Linear Free Energy *ortho*-Correlations in the Thiophen Series. Part I. The Kinetics of Piperidinodebromination of Some 2-Bromo-3-X-5-nitrothiophens in Methanol †

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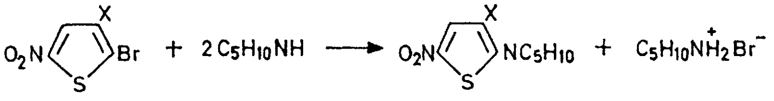
The rates of piperidinodebromination of some 2-bromo-3-X-5-nitrothiophens (I; X = Me, H, Br, $CONH_2$, CO_2Me, SO_2Me, CN, or NO_2) have been measured in methanol. The logarithm of the rate constants gives an excellent straight line (except for X = Br) when plotted against σ_p^- and against the logarithm of the rate constants of piperidinodebromination for the corresponding 2-bromo-3-nitro-5-X-thiophens (III). This confirms that a 3-substituent exerts an effect on the 2-position of the same kind (in this case extraconjugative) as that exerted from the 5-position. The $\rho_{2,3}$ value (+4·02) and the ratio $\rho_{2,3}/\rho_{2,5}$ (1·18) show there is a larger transmission of electronic effects between the 2- and 3-positions than between the 2- and 5-positions of the thiophen ring.

RECENTLY[1] we pointed out the peculiar behaviour of some derivatives of thiophen (a typical five-membered ring) leading to examples of linear free energy *ortho*-correlations in reactions which are not satisfactorily correlated[2] in the benzene series. This observation has led us to extend the study to other types of reactions *e.g.* dissociation of *ortho*-substituted thiophencarboxylic acids, basic hydrolysis of the corresponding esters, *etc.*[3]



(I) (II)

a; X = Me
b; X = H
c; X = Br
d; X = $CONH_2$
e; X = CO_2Me
f; X = SO_2Me
g; X = CN
h; X = NO_2

In this paper we report a study on the piperidinodebromination of some 2-bromo-3-X-5-nitrothiophens (I). The aim of the work was also to confirm the larger transmission of electronic effects between the 2- and 3-positions[1,3] in the thiophen ring than between the 2- and 5-positions of the thiophen ring and the 1- and 2-positions of the benzene ring.

RESULTS AND DISCUSSION

Reaction Products.—2-Bromo-3-X-5-nitrothiophens (I) gave the corresponding 2-piperidyl-3-X-5-nitrothiophens (II) on treatment with piperidine in methanol. These were obtained in almost quantitative yields as shown by t.l.c. and u.v.–visible (200—450 nm) spectral analysis of the reaction mixtures. The physical data are collected in Table 1.

Kinetic Data.—On the basis of the generally accepted mechanism (S_NAr), the increase expected for the nucleophilic substitution rate was observed on introduction of an electron-withdrawing group into the 3-position: rate constants and thermodynamic parameters are reported in Table 2.

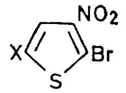
To test the possibility of a linear free energy relationship for our kinetic data log *k* at 20° was plotted against σ_p^-[4] or against log *k* at the same temperature for the piperidinodebromination of the corresponding 2-bromo-3-nitro-5-X-thiophens (III) previously studied by us.[5]

TABLE 1

Physical and spectroscopic data for piperidino-derivatives (IIa—h)

Compounds	Crystallization solvent	Colour	M.p. (°C)	$\lambda_{max.}$/nm [a]	log ε [a]
(IIa)	Ligroin	Orange	75	440	4·16
(IIb) [b]	Ligroin	Orange	126	448	4·50
(IIc) [c]	Methanol	Orange	77	428	4·10
(IId)	Methanol	Orange	155	432	4·21
(IIe)	Methanol	Yellow	71	420	4·22
(IIf)	Methanol	Orange	120	404	4·12
(IIg)	Ethanol–dioxan	Orange	155	418	4·30
(IIh) [d]	Ethanol	Orange	103	380	4·20

[a] In methanol. [b] See ref. 14. [c] See ref. 12. [d] See ref. 11.



(III)

In both cases we have observed an excellent correlation

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† Presented to a meeting of the Società Chimica Italiana, Catania, 1973.

[1] D. Spinelli, G. Guanti, and C. Dell'Erba, *J.C.S. Perkin II*, 1972, 441.

[2] A. M. Porto, L. Altieri, A. J. Castro, and J. A. Brieux, *J. Chem. Soc.* (*B*), 1966, 963.

[3] D. Spinelli, R. Noto, and G. Consiglio, unpublished results.

[4] D. Spinelli and G. Consiglio, Società Chimica Italiana Meeting, Catania, 1973.

[5] D. Spinelli, G. Consiglio, and A. Corrao, *J.C.S. Perkin II*, 1972, 1866 and references therein.

(except for X = Br, which has been excluded from the calculation).*

The absence of steric effects for methyl and methylsulphonyl groups seems to be linked for methyl to the more favourable geometry of the five- than a six-membered ring while for the methylsulphonyl group it can be related to the ability[5] of this group to exert its electronic effects even when the C_{Ar}–S bond is out of the plane of the aromatic ring.

TABLE 2

Kinetic data and thermodynamic parameters for the piperidinodebromination in methanol of compounds (Ia—h)

Compound	10^4k/l mol^{-1} s^{-1} (°C) [a]			$\Delta H^{\ddagger}$ [b] kcal mol^{-1}	$-\Delta S^{\ddagger}$ [c] kcal mol^{-1} K^{-1}	σ_p- [d]
(Ia)	0·0410 (19·95)	0·106 (30·00)	0·192 (37·75)	15·2	31·3	−0·10
(Ib) [e]	0·163 (20·01)	0·389 (30·01)	0·937 (40·03)	15·3	28·1	0·00
(Ic) [f]	0·765 (20·00)	1·74 (30·00)	3·69 (40·39)	13·5	31·3	+0·35
(Id)	27·9 (19·99)	58·2 (30·13)	116 (40·00)	12·4	27·7	+0·55
(Ie)	92·0 (20·00)	190 (30·02)	366 (39·90)	12·1	26·6	+0·71
(If)	433 (20·04)	848 (30·03)	1600 (40·00)	12·0	25·9	+0·85
(Ig)	154 (10·08)	378 (19·88)	764 (30·02)	13·1	20·2	+0·92
(Ih) [g]	10600 (10·82)	19900 (20·06)	37800 (30·02)	10·7	20·5	+1·27

[a] The rate constants are accurate to within ±3%. [b] At 20°, the probable error is 0·5 kcal mol^{-1}. [c] At 20°. [d] See refs. 3 and 4. [e] Data from ref. 14. [f] Data from ref. 12. [g] Data from ref. 17.

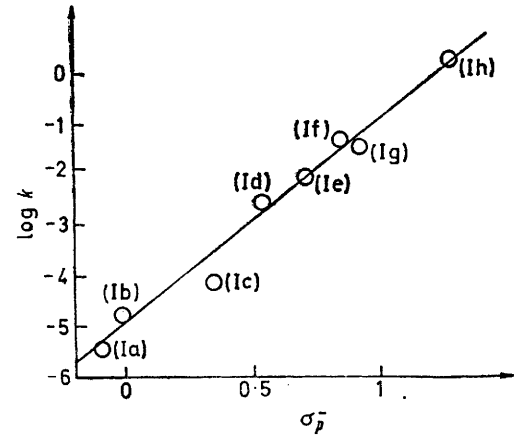

FIGURE 1 Hammett plot for the piperidinodebromination of (Ia—h) in methanol at 20°; ρ + 4·02, *r* 0·998, *s* 0·12. Data for (Ic) has been excluded from calculation of ρ

In the first plot a high and positive ρ value (Figure 1; ρ +4·02, *r* 0·998, *s* 0·12) was obtained and in the second the observed slope is 1·18 (Figure 2; *r* 0·997, *s* 0·05). This indicates that the effects exerted by the substituents are of the same type, *i.e.* extraconjugative, in the two series of compounds, (I) and (III). A comparison of data related to compounds (I) and (III) shows that with the same substituent the reactivity of compound (III) is always greater than that of (I) and the rate constants converge to the same value for X = NO_2. Therefore the sensitivity to substituent effects is higher in series (I) than in (III).

This datum is of particular interest because it represents the first case in which the sensitivity to electronic effects of substituents in a reaction on the nucleus is greater from an *ortho-* than from a *para*-like position. For example, in the benzene series reactivity data for the piperidinodehalogenation of halogenonitrobenzenes give linear free energy relationships[6] for both *ortho-* and *para*-substituted derivatives, but the observed trend is $\rho_o < \rho_p$ (ρ_o/ρ_p = 0·78),† while in thiophen series for the case studied we have observed $\rho_o > \rho_p$ (ρ_o/ρ_p = **1·18**).

We think that this difference in behaviour must be linked to steric factors: in benzene compounds an *ortho*-substituent cannot exert its full electronic effects because of steric interactions with the reaction centre. In thiophen compounds the peculiar geometry of the five-membered ring[7] practically eliminates these

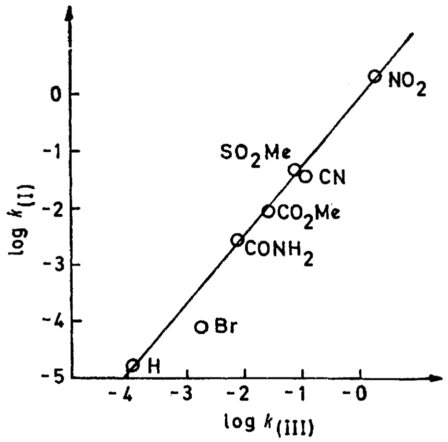

FIGURE 2 Logarithmic plot for the piperidinodebromination of (Ib—h) *versus* (IIIb—h) in methanol at 20°; slope 1·18, *r* 0·997, *s* 0·05. Data for (Ic) and (IIIc) have been excluded from the calculation

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* In the course of the study of the piperidinodechlorination of a series of 6-X-2-nitrochlorobenzenes (X = NH_2, Me, OMe, H, Br, Cl, CO_2H, CO_2Et, or NO_2) in benzene, Sbarbati[6] observed a linear Hammett plot for substituents with a *VdW* radius < *ca.* 1·9 Å, *i.e.* excluding Br and Me from the correlation. In our case Me, Br, and SO_2Me exceed the radius indicated by Sbarbati,[6] but only Br, a bulky but compact substituent, need be excluded from the correlation.

† Ratio calculated by us from the plot of log k_o *versus* log k_p at the same temperature (75°) from data in ref. 6.

[6] N. E. Sbarbati, *J. Org. Chem.*, 1965, **30**, 3365.

[7] A. J. H. Wachters and D. W. Davies, *Tetrahedron*, 1964, **20**, 2841; M. Nardelli, F. Fava, and G. Giraldi, *Acta Cryst.*, 1962, **15**, 737 and references therein.

unfavourable steric effects and makes an *ortho*-like substituent more efficient than in benzene.

The difference in the transmission of electronic effects in the two aromatic rings compared can be also explicable in terms of their different electronic structures. In fact the greater 'bond fixation' in the thiophen ring (with respect to benzene) give rise to a C(2)–C(3) bond * with a higher π-bond order than in benzene and this factor enhances the ρ value.

EXPERIMENTAL

Synthesis and Purification of Compounds.—Compounds (Ib),[8] (Ic),[9] (Ih),[10] (IIIb),[11] (IIIc),[12] and (IIIh),[13] methanol,[13] and piperidine [14] were prepared and/or purified according to the literature methods. The other compounds were prepared as below and gave correct analyses and n.m.r. spectra.

2-*Bromo*-3-*methyl*-5-*nitrothiophen* (Ia).—Nitric acid (*d* 1·52; 12·5 ml) in acetic anhydride (25 ml) was slowly added with stirring to a solution of 2-bromo-3-methylthiophen [15] (13·5 g) in acetic anhydride (25 ml) at −5 to −10°. After being kept at −10° for 1 h, the mixture was poured onto crushed ice. The separated oil was extracted with ether. The ethereal extracts were washed with aqueous $NaHCO_3$ (10%) and water, dried (Na_2SO_4), decoloured with charcoal, and the ether distilled off. The residue was purified by column chromatography on silica gel (eluant light petroleum), m.p. 41° (from light petroleum).

2-*Bromo*-5-*nitrothiophen*-3-*carboxamide* (Id).—Crude 2-bromo-5-nitrothiophen-3-carboxylic acid was converted to the acid chloride (by thionyl chloride) and then to the *amide* (Id) by treatment with aqueous ammonia. The solid obtained was crystallized from methanol–dioxan, m.p. 212°.

2-*Bromo*-5-*nitrothiophen*-3-*carboxylic Acid.*—Methyl 2-bromo-5-nitrothiophen-3-carboxylate (Ie) (2·7 g) was hydrolysed by boiling for 6—10 h in the presence of concentrated H_2SO_4 (45 ml) and water (90 ml) to give the acid, m.p. 160°, used (see above) without further purification.

Methyl 2-*Bromo*-5-*nitrothiophen*-3-*carboxylate* (Ie).—Ester (Ie) was obtained from methyl 5-nitrothiophen-3-carboxylate [16] by mercuriation and bromination according to the method previously used by us [17] for the synthesis of other thiophen compounds, m.p. 89° (from ligroin).

2-*Bromo*-3-*methylsulphonyl*-5-*nitrothiophen* (If).—Compound (If) was obtained from 2-nitro-4-methylsulphonylthiophen by mercuriation and bromination as for the previous compound, m.p. 133° (from ligroin–benzene).

2-*Nitro*-4-*methylsulphonylthiophen.*— 3-Methylsulphonylthiophen [18] (1 g) was slowly added with stirring, at 0—10°, to fuming nitric acid (*d* 1·52; 10 ml). After being kept under stirring for 30 min, the mixture was poured onto crushed ice. The precipitated solid was filtered off and crystallized from methanol, m.p. 152°.

2-*Bromo*-5-*nitrothiophen*-3-*carbonitrile* (Ig).—Nitric acid (*d* 1·52; 1·3 ml) was slowly added with stirring, at 10—12°, to a solution of 2-bromothiophen-3-carbonitrile [19] (2·5 g) in acetic anhydride (2·5 ml). After being kept for 3 h the mixture was poured onto crushed ice. The precipitated solid was filtered off and crystallized from ethanol, m.p. 123°.

Piperidino-derivatives.—These compounds (physical and spectroscopic data in Table 2) were prepared by reacting the corresponding bromonitrothiophens (Ia, d—g) with piperidine according to the general method of ref. 20.

Kinetic Measurements.—The kinetics were carried out in the presence of piperidine hydrochloride to avoid competitive methoxydebromination [5,17,21] and followed spectrophotometrically as previously described.[14] The concentrations used were 10^{-3}M for the bromonitrothiophens, 6×10^{-3}M for piperidine, and 3×10^{-2}M for piperidine hydrochloride.

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* The calculated [7] value of π-bond order in thiophen is C(2)–C(3) = 0·863.

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