Conformational Analysis in Heteroaromatic Carbonyl Compounds. Part I. Radical Anions of Thiophen-2,5-dicarbaldehyde and Related Derivatives

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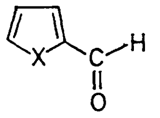
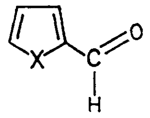
The room-temperature e.s.r. spectrum of the photolytically generated radical anion of thiophen-2,5-dicarbaldehyde shows the existence of two of the three possible rotational isomers. The less stable could be straightforwardly identified as the *O-cis–trans* because of the non-equivalence of the thiophen proton splittings. Examination of a number of derivatives having different steric requirements allowed the assignment of the *O-cis–cis* conformation to the other rotamer.

THE existence of relatively stable rotational isomers of carbonyl derivatives of furan and thiophen has been discussed and studied by several authors who have employed different techniques. Unambiguous evidence of the existence of such rotamers has been reached by Dahlqvist and Forsen [1] for the furan-2-carbaldehyde and by Hudson and Lewis [2] for the radical anion of the thiophen-2-carbaldehyde since they detected different n.m.r. and e.s.r. signals given by the two rotational isomers. A very important point which has not been settled concerns the assignment of the two conformers *O-cis* (I) and *O-trans* (II), for there is not unanimous agreement on which is the more stable and whether furan and thiophen derivatives have the same preferred conformations.


(I)


(II)

X = O or S

Another question is the validity of analogies between neutral molecules and corresponding radical anions as far as the conformational analysis is concerned.[2]

Different conclusions have been reached on the first point; for the furan derivatives i.r. and microwave investigations [3] agreed in indicating the *O-trans* as the more stable isomer while dipole-moment measurements were interpreted first on the basis of solely one species (*O-cis*) [4] but later as a mixture of *trans*- and *cis*-conformers in the ratio 5 : 3.[5] N.m.r. data were also interpreted in opposite ways; Dahlqvist and Forsen assigned to the more stable isomer the *O-trans*-conformation [1,6] because of the downfield shift induced by the carbonyl group on 3-H, while Karabatsos *et al.* reversed this attribution on the ground of the *trans–trans* rule and by a reinterpretation of the carbonyl shift.[7] The latter conclusion has also been reached by examining the n.m.r. spectra of substituted furan-2-carbaldehydes exhibiting steric hindrance effects and by preliminary *X*-ray diffraction measurements.[8] However a CNDO calculation indicates that the *trans–trans* rule is indeed violated in the case of the furan-2-carbaldehyde,[9] thus supporting the earlier interpretation [1] of Dahlqvist and Forsen.

For the conformations of thiophen derivatives substantial agreement seems to have been reached, although the assumption of a stabilizing effect due to the sulphur–

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oxygen interaction played an important role[8,10] in assigning the more stable isomers. Dipole-moment[10-12] and n.m.r.[8,13] investigations agree that the *O-cis* is either the only or the preferred form. Also the *O-cis*-conformer of the corresponding ketyl seems to be more stable than the *O-trans*, as suggested by the relative values of the *g*-factor and hyperfine splittings,[2] thus indicating a similar behaviour of radical anion and parent molecule.

However, since many authors[2,8,13,14] take for granted the analogy between the conformations of thiophen and furan derivatives, the situation remains ambiguous for the thiophen compounds.

We have undertaken e.s.r. and liquid-crystal n.m.r.[15] investigations on the rotational isomerism of thiophen-2,5-dicarbaldehyde and some related derivatives.

EXPERIMENTAL

The radical anions were generated by photolysis of alcoholic 10^{-2}M solution containing sodium methoxide within the cavity of a Varian V 4502 spectrometer; in some cases the addition of 1,2-dimethoxyethane was found to improve the signal-to-noise ratio.

Thiophen-2,5-dicarbaldehyde[16] and 2,5-diacetylthiophen[17] were prepared as described in the literature.

2,5-*Bistrifluoroacetylthiophen*.—To an ether solution of n-butyl-lithium (from 1·6 g of lithium) at −60 °C, a solution of 2,5-di-iodothiophen[18] (17·8 g) in ether (60 ml) was added dropwise; the mixture was stirred for 30 min and *NN*-diethyltrifluoroacetamide[19] (17·9 g) dissolved in ether (40 ml) was added in small portions at −60 °C. The mixture was stirred for 2 h at the same temperature and then decomposed with dilute hydrochloric acid. The ether solution was separated, washed with water, dried, and evaporated. The solid residue was purified by trituration with light petroleum; 2,5-*bistrifluoroacetylthiophen* (5·2 g) was obtained as a hygroscopic solid, m.p. 46—48 °C (Found: C, 34·7; H, 0·9; S, 11·55; F, 41·1. $C_8H_2F_6O_2S$ requires C, 34·8; H, 0·8; S, 11·6; F, 41·3%). The n.m.r. spectrum of this compound in trifluoroacetic anhydride showed a multiplet centred at δ 8·09 p.p.m.

2,5-*Bis*-(2,2-*dimethylpropionyl*)*thiophen*.—This was prepared from n-butyl-lithium (from 0·5 g of lithium), 2,5-di-iodothiophen (5 g), and *NN*-dimethylpivalamide (5·2 g) as for the trifluoroacetyl derivative. The *product* was purified by column chromatography on silica gel with hexane–diethyl ether (19 : 1) as eluant, and then had m.p. 104—106 °C; yield 2·8 g; its n.m.r. spectrum (CS_2) presented two sharp singlets at 1·35 and 7·6 p.p.m., with a relative intensity of 9 : 1 (Found: C, 66·6; H, 7·9; S, 12·8. $C_{14}H_{20}O_2S$ requires C, 66·6; H, 8·0; S, 12·7%).

Thieno[3,2-*b*]*thiophen*-2,5-*dicarbaldehyde*.—This compound was similarly prepared from n-butyl-lithium (from 0·24 g of lithium), 2,5-dibromothieno[3,2-*b*]thiophen,[20] (1 g), and *NN*-dimethylformamide (2 ml); the reaction was carried out at −20 °C. After hydrolysis with dilute hydrochloric acid a product separated which was insoluble in ether and was dissolved in chloroform; the organic phases were combined and evaporated. Crystallization of the residue from nitromethane afforded the *product* (0·5 g) as yellow needles, m.p. 280—282 °C. The n.m.r. spectrum was recorded in CCl_4–CF_3CO_2H and showed two singlets of equal intensity at 8·2 and 10·1 p.p.m. (Found: C, 48·75; H, 2·1; S, 32·5. $C_8H_4O_2S_2$ requires C, 48·95; H, 2·05; S, 32·65%).

3,4-*Dimethylthiophen*-2,5-*dicarbaldehyde*.—A solution of methyl 3,4-dimethylthiophen-2,5-dicarboxylate[21] (3·6 g) in ether was added to lithium aluminium hydride (4 g) in ether. The mixture was refluxed for 5 h and then treated with dilute hydrochloric acid. The organic layer was separated, washed with water, dried, and evaporated. The residue was crystallized from carbon tetrachloride and afforded 3,4-*dimethyl*-2,5-*bis*(*hydroxymethyl*)*thiophen* (1·5 g), m.p. 92—94 °C (Found: C, 55·6; H, 6·95; S, 18·6. $C_8H_{12}O_2S$ requires C, 55·8; H, 7·0; S, 18·6%). A mixture of this product (0·75 g) and MnO_2 (9 g) in chloroform (50 ml) was refluxed for 14 h. After filtration, the solvent was evaporated and the residue crystallized from CCl_4; the *dialdehyde* (0·4 g) was obtained as yellow needles, m.p. 179—181 °C. Its n.m.r. spectrum ($CDCl_3$) showed two singlets at 2·5 and 10·15 p.p.m., with a relative intensity of 3 : 1 (Found: C, 57·15; H, 4·75; S, 19·0. $C_8H_8O_2S$ requires C, 57·1; H, 4·8; S, 19·05%).

RESULTS AND DISCUSSION

The e.s.r. spectra of a variety of radical anions obtained from aromatic mono- and di-aldehydes has been reported.[2,22] They always indicate that the carbonyl group is locked, in the e.s.r. time scale, in orientations coplanar with the aromatic system as shown either by the non-equivalence of the *ortho* and *meta* splittings, or by the presence of different signals for each rotational isomer.

Also the e.s.r. spectrum of the radical anion of thiophen-2,5-dicarbaldehyde (III), photolytically generated in methanol and sodium hydroxide [Figure 1(a)], shows the existence of two species having the same number of coupled protons, very similar hyperfine splittings, and slightly different *g* factors.

They were thus identified as two of the three possible rotational isomers which, in principle, have to be ex-

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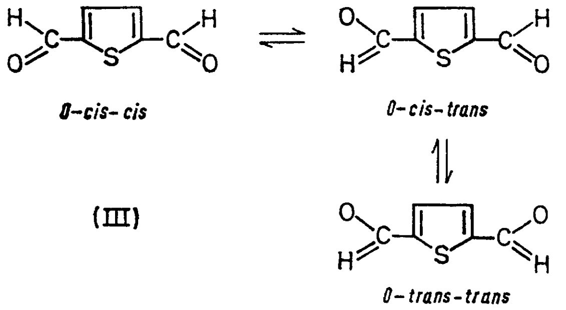
pected for such a compound, the smaller coupling being associated with the thiophen and the larger with the aldehydic protons. The less intense spectrum is due to a species having three different splitting constants which can be easily identified as the asymmetric isomer *O-cis–trans*. Actually all four coupling constants ought to be non-equivalent but the larger ones are accidentally degenerate; in t-butyl alcohol the degeneracy is removed so that each proton actually shows different a_H values. The more intense spectrum is characteristic of a symmetric species which could be either the *O-cis–cis* or the *O-trans–trans* isomer. Since there is no way of deciding between the two possibilities by spectral inspection alone, we tried to get more information by examining several derivatives having different steric requirements.

Hyperfine splitting constants (gauss) of the radical anions of derivatives (III)—(VIII)

	Isomer	Relative amount (%)	$a^H_{thiophen}$	a^H_{CHO}	a^H_{Me}
(III)	*O-cis–cis*	92	1·52	5·02	
	O-cis–trans	8	1·00—1·61	4·90	
(IV)	*O-cis–cis*	75	1·46		4·27
	O-cis–trans	25	1·28—1·49		3·67—4·30
(V)	*O-cis–cis*	Undetermined	1·41		0·20 [a]
(VI)	*O-cis–cis*	*ca.* 100		5·32	0·95
(VII)	*O-cis–cis*	$\geqslant$95	1·35		7·38 [b]
(VIII)	*O-cis–cis*	90	2·13	4·14	
	O-cis–trans	10	2·28—2·13	3·39—4·35	

[a] t-Butyl proton splitting. [b] Fluorine splitting.



The introduction of a bulkier substituent in the carbonyl group is expected to reduce the stability of the three conformers in the order *O-cis–cis* > *O-cis–trans* > *O-trans–trans*. If in the dialdehyde (III) the *O-cis–cis* is the preferred conformation we should observe a decrease of the relative amount of this isomer in favour of the *O-cis–trans* form, while the opposite effect should occur if the *O-trans–trans* is the more stable conformer.

We thus investigated 2,5-diacetyl- (IV) and 2,5-bis-(2,2-dimethylpropionyl)-thiophen (V). In the first case we found a definite increase of the asymmetric species [Figure 1(b)] from the previous 8 to 25% which supports the conclusion that the *O-cis–cis* is the most stable conformer. Unfortunately in the radical (V), where an even greater change is expected, the occurrence of a relatively large butyl proton splitting prevents the detection of the two isomers; nevertheless the asymmetry of the spectral patterns seem to indicate the existence of at least two species with comparable concentrations. On the other hand in 3,4-dimethylthiophen-2,5-dicarbaldehyde (VI) the stability of the *O-cis–cis* isomer should be enhanced with respect to

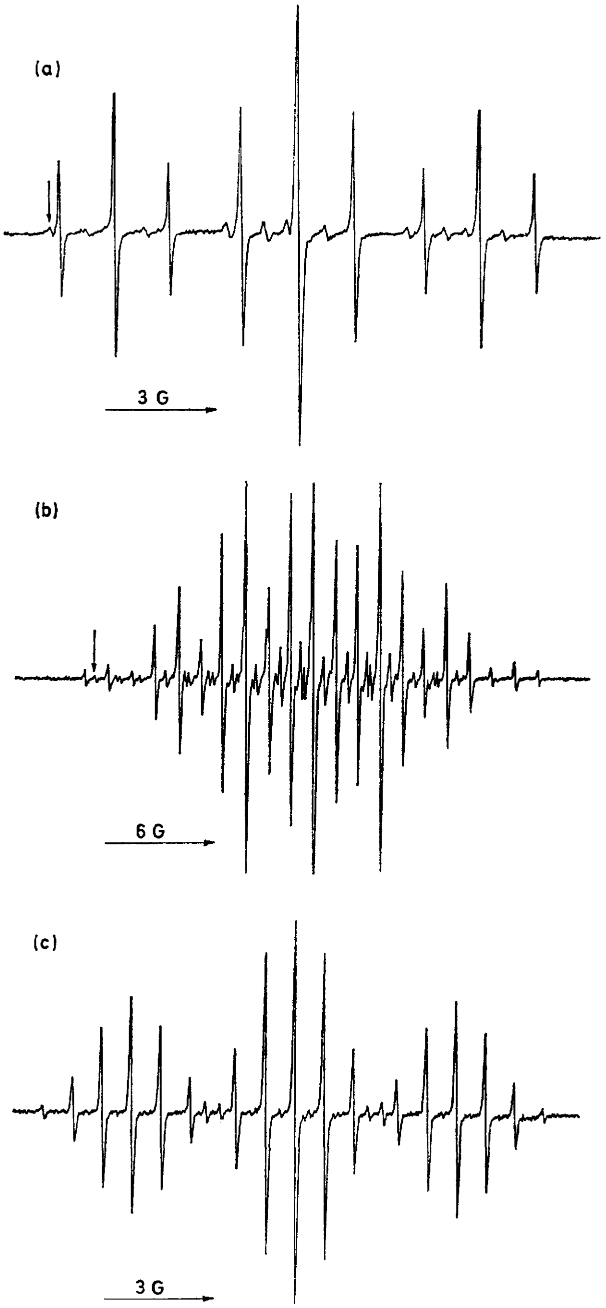
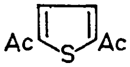


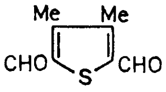
FIGURE 1 E.s.r. spectra of the radical anions of: (a) thiophen-2,5-dicarbaldehyde (III); (b) 2,5-diacetylthiophen (IV); (c) 3,4-dimethylthiophen-2,5-dicarbaldehyde (VI). The first line of the spectrum relative to the asymmetric species is marked by an arrow

(III) because of the greater methyl–oxygen repulsion; actually only the symmetric rotamer was experimentally detected without traces of the *O-cis–trans* isomer [Figure 1(c)].

All these results seem therefore to agree in assigning to the more stable conformer the *O-cis–cis* structure.


(IV)


(V)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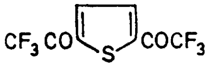
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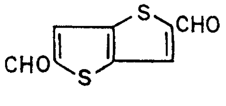
(VIII)

A further test has been also performed by examining the radical anion of the 2,5-bistrifluoroacetylthiophen (VII) where strong fluorine–hydrogen bonding should enhance the stability of this form. Indeed the e.s.r. spectrum shows only the symmetric species even though, because of the not too favourable signal-to-noise ratio, the presence of the *O-cis–trans* rotamer cannot be definitely ruled out: its amount, however, should not exceed 5%. This compares favourably with the 25% observed in the corresponding diacetyl compound (IV) and clearly indicates that, despite the presence of the bulky CF$_3$ groups, the fluorine–hydrogen bond stabilizes the *O-cis–cis* form and confirms the results of the previous experiments.

An alternative way of deciding between the two possibilities has been put forward by Hudson and Lewis [2] who suggested that larger spin densities are expected on the atoms adjacent to C(2) when they are *trans* to the carbonyl group. In this case the symmetric isomer, having thiophen proton splittings larger than the average value in the asymmetric and a lower *g* factor owing to a smaller spin density on the sulphur atom, should be *O-cis–cis*; this result is in agreement with the other experimental findings.

Although conclusive evidence of the greater abundance of the *O-cis–cis* conformation than the *O-trans–trans* has been reached, the effects which cause its stabilization are not clearly understood. It has been suggested [8,10,23] that attrative forces between partially charged sulphur and oxygen atoms could possibly stabilize the *O-cis*-form in thiophen-2-carbaldehyde. In the present case this kind of interaction should be less important owing to the presence of two partially negative oxygen atoms with only one positive sulphur atom; nevertheless the *O-cis–cis* conformation is by far the predominant species.

In a derivative such as thieno[3,2-b]thiophen-2,5-dicarbaldehyde (VIII), where there is only one sulphur for each oxygen atom, this interaction is expected to be different and so it would have been of some interest to investigate the corresponding radical anion.

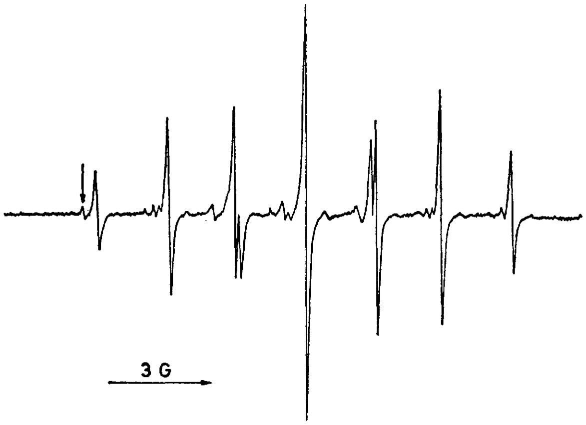

FIGURE 2 E.s.r. spectrum of the radical anion of thieno[3,2-*b*]-thiophen-2,5-dicarbaldehyde. The first line of the spectrum relative to asymmetric species is marked by an arrow

The spectrum (Figure 2) shows that the asymmetric rotamer is about one tenth of the symmetric one, which is almost the same as found for the thiophen-2,5-dicarbaldehyde (III); it seems therefore that this kind of stabilization is not substantially affected by the presence of two oxygen atoms sharing a single sulphur atom. On the other hand this result could be also interpreted as an indication that the importance of this interaction has been overestimated and other effects, such as steric hindrance, might also account for the preferred *O-cis*-conformation.

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