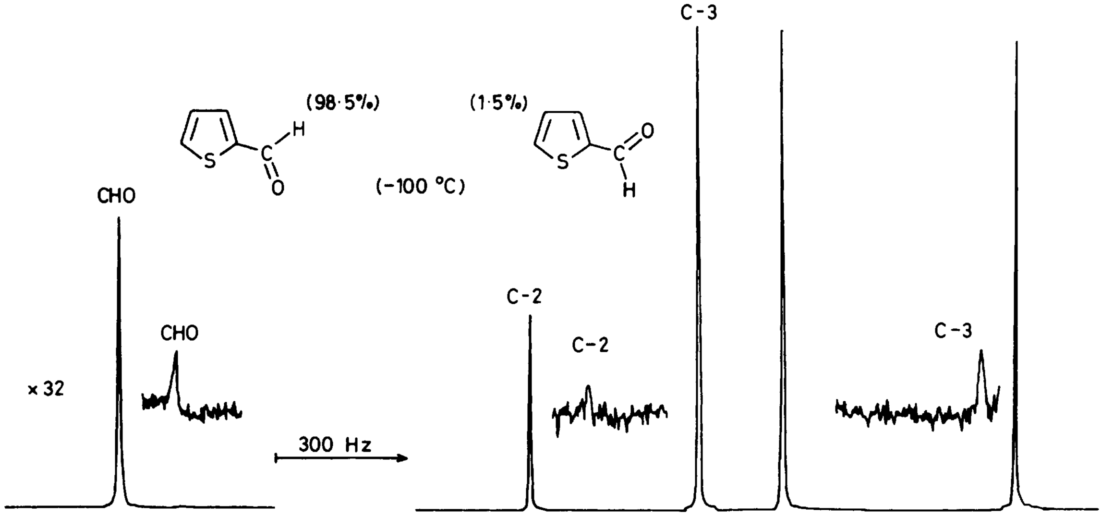


Figure. ^{13}C N.m.r. spectrum (75.48 MHz) of thiophene-2-carbaldehyde (1) taken at −100 °C in CD_2Cl_2; by amplifying the signals 32 times one observes three lines due to the presence (1.5%) of the *S,O-anti*-conformer (1b)

of activation for the interconversion (2b) $\rightleftharpoons$ (2a): $\Delta G^\ddagger = 8.5 \pm 0.1$ kcal mol^{-1}.

In the case of thiopene-2-carbaldehyde (1) the signals of the second conformer could not be detected under the conditions used for (2), indicating that in (1) the proportion of the minor conformer is even lower than in (2). However, the line corresponding to C-3 becomes much broader than the other lines at low temperature (maximum width 8.5 Hz at −75 °C) and sharpens again when the temperature is further lowered. It has been shown [21–24] that for a very biased equilibrium the maximum width of an exchange-broadened line depends upon the product ($p\Delta\nu$) of the amount of the less stable conformer (p) and the chemical shift difference ($\Delta\nu$) between the two exchanging lines. In other words, if the term $p\Delta\nu$ is not properly chosen, the maximum attainable value for the computed linewidth will be either larger or smaller than that found experimentally. The value of $p\Delta\nu$ matching the experimental width was 6, and the corresponding rate constant 30 ± 5 s^{-1}. The corresponding $\Delta G^\ddagger$ value was 10.1 ± 0.15 kcal mol^{-1} (Table 1) at −75 °C, in remarkably good agreement with the approximate estimate of $\Delta H^\ddagger$ (10.3 ± 0.3 kcal mol^{-1}) obtained for the pure liquid by ultrasonic relaxation measurements.[25] Although the *S,O-anti*-conformer (1b) has not been observed, its amount can be quite accurately derived from $p\Delta\nu$. In fact the chemical shift difference ($\Delta\nu$) is expected to be in the range 8—10 p.p.m. (200—250 Hz at 25.16 MHz) as indicated by the similar values observed for isomer (2) and in analogous molecules.[4,6,19,20] Accordingly,

Table 2. ^{13}C Chemical shifts (p.p.m. from Me_4Si) for the conformers (1a) and (1b) of thiophene-2-carbaldehyde (in CD_2Cl_2) and for the conformers (2a) and (2b) of thiophene-3-carbaldehyde (in $CHFCl_2$–CCl_2F_2); the lines of the minor conformers that were undetected are probably underneath the corresponding signals of the major conformers: in fact these lines broaden very little in the region where exchange occurs

Conformer	T/°C	C-2	C-3	C-4	C-5	–CHO
(1a) (98.5%)	–100	142.7	137.7	128.2	135.2	183.7
(1b) (1.5%)	–100	141.0	129.3			182.0
(2a) (3%)	–140	132.9_5		130.8		
(2b) (97%)	–140	141.8	143.9	125.3_5	129.4	188.3

the amount of the unobserved *S,O-anti*-conformer of (1) is about 3% at –75 °C. This explains why at the temperatures where exchange is slow ($\leqslant -100$ °C) we could not detect unambiguously the signals of (1b) in a conventional spectrometer: its amount under these conditions would be 2% or less, according to the Boltzmann distribution. To check this prediction the spectrum was run in a superconducting spectrometer (75.48 MHz): the greater sensitivity and the larger separation of chemical shifts allowed us to detect, at –100 °C, the C-3 signal of the minor conformer, with a relative integrated intensity estimated as 1.5% (Figure). On raising the temperature this line disappears in conjunction with the broadening [26] of the related line of the major conformer (1a). With respect to the C-3 line of the latter, the weak C-3 signal of (1b) lies 8.40 p.p.m. (634 Hz) upfield, as expected. The relative intensities obtained at –100 and –75 °C indicate that at room temperature the proportion of the minor conformer (1b) would reach 8%, a value that seems to support the conclusions reported in ref. 15 and is not in too serious disagreement with the CNDO calculations predicting an amount of 3% for the *S,O-anti*-conformer (1b).[14]

The $\Delta G^\ddagger$ value measured for (1) is larger than that of (2) (Table 1), in agreement with the widespread belief that conjugation in position 2 is more efficient than in position 3. Furthermore steric interactions, due to the hydrogen atoms in positions 2 and 4, make the ground state of thiophene-3-carbaldehyde less stable than that of thiophene-2-carbaldehyde, where there is only one hydrogen atom (H-3) interacting with the HCO moiety, the other being replaced by the heteroatom. Since the perpendicular transition state may be unaffected by this interaction,[20,27,28] the net result is a smaller difference between the ground and the excited rotational states in (2) with respect to (1), and hence a smaller activation energy. Both electronic and steric effects thus co-operate in reducing the $\Delta G^\ddagger$ value in (2) with respect to (1).

The rotational barrier in thiophene-2-carbaldehyde is lower than in the corresponding pyrrole and furan derivatives, but higher than in benzaldehyde (Table 1). This effect results, in our opinion, from the aromaticity of thiophene being higher than that of pyrrole and furan, although lower than that of benzene. In fact pyrrole and furan, having a lower aromatic and therefore a higher ethylenic character, conjugate with –CHO to a greater extent, increasing the double-bond character of the C(2)–CHO linkage and therefore increasing their rotational barriers with respect to thiophene.

Experimental

The Fourier transform ^{13}C spectra were taken at 25.16 MHz (Varian XL-100 instrument) in the external lock mode (F-19); the temperature was monitored with a thermocouple introduced into the probe before or after each scan. The spectra at 75.48 MHz were recorded with the instrument (Bruker CXP-300) of the High Field NMR Service of the Italian C.N.R. in Bologna.

In the superconducting instrument it was not possible to insert a thermocouple into the sample position because of interference due to the short radio wavelength. Temperature calibration was therefore carried out as follows. A sample was prepared using [$^2H_6$]acetone (1 ml at 0 °C) and CHF_2Cl (3 ml at –80 °C). The difference in chemical shift between the carbon of CHF_2Cl and the carbonyl carbon of acetone was measured at various temperatures at 25.16 MHz using a thermocouple. On lowering the temperature the shift difference increased by 6.3 ± 0.7 Hz every 10 °C. The same sample was subsequently introduced into the superconducting instrument and from the shift difference multiplied by three the real temperature of the probe was obtained.

The estimate of the errors in $\Delta G^\ddagger$ derives from the averaged measurements carried out on different samples and also from the uncertainty (at least ±1 °C) in the temperature determination.

The samples requiring gaseous solvents were prepared by connecting a 10 mm tube containing the solute to a vacuum line. The gaseous materials were condensed by use of liquid nitrogen, and the tubes sealed under vacuum. The samples were then introduced into the precooled probe of the spectrometer. The carbon chemical shifts, assigned according to ref. 29, are collected in Table 2. The linewidths in the absence of exchange were in the range 2—4 Hz, owing to the viscosity of the solutions at the low temperatures employed. The lineshape analysis was carried out with a two-site exchange program written for an Apple II computer connected to a plotter. The outputs were randomly checked against the DNMR program [30] run on the CDC 7600 computing system of the University of Bologna.

Acknowledgements

L. L. and G. P. thank the Ministry of Public Education, Rome, for financial support.

References

1 Part 25, L. Lunazzi, D. Macciantelli, and L. Grossi, *Tetrahedron*, 1983, **39**, 305.
2 K. I. Dahlqvist and S. Forsén, *J. Phys. Chem.*, 1965, **69**, 4062.
3 R. J. Abraham and T. M. Siverns, *Tetrahedron*, 1972, **28**, 3015.
4 D. J. Chadwick, G. D. Meakins, and E. E. Richards, *Tetrahedron Lett.*, 1974, 3183.
5 D. J. Chadwick, *J. Chem. Soc., Perkin Trans. 2*, 1976, 451.
6 B. P. Roques, S. Combrisson, and F. Wehrli, *Tetrahedron Lett.*, 1975, 1047.
7 (*a*) L. Arlinger, K. I. Dahlqvist, and S. Forsén, *Acta Chem. Scand.*, 1970, **24**, 662; (*b*) K. I. Dahlqvist and A. B. Hörnfeldt, *Tetrahedron Lett.*, 1971, 3837.
8 B. Roques, C. Jaureguiberry, M. C. Fournié-Zaluski, and S. Combrisson, *Tetrahedron Lett.*, 1971, 2693.
9 C. Jaureguiberry, M. C. Fournié-Zaluski, B. Roques, and S. Combrisson, *Org. Magn. Reson.*, 1973, **5**, 165.

10 M. C. Fournié-Zaluski, C. Jaureguiberry, and B. Roques, *Tetrahedron Lett.*, 1973, 4177.

11 B. Roques, S. Combrisson, C. Riche, and C. Bascard-Billy, *Tetrahedron*, 1970, **26**, 3555.

12 B. Roques and M. C. Fournié-Zaluski, *Org. Magn. Reson.*, 1971, **3**, 305; S. Combrisson, B. Roques, P. Riguy, and J. J. Basselier, *Can. J. Chem.*, 1971, **49**, 904.

13 A. Abraham, D. J. Chadwick, and F. Sancassan, *Tetrahedron*, 1982, **38**, 1485.

14 L. Lunazzi and C. A. Veracini, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1739.

15 S. A. Salman, *Org. Magn. Reson.*, 1982, **20**, 151.

16 M. C. Fournié-Zaluski and B. Roques, *Tetrahedron Lett.*, 1970, 4909; B. P. Roques and S. Combrisson, *Can. J. Chem.*, 1973, **51**, 573.

17 R. J. Abraham, D. J. Chadwick, and F. A. E. G. Sancassan, *Tetrahedron*, 1982, **38**, 3245.

18 K. J. Dahlqvist and S. Forsén, *J. Phys. Chem.*, 1969, **73**, 4124.

19 L. Lunazzi, D. Macciantelli, and A. C. Boicelli, *Tetrahedron Lett.*, 1975, 1205.

20 L. Lunazzi, D. Macciantelli, and G. Cerioni, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1791.

21 F. A. L. Anet, I. Yavari, I. J. Ferguson, A. R. Katritzky, M. Moreno-Manas, and M. J. T. Robinson, *J. Chem. Soc., Chem. Commun.*, 1976, 399; F. A. L. Anet and V. J. Basus, *J. Magn. Reson.*, 1978, **32**, 339.

22 T. Drakenberg, *J. Chem. Soc., Perkin Trans. 2*, 1976, 147.

23 G. Cerioni, P. Piras, G. Marongiu, D. Macciantelli, and L. Lunazzi, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1449; L. Lunazzi, M. Guerra, D. Macciantelli, and G. Cerioni, *ibid.*, 1982, 1527.

24 J. Sandström, ' Dynamic NMR Spectroscopy,' Academic Press, London and New York, 1982, p. 82.

25 R. A. Pethrick and E. Wyn-Jones, *J. Chem. Soc. A*, 1969, 713.

26 F. A. L. Anet and I. Yavari, *Tetrahedron Lett.*, 1977, 3210.

27 L. Lunazzi, D. Macciantelli, G. Spunta, and A. Ticca, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1121.

28 L. Lunazzi, G. Magagnoli, and D. Macciantelli, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1704.

29 K. Takahashi, T. Stone, and K. Fujieda, *J. Phys. Chem.*, 1970, **74**, 2765.

30 G. Binsch and D. A. Klein, DNMR Program No. 140, Quantum Chemistry Program Exchange, University of Indiana.

Received 4*th August* 1983; *Paper* 3/1373