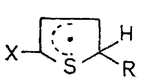
Substituent Effects in Heterocyclic Rings. An Electron Spin Resonance Study of Some 5-Substituted 2-Thienyl Nitroxides and Nitro-anions

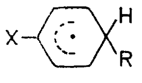
By **Carlo Maurizio Camaggi,* Rino Leardini,** and **Giuseppe Placucci,** Istituto di Chimica Organica, Viale Risorgimento 4, 40136 Bologna, Italy

E.s.r. spectra of some 5-substituted 2-thienyl nitroxides, generated by scavenging triethylsilyl radicals with substituted nitrothiophens, and nitro-anions have been recorded in order to determine the effective substituent delocalising power with respect to an unpaired electron in the thiophen series. The results are discussed in connection with chemical data. Hyperfine splitting constants calculated for the substituted nitro-anions by the INDO method, using an *s,p* basis set for the sulphur atom, are in good agreement with the experimental values.

SUBSTITUENT effects on the thiophen ring have been the subject of extensive investigations, but the available data are mainly confined to heterolytic reactivity. Rate constants of several electrophilic substitution reactions have been found[1] to correlate well with Hammett σ^+ values, thus indicating that substituents exhibit a similar influence, in this kind of reaction, on benzene and thiophen derivatives. Butler[2] has studied the dissociation constants of a number of thenoic acids and has calculated σ constants for substituents on the thiophen ring; the values of these parameters are very close to those determined for the corresponding benzoic acids.

Different results have been obtained recently from the homolytic phenylation of substituted thiophens.[3a,b]


(Ia)

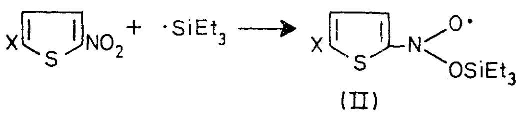

(Ib)

The reactivity pattern is different from that expected by assuming simple additivity of substituent effects, as determined for the phenylation of benzene derivatives. This behaviour can be explained *a priori*, if it is assumed that the influence of substituents on the radical σ complexes (Ia and b) is different in the benzene and thiophen series. This is not unreasonable, thiophen being an odd, non-alternant aromatic system: the stabilising factors in this system are not expected to be the same as those observed in the even, alternant benzene nucleus.[4] It is therefore worth determining in an unequivocal way the effective delocalising power of substituent groups with respect to an unpaired electron on thiophen substrates. E.s.r. is a suitable tool for the study of the factors influencing the electronic distribution and stability of radicals;[5,6] nitrogen hyperfine coupling constants of a number of aryl nitroxides were found[7] to correlate well with the σ^- values of substitutents and analogous results have been found for aryl nitro-anions.[6] We have therefore generated a number of substituted thienyl nitroxides and nitro-anions in order to test if a similar relationship holds for thiophen substrates.

Generation of Radicals.—Nitroxides. Triethylsilyl radicals were generated by hydrogen abstraction from triethylsilane in the presence of substituted nitrothiophens in the cavity of an e.s.r. spectrometer. Strong signals attributed to (II) were observed at room temperature. The mechanism of formation of these radicals is probably similar to that suggested by Sutcliffe to rationalise the photochemistry of a number of nitro-derivatives

$$(\mathrm{Me_3CO_2CO})_2 \xrightarrow{25^\circ} 2\ \mathrm{Me_3CO}\cdot + 2\ \mathrm{CO_2}$$

$$\mathrm{Me_3CO}\cdot + \mathrm{HSiEt_3} \longrightarrow \mathrm{Me_3COH} + \cdot\mathrm{SiEt_3}$$


(II)

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[1] G. Marino, *Adv. Heterocyclic Chem.*, 1971, **13**, 235.

[2] A. R. Butler, *J. Chem. Soc.* (*B*), 1970, 867.

[3] C. M. Camaggi, G. De Luca, and A. Tundo, *J.C.S. Perkin II*, 1972, (*a*) 412; (*b*) 1594.

[4] J. M. S. Dewar, ' The Molecular Orbital Theory of Organic Chemistry,' McGraw-Hill, New York, 1969.

[5] E. G. Jansen, *Accounts Chem. Res.*, 1969, **2**, 279.

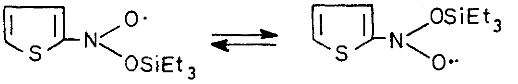
[6] K. W. Bowers in ' Radical Ions,' eds. E. T. Kaiser and L. Kevan, Interscience, New York, 1968, p. 211.

[7] H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191; H. Lemaire, Y. Marechal, R. Ramasseul, and A. Rassat, *Bull. Soc. chim. France*, 1965, 372; G. Barbarella and A. Rassat, *ibid.*, 1969, 2378.

in the presence of hydrogen donors,[8] the hydrogen-abstracting species in our case being t-butoxyl radicals obtained from t-butyl peroxyoxalate instead of nitroarene triplets. Identical spectra were also obtained by photolysing nitrothiophens in triethylsilane in the absence of t-butoxyl radical, but the signals were much weaker and less persistent.

Triethylsilane was chosen as the hydrogen-donor solvent in order to produce simpler spectra (no splitting from the silyl group) and because of the ease with which this substrate undergoes hydrogen abstraction.

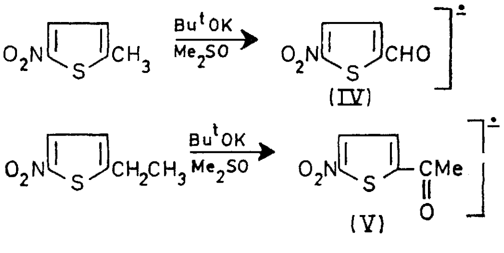
In some cases below 0° two superimposed spectra were observed, the two species collapsing reversibly to a single spectrum at higher temperatures. This phenomenon was attributed to the formation of two equilibrating rotational isomers (IIIa and b). Experiments to determine kinetic parameters for this process by analysis of line shapes have been performed, and will be published elsewhere.[9]



(IIIa) (IIIb)

Nitro-anions. These were generated by electrolysis [6] of solutions of the appropriate nitro-derivative in dimethylformamide or acetonitrile using tetra-n-propylammonium perchlorate as the electrolyte. Well resolved spectra were obtained for all substituents.

Attempts have been made to generate these radicals by use of the dimethyl sulphoxide–potassium t-butoxide[10] method. Even if in some cases good results were obtained, spectra were less intense and sometimes mixtures of radicals were observed. In the case of 2-nitro-5-methyl- and 2-nitro-5-ethyl-thiophen the only recorded spectra, using this radical source, were due to the anions of 2-nitro-5-formyl- and 2-nitro-5-acetyl-thiophen (IV) and (V) possibly formed through an oxidation process.



RESULTS AND DISCUSSION

Hyperfine coupling constants for the radicals investigated are reported in Tables 1 and 2 which show close similarities between the hyperfine splittings of the nitro-anions and the nitroxides.

The assignment of coupling constants is fairly straightforward. In the unsubstituted thienyl nitroxide (III) the largest hydrogen hyperfine coupling constant, 5·45 G, is due to 3-H, as demonstrated by methyl-substitution. The smallest, 1·07 G, derives from 4-H, as generally observed in other thiophen radicals.[11] Hyperfine splittings in the unsubstituted nitro-anion have been previously assigned by Lucken;[12] these assignments

TABLE 1

Hyperfine splitting constants of 5-X-2-thienyl nitroxides in triethylsilane

	Splitting (G)			
X	3-H	4-H	X	$N\langle^{O\cdot}_{OSiEt_3}$
H [a]	5·60	1·07	4·65 (5-H)	13·40
Me	6·00	0·70	4·30 (Me)	14·50
Et	5·80	1·00	4·20 (CH_2)	13·85
Ph	5·60	1·35	1·00 (3H), 0·35 (2H)	12·50
SMe	5·60	1·20	0	12·95
Cl	5·85	1·20	0·4 (Cl)	13·25
CO_2Me	5·00	1·35	0·21 (OMe)	12·05
SO_2Me	5·05	1·30	0·75 (Me)	11·75
Ac	4·95	1·35	0·45 (Me)	11·45
CHO	4·90	1·40 *	0·65 (CHO) *	11·30
CN	5·10	1·40	0·70 (CN)	11·70
NO_2	5·00	1·45	1·10 (NO_2)	10·85

* Tentative assignment.

[a] Coupling constants recorded at 30°. Two conformers are present at lower temperatures.

TABLE 2

Hyperfine splitting constants in 5-X-2-nitrothiophen radical-anions

	Splitting (G)			
X	3-H	4-H	X	NO_2
H	5·70 [a]	1·25	4·75 (5-H)	9·15
	5·80 [b]	1·25	4·75	10·10
Me	6·00	1·20	4·90 (Me)	9·60
	6·10	1·30	4·80	10·80
Et	6·00	1·20	4·15 (CH_2)	9·50
	6·15	1·20	4·25	11·00
Ph	5·50	1·30	1·30 (3H), 0·45 (2H)	7·85
	5·30	1·30	1·30 (3H), 0·50 (2H)	8·20 8·20
SMe	5·50	1·25	0	8·00
	5·60	1·30	0	8·75
Cl	6·20	1·50	0	8·65
	6·00	2·00	0	9·80
CO_2Me	4·23	0·98	0·43 (OMe)	6·00
	4·50	1·10	0·40	6·75
SO_2Me	4·70	0·95	0·95 (Me)	6·55
	4·70	0·95	0·95	7·00
Ac	3·75	0·75	1·35 (Me)	5·15
	4·10	1·15	1·15	6·50
CHO *	2·00	0·55	3·50 (CHO)	4·50
	1·75	0·80	3·85	5·70
CN	4·55	1·00	1·00 (CN)	6·00
	4·70	1·05	1·05	6·60
NO_2	1·20		1·54 (NO_2)	
	1·25		1·63	

* Tentative assignment.

[a] Dimethyl formamide as solvent. [b] Acetonitrile as solvent.

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[8] R. B. Sleight and L. H. Sutcliffe, *Trans. Faraday Soc.*, 1971, **67**, 2195.

[9] C. M. Camaggi, L. Lunazzi, G. F. Pedulli, and G. Placucci, *J.C.S. Perkin II*, 1974, 1226.

[10] E. R. Talaty and G. A. Russell, *J. Amer. Chem. Soc.*, 1965, **87**, 3867.

[11] L. Lunazzi, A. Mangini, G. F. Pedulli, and M. Tiecco, *Gazzetta*, 1971, **101**, 10.

[12] E. A. C. Lucken, *J. Chem. Soc.* (*A*), 1966, 991.

have been fully confirmed by INDO calculations (Table 3).

TABLE 3

Calculated hyperfine splittings (G) in nitrothiophen radical-anions

X	3-H	4-H	X	NO_2 [a]	NO_2 [b]
H	−6·39	2·76	−4·93	5·42	12·50
Me	−6·04	3·29	8·51 [c]	4·66	9·84
SMe	−6·40	3·57	−0·09 [c]	4·67	9·77
CO_2Me	−3·20	1·11	0·14 [c]	0·93	2·29
Ac	−2·81	1·26	−2·84 [c]	0·68	2·88
CHO	−0·32	−0·19	2·0	−0·40	4·90
CN	−5·05	2·79	1·33	2·67	3·13
NO_2	−1·08			−0·49	5·9

[a] Calculated from ρ_{2s} spin density. [b] Calculated using the Rieger–Fraenkel equation. [c] Rotationally averaged values.

In both substituted nitroxides and nitro-anions the largest hydrogen splitting is generally due to 3-H, the hydrogen near the radical centre, as shown by the INDO results for nitro-anions. In the case of the formyl derivative MO calculations indicate that the formyl hydrogen should bear the highest spin density in the radical-anion. A 0·4 G halogen hyperfine splitting constant in the chloro-substituted nitroxide, not present in the corresponding nitro-anion, and the methyl splitting in the methoxycarbonyl substituted radicals are both noteworthy. The absence of methyl splitting in the SMe and CH_2Me cases possibly indicates that ' through-space interactions ' between the methyl group and the thiophen π-cloud are involved in this splitting. INDO calculations support this assumption rather than the alternative interaction through the π system of the ester group. Analogous results have been observed for some α-carbonyl substituted nitroxides.[13]

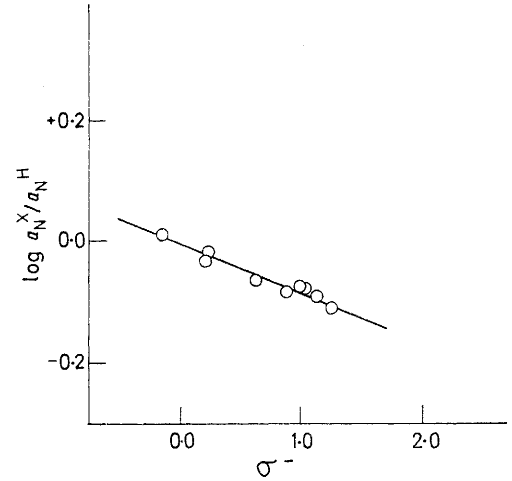

FIGURE 1 Plot of log a_N^X/a_N^H against σ^- constants for 5-X-2-thienyl nitroxides in triethylsilane at room temperature (slope −0·077, m.s.e. 0·008)

The nitrogen hyperfine coupling constants of the nitroxides investigated were plotted against the Hammett σ^- constants (Figure 1). Least-squares analysis yields a slope of −0·077 [mean square error (m.s.e.) 0·008]; thus electron-donating groups increase and electron-withdrawing substituents decrease the nitrogen splitting. This trend parallels that found for substituted phenyl nitroxides.[7]

The nitrogen splitting constants of the thiophen nitro-anions correlate equally well with Bower's σ constants [6] (slope −0·30, m.s.e. 0·012 in acetonitrile) (Figure 2).

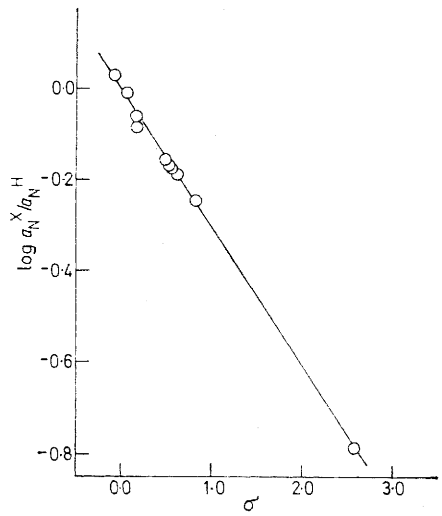

FIGURE 2 Plot of log a_N^X/a_N^H against Bower's σ constants[6] for 5-X-2-nitrothiophen radical-anions in acetonitrile obtained by electrolytic reduction at room temperature (slope −0·30, m.s.e. 0·012)

Bower's σ constants were especially chosen to fit hyperfine splittings in arene nitro-anions. The constants for the SMe and SO_2Me groups, which were not reported originally, were determined from the corresponding arene nitro-anions, the values being 0·180 and 0·488 respectively.

These experimental data indicate that it is possible to correlate substituent effects with a property of free radicals using the same set of substituent parameters for benzene and thiophen derivatives. The delocalising power of a substituent with respect to an unpaired electron is the same in the benzene and thiophen series.

For this reason, the anomalous results obtained in the phenylation of some substituted thiophens can probably be better explained by the assumption that the relative stability of σ complexes is less important in governing the reaction path for phenylation of thiophen derivatives than for benzene derivatives; in other words thiophen σ complexes are poor models of the transition state during phenylation. This is perhaps not surprising, as addition of radicals to aromatic substrates is normally exothermic and the transition state occurs early in the addition step.

MO Calculations.—The Pople INDO [14] wave function in the open shell form was used to calculate spin densities for the thiophen nitro-anions. The sulphur atom, not previously parametrised for this kind of calculation, was

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[13] C. M. Camaggi, R. J. Holman, and M. J. Perkins, *J.C.S. Perkin II*, 1972, 501.

[14] J. A. Pople and D. L. Beveridge, ' Approximate Molecular Orbital Theory,' McGraw-Hill, New York, 1970.

described by an *s,p* basis set: ground-state properties such as spin distribution were not improved, at this approximation level, by using a more extended basis set including 3*d* functions.

With this limitation the extension of INDO method to sulphur-containing molecules is straightforward. Bonding parameters $\beta_{AB}{}^0$ were approximated by equation (1).

$$\beta_{AB}{}^0 = (\beta_A{}^0 + \beta_B{}^0)/2 \qquad (1)$$

$\beta_S{}^0$ For sulphur was estimated from $\beta_O{}^0$ for oxygen as in CNDO/2 theory[13] [equation (2) in which $U_{\mu,\mu}$ are core matrix elements].

$$\beta_S{}^0 = \beta_O{}^0 \frac{U_{3s,3s}{}^{(S)} + U_{3p,3p}{}^{(S)}}{U_{2s,2s}{}^{(O)} + U_{2p,2p}{}^{(O)}} \qquad (2)$$

Two-electron integrals were calculated as in the Pople INDO method, the parameters G^1 and F^2 for sulphur atom being respectively 0·24975 and 0·16673. The relationships (3) and (4) between orbital electronegativities and core integrals were used for the sulphur atom.

$$-\tfrac{1}{2}(1 + A)_s = U_{ss} + (Z_A - \tfrac{1}{6})F^0 - \tfrac{1}{6}(Z_A - \tfrac{3}{2})G^1 \qquad (3)$$

$$-\tfrac{1}{2}(1 + A)_p = U_{pp} + (Z_A - \tfrac{1}{2})F^0 - \tfrac{2}{25}(Z_A - \tfrac{5}{2})F^2 \qquad (4)$$

Hyperfine coupling constants were calculated in two different ways. Using equation (5) and the Pople

$$a_N = \frac{4\pi}{3}[g_\beta\, \gamma_N\, \hbar\langle S_z\rangle^{-1}\, |S_N(R_N)|^2]\rho_{S_NS_N}^{\text{spin}} \qquad (5)$$

value for the quantity in brackets, splitting constants for hydrogen atoms were accurately reproduced, but nitrogen hyperfine splittings for the nitrogen atom in the nitro-anions were found to be consistently too low (Table 3), particularly when electron-withdrawing substituents were present in the molecule.

This does not depend upon our treatment of the sulphur atom, this trend also being present in the benzene series. Calculations on some benzene nitroxides show the same feature. This may depend either on the standard geometry chosen to describe the molecules, which may be unrealistic for radicals, or on an improper parametrisation of the nitrogen atom.

For this reason, we calculated nitrogen splitting from π spin populations on the nitrogen and oxygen atoms of the nitro-group, using the semiempirical equation and parameter values given by Rieger and Fraenkel,[15] which may be expressed in the form (6) where $\rho_N{}^\pi$ and $\rho_O{}^\pi$ are

$$Q_N = \rho_N{}^\pi 2B + \rho_O{}^\pi \qquad (6)$$

the spin populations of the π orbital of nitrogen and oxygen, and A and B have the values $\pm 99{\cdot}0$ and $\mp 35{\cdot}8$ G respectively.

As shown in Table 3, the agreement with the experimental values is much better using equation (6).

EXPERIMENTAL

Spectral Measurements.—Nitroxides. To a carefully degassed 10^{-3}M solution of the appropriate nitro-derivative in triethylsilane placed in a standard e.s.r. tube were directly added a few crystals of t-butyl peroxyoxalate. The e.s.r. spectrum was immediately recorded (Varian 4502 instrument) without any heating of the sample.

Alternatively, 10^{-3}M solutions of substituted nitrothiophens in triethylsilane were irradiated in the cavity of the e.s.r. spectrometer with a 500 W xenon lamp. E.s.r. signals persisted even after irradiation was discontinued.

Nitro-anions. The electrolysis of 10^{-3}M solutions of the appropriate nitro-derivative in dimethylformamide or acetonitrile was carried out in a flat cell with a mercury cathode and a platinum anode, using tetra-n-propylammonium perchlorate (10^{-1}M) as the electrolyte.

Syntheses.—Substituted nitrothiophens were prepared as reported in the literature. When products were prepared by nitration of the monosubstituted thiophen, some 3-nitro-isomer was always detected by n.m.r. spectroscopy of the crude product. Purification was carried out using the method of Östman.[16]

Nitration of 2-methylthiophen. The procedure described by Cymerman-Craig *et al.*[17] was followed. Chromatography on silica gel of the reaction mixture gave two isomeric nitro(methylthio)thiophens, the m.p.s of the two products (A and B) being respectively 61—62 and 90—91° [compound A (Found: C, 34·2; H, 2·9; N, 8·0; S, 36·7. Calc. for $C_5H_5NO_2S_2$: C, 34·3; H, 2·85; N, 8·0; S, 36·55%); compound B (Found: C, 34·3; H, 2·85; N, 8·0; S, 36·7%)], δ (60 MHz) A 2·56 (s) and 6·85 and 7·70 (AB, J_{AB} 4·3 Hz); B 2·63 (s) and 7·06 and 7·52 (AB, J_{AB} 5·75 Hz). Compound B was assigned as 2-methylthio-3-nitrothiophen and A as the 2,5-isomer, in disagreement with the literature, on the basis of n.m.r. spectroscopy and chemical evidence.

(a) Treatment of a mixture of A and B with chlorosulphonic acid in chloroform at 0—5°, and analysis of the reaction mixture by n.m.r. spectroscopy,[16] showed that the AB system due to product B disappeared, while the corresponding spectrum of A remained unchanged. This is consistent with the high reactivity of the free α-position in 2-methylthio-3-nitrothiophen toward electrophilic substitutions.

(b) Photolysis of a solution of 2-nitro-5-iodothiophen in dimethyl disulphide, gave a product, m.p. 61—62°, identical with A. A and B were found to be stable under these irradiation conditions.

2-Methylsulphonyl-5-nitrothiophen. Compound A was oxidised with 30% H_2O_2 in acetic acid to give the *product*, m.p. 93—94° (Found: C, 29·0; H, 2·5; N, 6·85; S, 31·0. $C_5H_5NO_4S_2$ requires C, 29·0; H, 2·45; N, 6·75; S, 30·95%).

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[16] B. Östman, *Acta Chem. Scand.*, 1968, **22**, 1687.

[17] J. Cymerman-Craig, G. N. Vaughan, and W. K. Warburton, *J. Chem. Soc.* 1956, 4115.