Linear Free Energy *ortho*-Correlations in the Thiophene Series. Part 12.[1] The Kinetics of Piperidinodebromination of Some 2-Bromo-3-X-4-methyl-5-nitrothiophenes in Methanol

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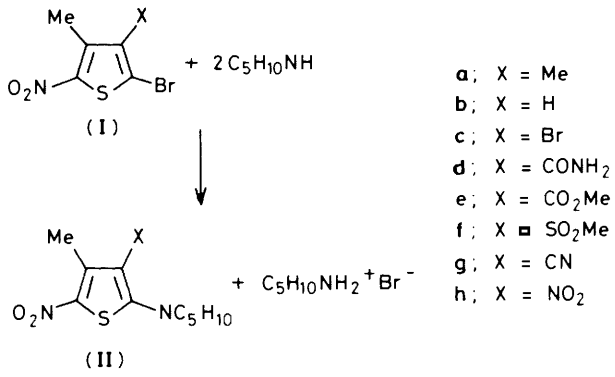
The rates of piperidinodebromination of some 2-bromo-3-X-4-methyl-5-nitrothiophenes (**I**; X = Me, H, Br, $CONH_2$, CO_2Me, SO_2Me, CN, or NO_2) have been measured in methanol. The logarithm of the rate constants gives an excellent straight line when plotted against the logarithm of the rate constants of piperidinodebromination for the corresponding 2-bromo-3-X-5-nitrothiophenes (**III**) (except for X = $CONH_2$) and against σ^- (except for X = Br and $CONH_2$). The good fit obtained confirms the applicability of Hammett-type relationships to fully *ortho*-tetrasubstituted thiophene derivatives. Kinetic data show the occurrence of a significant secondary steric effect in the piperidinodebromination of compound (**Id**).

Some of our recent results on S_NAr reactions of thiophene derivatives have shown that a methyl group *meta* to the seat of substitution increases the reactivity of the parent compound by a factor of 2—3.[2] Traditionally, a methyl group attached to an aromatic system is considered to be electron-releasing in that it stabilizes cations and destabilizes anions. However, the above weak activation represents an exception to this generalization.

In this paper we report a study on the piperidinodebromination of some 2-bromo-3-X-4-methyl-5-nitrothiophenes (**Ia—h**) in methanol. This study was designed to ascertain whether the activation by the *meta*-methyl group is dependent or not on the 5-X substituent, *i.e.*, on the overall degree of activation of the aromatic substrate. Incidentally, the kinetic data give additional information on the applicability of the Hammett relationship to a series of fully *ortho*-tetrasubstituted compounds.[3]



Scheme.

Results and Discussion

Reaction Products.—2-Bromo-3-X-4-methyl-5-nitrothiophenes (**Ia—h**), on treatment with piperidine in methanol, gave the corresponding piperidino-derivatives (**IIa—h**) in high yield, as shown by t.l.c. and u.v.-visible spectral analysis (200—450 nm) of the reaction mixtures. The relevant physical data are shown in Table 1.

Kinetic Data.—Rate constants and activation parameters for the piperidino-substitution reactions of compounds (**Ia—h**) in methanol are reported in Table 2. All the reactions were first-order both in (**I**) and piperidine. The nucleophilic substitution rate increases as expected on introduction of an electron-withdrawing group into the 3-position. On the other hand, a methyl group at C(3) reduces the reaction rate with respect to hydrogen.

Linear Free Energy Relationships.—Good linear correlations are observed when log k at 293.2 K for the reactions of compounds (**Ia—h**) are plotted against log k at 293.2 K for the reactions of the corresponding 2-bromo-3-X-5-nitrothiophenes (**III**) (Figure 1; slope 0.93, r 0.997, s 0.16, n 7) and 2-bromo-3-nitro-5-X-thiophenes (**IV**) (slope 1.08, r 0.994, s 0.20, n 5; plot not shown) except for the points relative to X = $CONH_2$ (in the first case) and to X = Br and X = $CONH_2$ (in the second case), which deviate markedly from the straight lines.

On the other hand, the Hammett plot (Figure 2) of log k at 293.2 K for the piperidinodebromination of (**Ia—h**) against σ^- is satisfactorily linear (ρ 3.77, r 0.996, s 0.21, n 6) provided that

Table 1. Physical and spectroscopic data[a] for piperidino-derivatives (**IIa—h**)

Compound	Crystallization solvent	Colour	M.p. (°C)	$\lambda_{max.}$/ nm[b]	log ε[b]
(**IIa**)	Light petroleum–benzene	Orange	70	430	4.14
(**IIb**)[c]	Ligroin–benzene	Orange	162	440	4.54
(**IIc**)[d]	Methanol	Orange	110	425	4.12
(**IId**)	Methanol–dioxane	Orange	210	434	4.38
(**IIe**)	Ligroin	Yellow	96	426	4.32
(**IIf**)	Ligroin–benzene	Orange	116	404	4.03
(**IIg**)	Methanol–dioxane	Orange	182	416	4.33
(**IIh**)[e]	Ethanol	Orange	143	408	4.25

[a] All the new substitution products gave correct analyses. [b] In methanol. [c] See ref. 2*c*. [d] See ref. 2*a*. [e] See ref. 4.

Table 2. Kinetic data and activation parameters for the reactions of compounds (**Ia**—**h**) with piperidine in methanol, at various temperatures[a]

Compound	10^4k/l mol^{-1} s^{-1} (T/K in parentheses)			$\Delta H^{\ddagger}$/kJ mol^{-1}[b]	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}[c]	σ^-[d]
(**Ia**)	0.0526 (293.2)	0.115 (303.2)	0.241 (313.2)	55.6	156	−0.10
(**Ib**)[e]	0.286 (293.1)	0.658 (303.1)	1.43 (313.2)	58.6	131	0.00
(**Ic**)[f]	1.09 (293.3)	2.59 (303.2)	5.24 (313.2)	57.7	123	0.35
(**Id**)	2.51 (293.0)	5.78 (303.2)	11.6 (313.2)	55.2	124	0.55
(**Ie**)	60.0 (293.1)	120 (303.1)	234 (313.3)	49.0	120	0.71
(**If**)	534 (293.1)	1 080 (303.2)	1 950 (313.2)	46.4	110	0.85
(**Ig**)	244 (283.1)	491 (293.2)	950 (313.2)	45.6	113	0.92
(**Ih**)[g]	5 630 (284.0)	9 910 (293.2)	20 000 (303.2)	44.8	92	1.27

[a] The rate constants are accurate to within ±3%. [b] At 293.2 K; the maximum error is 2.1 kJ mol^{-1}. [c] At 293.2 K; the maximum error is 7 J K^{-1} mol^{-1}. [d] See ref. 5*b*. [e] See ref. 2*c*. [f] See ref. 2*a*. [g] See ref. 4.

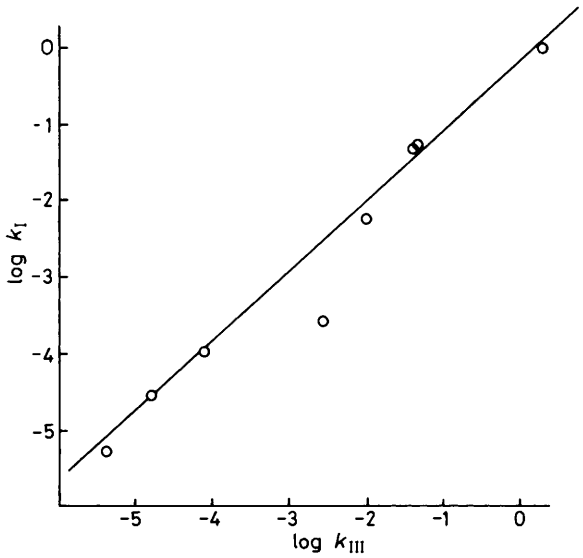


Figure 1. Logarithmic plot for the piperidinodebromination of (**Ia**—**h**) *versus* (**IIIa**—**h**) in methanol at 293.2 K; slope 0.93, r 0.997, s 0.16, n 7. Data for (**Id**) and (**IIId**) have been excluded from the calculation

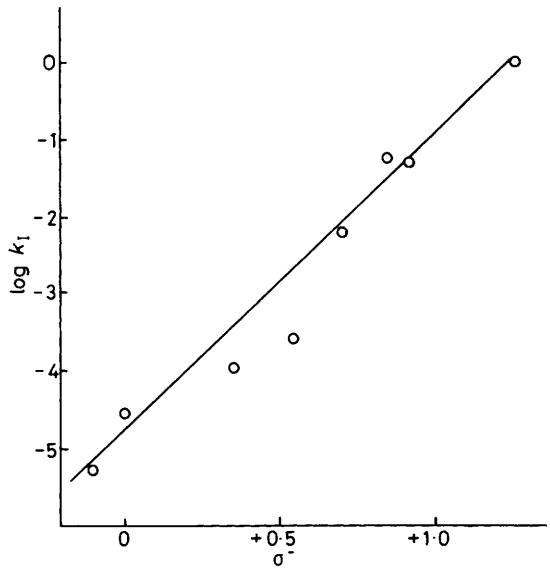
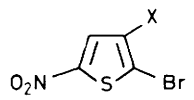
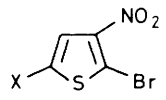


Figure 2. Hammett plot for the piperidinodebromination of (**Ia**—**h**) in methanol at 293.2 K; ρ +3.77, r 0.996, s 0.21, n 6. Data for (**Ic**) and (**Id**) have been excluded from the calculation.



(III)



(IV)

the points for X = Br and $CONH_2$ are excluded from the calculation.*

The latter plot brings to notice the primary steric effect exerted by the bromine atom at C(3) on the piperidino-substitution; indeed, due to some compensation, this effect escapes notice upon consideration only of the first correlation.

However, the good fit obtained confirms the applicability of Hammett-type relationships to fully *ortho*-tetrasubstituted thiophene derivatives.[3]

The Effect of the 4-Methyl Group on the Reactivity.—The k_I/k_{III} ratios (Table 3) show that the insertion of the methyl group at C(4), between the 3-X substituent and the activating 5-nitro-group, causes a variation of reactivity which ranges within a small factor and this accounts for the good linear correlations observed. However, the effect exerted by the 4-methyl group, compared with hydrogen, is by no means constant but it depends in a definite way both on the shape and the size of 3-X substituent.

Thus, the effect exerted by the 4-methyl group is weakly activating† when X is small (H) or 'linear' (CN), or when it is able to exert its electronic effects even when its bond with the aromatic carbon atom is out of the plane of the thiophene ring (SO_2Me). Weak activation by the *meta*-methyl group is also observed for X = Me and Br; however, whereas the top-symmetrical 3-Me group has no steric influence on the piperidino-substitution,[5b] the bulky and 'compact' 3-Br exerts a significant primary steric effect (see above).

When the head-atom of X has sp^2 symmetry (X = $CONH_2$, CO_2Me, or NO_2) there could be a steric interaction between this

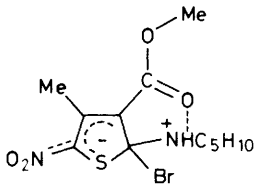
* The set of 'homogeneous' σ^- constants for the heteroaromatic system considered (Table 2) has been obtained, by the method of Brown,[5a] from S_NAr reactions of thiophene compounds. Since in the correlation of log k at 293.2 K for the piperidinodebromination of compounds (**III**) with σ^- only the 3-bromo substituent deviates from the straight line,[5b] the above deviation of 3-$CONH_2$ group has to be attributed to some peculiarity of the tetrasubstituted compound (**Id**).

† For a discussion concerning the activating effect of alkyl groups in S_NAr reactions, see ref. 2.

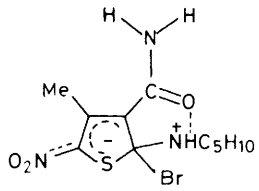
Table 3. Kinetic constants and reactivity ratios for the reactions of compounds (**Ia—h**) and (**IIIa—h**) with piperidine in methanol

X	10^4k_1 [a]	10^4k_{III} [a,b]	k_1/k_{III} [a]
Me	0.0523	0.418	1.3
H	0.287	0.161	1.8
Br	1.10	0.772	1.4
$CONH_2$	2.57	27.8	0.092
CO_2Me	60.0	92.0	0.65
SO_2Me	544	431	1.3
CN	492	361	1.4
NO_2	9 700	19 800	0.49

[a] Calculated at 293.2 K from activation parameters. [b] Values from ref. 5*b*.



(**V**)



(**VI**)

substituent and the 4-methyl group. The CO_2Me and NO_2 substituents are 'small' enough as to cause only a slight variation of the k_1/k_{III} ratio: however, in this case the 4-methyl group has a weakly deactivating effect. In contrast, the $CONH_2$ substituent displays a strong kinetic effect (k_1/k_{III} 0.092).

A plausible explanation for this secondary steric effect is the steric inhibition of resonance of the amido group caused by the adjacent 4-methyl group. An examination of molecular models shows that there is no relevant steric interaction between 4-methyl and 3-methoxycarbonyl in the reaction intermediate (**V**) of the S_NAr mechanism. In contrast, although the $CONH_2$ group has apparently much the same 'geometry' as the CO_2Me group, a steric interaction between the 4-methyl group and one of the two hydrogen atoms of the amino group does occur as in (**VI**).

In this situation the 3-$CONH_2$ substituent is forced to rotate about its bond with the aromatic ring and this causes both reduced conjugation and activation. Because of a small steric compression of the 4-methyl group on the NO_2 and CO_2Me substituents, these groups are also probably rotated out of the plane of the aromatic ring and this would account for the small deactivation observed (k_1/k_{III} 0.49 and 0.65 for X = NO_2 and CO_2Me, respectively).

The above interpretation concerning the 3-$CONH_2$ group has been confirmed by both a kinetic study of the piperidinodebromination in methanol of some *N*-substituted 2-bromo-5-nitro-4-R-thiophene-3-carboxamides (R = H and Me)[6] and an investigation, by dynamic n.m.r. spectroscopy, of the restricted rotation about the C–N bond of the amino group of some 2-bromo-5-nitro-4-R-thiophene-3-carboxamides (R = H and Me) and the corresponding *NN*-dimethylamides.[6]

Experimental

Synthesis and Purification of Compounds.—Compounds (**II**),[7] methanol,[8] and piperidine[7] were prepared and/or purified according to the methods reported. The other compounds were prepared as below and gave correct elemental analyses.

2-Bromo-3,4-dimethyl-5-nitrothiophene (**Ia**). Compound (**Ia**) was obtained from 3,4-dimethyl-2-nitrothiophene by mercuriation and bromination according to the method previously used[4] for the synthesis of other thiophene compounds, m.p. 49—50 °C (from light petroleum).

3,4-Dimethyl-2-nitrothiophene. Nitric acid (*d* 1.4; 5 ml) in acetic anhydride (15 ml) was slowly added with stirring to a solution of 3,4-dimethylthiophene (5.7 g) in acetic anhydride (15 ml), at −10 °C. After being kept at −10 °C for 30 min, the mixture was poured onto crushed ice. The precipitated solid was filtered off and chromatographed on a column of silica gel with light petroleum–benzene (1:1) as eluant. The compound was crystallized from light petroleum, m.p. 56 °C.

3,4-Dimethylthiophene. This compound was already known[9] but we have prepared it by the following completely different procedure. A solution of 3-bromo-4-methylthiophene[10] (28.5 g) in anhydrous ether (190 ml) was slowly added under nitrogen to a mixture of n-butyl-lithium (2M; 82 ml) and ether (43 ml), at −70 °C. The temperature was allowed to rise to −40 °C and a solution of dimethyl sulphate (58 g) in ether (65 ml) was added at such a rate that the temperature did not exceed −30 °C. After warming at room temperature the reaction mixture was stirred with concentrated aqueous ammonium hydroxide to destroy the excess of dimethyl sulphate. The organic phase was separated, washed with water, dried, and fractionated.

2-Bromo-4-methyl-5-nitrothiophene-3-carboxamide (**Id**). 2-Bromo-4-methyl-5-nitrothiophene-3-carboxylic acid was converted into the acyl chloride (by thionyl chloride) and then into the *amide* (**Id**) by treatment with aqueous ammonia. The solid obtained was crystallized from benzene, m.p. 184—185 °C.

2-Bromo-4-methyl-5-nitrothiophene-3-carboxylic acid. Methyl 2-bromo-4-methyl-5-nitrothiophene-3-carboxylate (**Ie**) (13.2 g) was hydrolysed by boiling for 48 h in the presence of concentrated H_2SO_4 (210 ml) and water (420 ml) to give the *acid*, m.p. 155 °C (from benzene).

Methyl 2-bromo-4-methyl-5-nitrothiophene-3-carboxylate (**Ie**). *Ester* (**Ie**) was obtained from methyl 4-methyl-5-nitrothiophene-3-carboxylate by mercuriation and bromination as above, m.p. 106—107 °C (from methanol).

Methyl 4-methyl-5-nitrothiophene-3-carboxylate. A solution of methyl 4-methylthiophene-3-carboxylate[1] (12.6 g) in acetic anhydride (22.5 ml) was slowly added with stirring to a solution of nitric acid (*d* 1.51; 32 ml) in acetic anhydride (85 ml), at −10 °C. After being kept at −10 °C for 30 min, the mixture was poured onto crushed ice. The precipitated solid was filtered off and crystallized from light petroleum–benzene, m.p. 102—104 °C.

2-Bromo-4-methyl-3-methylsulphonyl-5-nitrothiophene (**If**). *Compound* (**If**) was obtained from 3-methyl-4-methylsulphonyl-2-nitrothiophene by mercuriation and bromination as above, m.p. 156—157 °C (from ligroin–benzene).

3-Methyl-4-methylsulphonyl-2-nitrothiophene. Methyl 4-methyl-3-thienyl sulphone (4.8 g) was slowly added with stirring, at 0—10 °C, to fuming nitric acid (*d* 1.51; 45 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–dioxane, m.p. 150 °C.

Methyl 4-methyl-3-thienyl sulphone. Methyl 4-methyl-3-thienyl sulphide (11 g), prepared by an adaptation of the procedure described in ref. 11, was oxidized by refluxing with hydrogen peroxide (32 ml, 36%) in acetic acid (120 ml) for 2 h. The cooled solution was evaporated under reduced pressure and then poured onto ice, made alkaline, and extracted with ether. The ether phase was dried and the ether distilled off, leaving the crude *sulphone* which was used without further purification.

2-Bromo-4-methyl-5-nitrothiophene-3-carbonitrile (**Ig**) A solution of 2-bromo-4-methyl-5-nitrothiophene-3-carboxamide (**Id**) (2.2 g) in acetic anhydride (33 ml) was refluxed for 6 h. The reaction mixture was evaporated at reduced pressure and the

residue chromatographed on a column of silica gel with benzene as eluant. The *nitrile* obtained was crystallized from methanol, m.p. 125—126 °C.

Kinetic Measurements.—The kinetics, carried out in the presence of piperidine hydrochloride to avoid competitive methoxydebromination,[4] were followed spectrophotometrically as previously described.[1,2] The concentrations used were 10^{-3}M-substrate, 6×10^{-3}–1M-piperidine, and 3×10^{-2}M-piperidine hydrochloride.

Acknowledgements

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