

## CONFORMATIONAL ANALYSIS OF THIOPHENE-3-CARBALDEHYDE AND 3-METHOXY CARBONYL-THIOPHENE

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**Abstract**—Conformational analysis of 3-substituted thiophene carbonyl derivatives, thiophene-3-carbaldehyde and 3-methoxy carbonyl thiophene has been studied by means of NMR coupling constants, carbonyl shielding effects and solvent shifts, showing that *S-cis* form is preferable to *S-trans*. Moreover, the result of a semi-empirical calculation (CNDO/2 method) suggests that the most stable conformation may be the twisted form of *S-cis* type even though it may not be perpendicular one. This conclusion seems to be consistent with our present experimental results and other information through IR and ultraviolet spectroscopy.

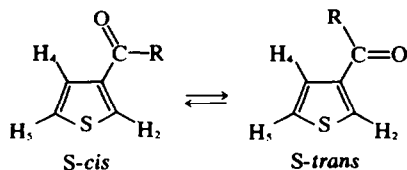
### INTRODUCTION

Recently some furan and thiophene carbonyl derivatives have been given much attention with respect to Nuclear Magnetic Resonance investigations in liquid crystals.<sup>1</sup> A number of studies concerning their conformations have used, e.g., NMR spectroscopy,<sup>2</sup> IR spectrometry,<sup>3</sup> dipole moment measurements<sup>4</sup> and ultrasonic experiments,<sup>5</sup> and these studies are usually concerned with the determinations of *cis* and *trans* isomers in 2-substituted furan and thiophene carbonyl derivatives. In our previous paper,<sup>6</sup> we have asserted that the difference of the amounts between *cis* and *trans* form of 2-substituted furan and thiophene carbonyl derivatives may be attributed to sulfur 3d-orbitals, i.e., the attractive through-space interaction between d-orbitals of sulfur atom and lone pair of carbonyl oxygen atom. In the present paper, we study 3-substituted thiophene carbonyl derivatives which may give interesting problems about not only con-

formations of themselves but the extent of d-orbital participation by comparing with 2-substituted thiophene carbonyl derivatives. NMR techniques, e.g., spin-spin coupling constants, carbonyl shielding effects and solvent shifts, have been used. Moreover, we carried out a CNDO/2 calculation without and with sulfur 3d-orbitals, in order to evaluate the energy difference and internal rotational barrier.

### RESULTS AND DISCUSSION

The NMR spectra in C<sub>6</sub>D<sub>6</sub> and the spin-spin coupling constants at room temperature (30.5°C) are given in Fig 1 and Table 1, respectively.\* It is easily seen from Fig 1 that the signal at  $\delta = 9.54$  ppm is apparently of the aldehyde group and split into quartet. According to the rule of the spin-spin coupling through the "straightest zig-zag path",<sup>8</sup> the aldehyde proton of *S-cis* form couples only with H-5 proton, while that of *S-trans* form has no protons to couple with and therefore the signal of the aldehyde proton is expected to be triplet as the result of superposition of the doublet from *S-cis* form and the singlet from *S-trans* one. Hence the experimen-



1: R = H  
2: R = OCH<sub>3</sub>

Table 1. Chemical shifts and spin-spin coupling constants (in CDCl<sub>3</sub>) in thiophene-3-carbaldehyde at room temperature (30.5°C)

Proton	Chem. shifts $\delta$ (ppm)	Spin-spin coupling constants (Hz)
CHO	9.91	$J_{\text{CHO-H}_5} = 0.80$
H-2	8.10	$J_{\text{CHO-H}_4} = 0.40$
H-4	7.54	$J_{\text{H}_2-\text{H}_4} = 1.3$
H-5	7.36	$J_{\text{H}_2-\text{H}_5} = 3.1$ $J_{\text{H}_4-\text{H}_5} = 4.9$

\*Just before submitting this manuscript, we found the NMR study by B. Roques and S. Combrisson<sup>7</sup> including the same compound. However, much of the present experimental results and discussions do not overlap and the subject for their study seems to be different from ours.

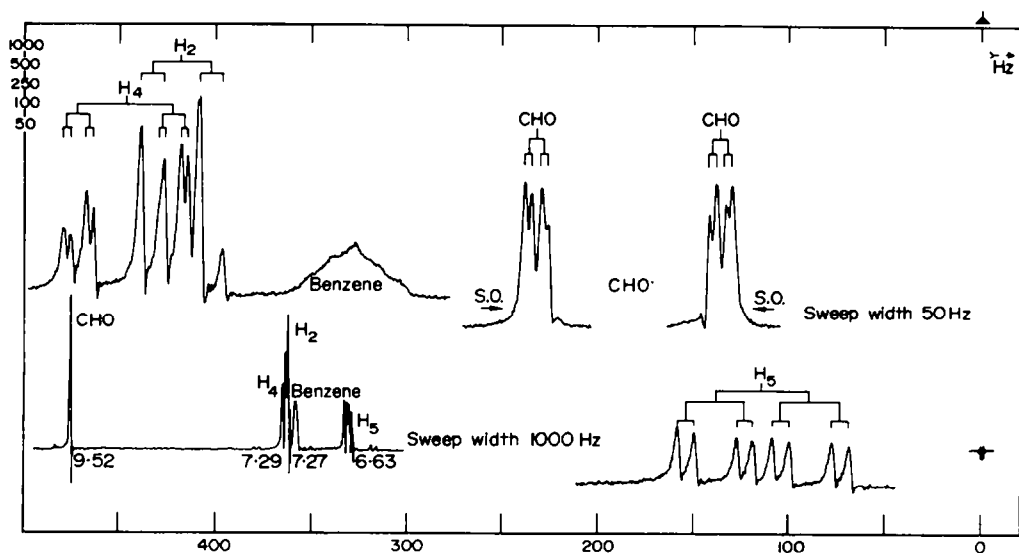


Fig 1. NMR spectrum of thiophene-3-carbaldehyde in  $C_6D_6$  at room temperature ( $30.5^\circ C$ ) at 100 MHz.

tal results cannot be explained by this consideration. We reinvestigated the assignments of the aldehyde proton by decoupling technique and found an unusual fact that the splitting of the aldehyde protons, i.e., the coupling 0.08 Hz in Table 1 may be reasonably assigned to the coupling between aldehyde and H-5 protons, while another coupling 0.40 Hz may be assigned to that of aldehyde and H-4 protons, and will be subsequently discussed. In 1963, Karabatsos and Vane<sup>9</sup> investigated the long-range couplings for substituted benzaldehyde ( $X = CH_3, Cl$ ) and found stereospecific long-range couplings, which split into triplet, in the perpendicular form, i.e., the plane of carbonyl group is almost perpendicular to that of the aromatic ring. Comparing our results with their coupling of the H-4 proton with aldehyde proton suggests that the carbonyl group exists in a twisted state.

Furthermore, to decide the conformation of compound 1 and 2, we measured the NMR chemical shifts of two kinds of solvents:  $C_6D_6$  and  $CDCl_3$ ,<sup>10</sup> which was successful for the conformational analysis of our previous study.<sup>6</sup> The results of NMR solvent shifts are listed in Table 2, which

shows that *S-cis* form is dominant to *S-trans*, since H-4 proton resonances of both compound 1 and 2 are hardly affected by solvent shifts in comparison with those of H-2 and H-5 protons. H-2 proton shift of compound 2 is small, which may be due to the effect of oxygen atom of methoxy group.

Moreover, let us consider the diamagnetic anisotropy effect of the carbonyl group, for which there are at least two models. One (Jackman model)<sup>11</sup> based on Pople's calculation,<sup>12</sup> predicts that the diamagnetic anisotropy effect of the carbonyl group will cause shielding of nuclei inside a conical surface over and under a trigonal  $C=O$  plane, and nuclei outside this surface will be deshielded (Fig 2a). The other has been critically discussed by Karabatsos *et al.*,<sup>13</sup> based on calculations by ApSimon *et al.*,<sup>14</sup> and this new model is illustrated in Fig 2b as the shape of the surface dividing the regions of diamagnetic and paramagnetic shielding effects of the  $C=O$  group. It is easily seen from Table 3 that the downfield shift of H-2 protons is large compared to H-4 and H-5 protons of compound 1 and 2, respectively. This fact cannot be explained by Jackman model which demonstrates that shifts of

Table 2. Solvents shifts between  $CDCl_3$  and  $C_6D_6$ .

	Compound 1			Compound 2		
	$CDCl_3$	$C_6D_6$	$\Delta\delta_{CDCl_3-C_6D_6}$	$CDCl_3$	$C_6D_6$	$\Delta\delta_{CDCl_3-C_6D_6}$
H-2	8.10	7.29	0.83	8.08	7.81	0.27
H-4	7.54	7.29	0.25	7.51	7.47	0.04
H-5	7.36	6.63	0.73	7.28	6.66	0.62
CHO	9.91	9.52	0.39			
$COOCH_3$				3.85	3.45	0.40

Table 3. Ring proton shifts of compound 1 and 2 in comparison with thiophene

	Thiophene	Compound 1	$\Delta\delta$	Compound 2	$\Delta\delta$
H-2	7.30 (ppm)	8.10 (ppm)	+0.80	8.08 (ppm)	+0.78
H-4	7.10	7.29	+0.19	7.51	+0.41
H-5	7.30	7.36	+0.06	7.28	-0.02

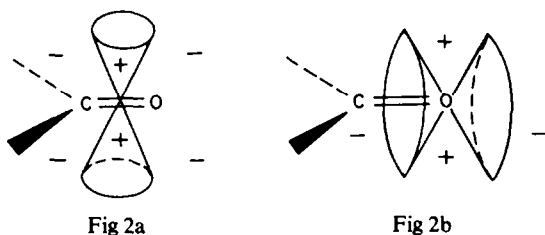
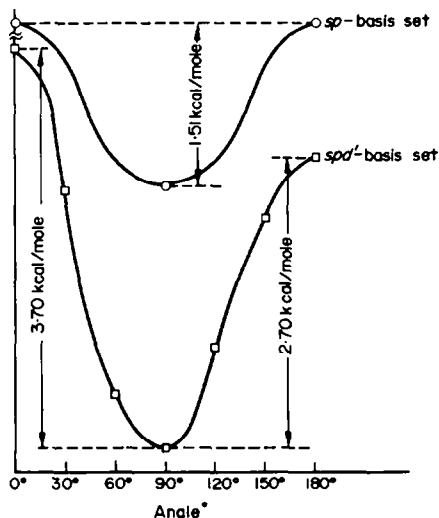


Fig. 2. Two models of the diamagnetic anisotropy effect of the carbonyl group.

H-2, H-4 and H-5 protons should be equally induced to the downfield, respectively. On the other hand, the new model proposed by Karabatsos *et al.* can explain well the experimental results of the ring-proton shifts by assuming the existence of only *S-cis* form. This conclusion—*S-cis* form is dominant—is in agreement with the experimental result of Roques *et al.*,<sup>15</sup> which demonstrates that thiophene-3-carbaldehyde adopts *S-cis*:*S-trans* 80:20 mixture, from spin-spin coupling constants between aldehyde and H-5 protons in comparison with the ones in the case of containing 4-hydroxy or 2-acetyl group. Their quantitative speculation, however, seems not to be accepted, because the values of the spin-spin coupling constants ought to be invariable for the relative amounts in equilibrium of two isomers. It appears unreasonable to start a *S-cis*:*S-trans* ratio from their experimental results. In fact, the result of IR spectrometry<sup>16</sup>—there exists only a single carbonyl absorption band in 3-substituted thiophene carbonyl derivatives—and that of low temperature NMR spectra ( $-30^{\circ}\text{C}$ )—we could find no new signals indicative of other conformations—indicate that the compound 1 and 2 are conformationally-pure. Conclusions obtained from present NMR and IR experimental results may seem to be strange, since superficially we find no significant differences between *S-cis* form and *S-trans* one in, e.g., steric hindrance, electronic states, sulfur 3d-orbital participation, etc. In order to ascertain the most stable conformation, we carried out a semi-empirical calculation of 3-carbonyl-substituted thiophenes by use of the CNDO/2 method<sup>17</sup> which was successful to predict the internal rotational barrier and relative stability. Total energies of thiophene-3-carbaldehyde for various angles between ring-plane and carbonyl group are shown in Fig 3, from which we can see a total energy minimum at the angle  $90^{\circ}$ . The difference of

Fig. 3. Total energies by CNDO/2 calculation, *sp* and *spd'*-basis sets, for thiophene-3-carbaldehyde  $0^{\circ}$ : *S-trans* form  $180^{\circ}$ : *S-cis* form between ring and aldehyde group.

total energies between two basis sets originates from  $E_{AB}$  values (diatomic part) rather than  $E_A$  values (monatomic part). Moreover, it follows by dividing  $E_{AB}$  values into two parts:  $E_{AB} = E^{\text{neigh.}} + E^{\text{th}}$ , where  $E^{\text{neigh.}}$  = energy values among neighboring atoms, which includes the stabilization energy by  $\pi$ -conjugation, and  $E^{\text{th}}$  = energy values among non-neighboring atoms, that the stabilization of  $E^{\text{th}}$  is superior to  $E^{\text{neigh.}}$  representing the internal rotational barrier at the angle  $90^{\circ}$  as seen in Fig 4. Furthermore, examining the  $E^{\text{th}}$  values one by one, it is found that the main factor to afford such large  $E^{\text{th}}$  is the attractive through-space interactions between sulfur 3d-orbitals and carbon atoms  $c_3$  and  $c_4$  on the ring.

Although the present calculation predicts that the carbonyl group and the five-membered ring lie perpendicularly in slight disagreement with the experiment, the result obtained suggests, at least, that the aldehyde group of thiophene-3-carbaldehyde may lie out of the plane. Recently, Gropen and Seip<sup>18</sup> have pointed out that the CNDO/2 method do not always give correct results for the stable conformations of some conjugated systems, e.g., glyoxal, 1,3-butadiene, biphenyl and 2,2'-difluorobiphenyl. On the other hand, Pople *et al.*<sup>19</sup> and Morokuma<sup>20</sup> obtained a good account of ground-state conformations for various molecules,

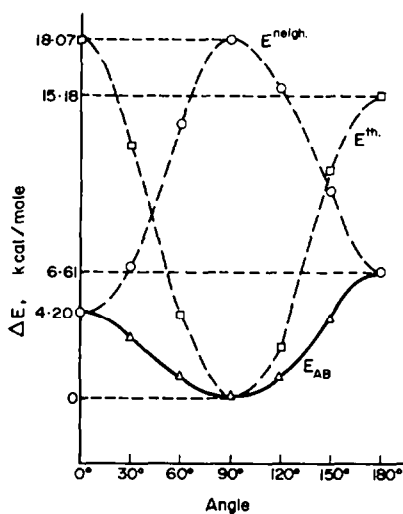


Fig 4.  $E_{AB}$  values dividing into  $E^{neigh}$  and  $E^{th}$ .

including conjugated systems, by the same method. For MO-calculations of furan and thiophene carbonyl derivatives by this method,<sup>6,21</sup> the results obtained were in good agreement with the experimental values.

From the situation mentioned above, however, it is hoped to be confirmed by more accurate methods, e.g., variation-perturbation method by Perahia and Pullman,<sup>22</sup> *ab-initio* calculation, etc. Such a conclusion seems to be consistent with the experimental results of NMR solvent shifts and carbonyl diamagnetic anisotropy effects and is also supported by the IR<sup>21</sup> and UV experimental results<sup>23</sup> which demonstrates that conjugation of the carbonyl group of 3-carbonyl substituted thiophenes is much weaker than that of 2-substituted ones.

#### CONCLUSION

The result of NMR experiments and CNDO/2 calculation suggests that 3-carbonyl substituted thiophenes may exist in non-planar *S-cis* forms. However, the problem about the conformations of these compounds should be quantitatively resolved by more accurate experiments and calculations, as mentioned above. The study of the same compound by Nuclear Magnetic Resonance spectroscopy in liquid crystals is under investigation.

#### EXPERIMENTAL

Compound 1 was synthesized from bromination of 3-methyl-thiophene by N-bromosuccinimide and steam-distillation after reaction with hexamethylenetetramine.<sup>24</sup> Compound 2 was obtained from esterification of 3-thenoic acid. Both compounds were purified by several distillations. Proton magnetic resonance spectra were recorded on a Varian HA-100 NMR spectrometer. The NMR measurements were performed on a 10% solution containing ca 1% of tetramethylsilane. The solvents,

deuteriochloroform and hexadeuterobenzene, were of commercial quality and used without further purification.

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