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THIOPHENE SERIES—VI*

SUBSTITUENT EFFECT ON THE RATE OF NUCLEOPHILIC SUBSTITUTION: KINETICS OF THE REACTION BETWEEN 2-BROMO-3-NITRO-5-X-THIOPHENES AND PIPERIDINE IN ETHANOL

C. DELL'ERBA and D. SPINELLI
Institute of Organic Chemistry, University Genova, Italia

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Abstract—In continuation of the research on thiophenic compounds and in order to study the effect of various substituents in position 5 (which is conjugated with the halogen and is free from steric hindrance the rate constants for the reaction in ethanol between piperidine and several 2-bromo-3-nitro-5-X-thiophenes ($X = H$, Br, $COOC_2H_5$, $CONH_2$, SO_2CH_3, $COCH_3$, CN, $SO_2OC_6H_5$, NO_2) have been measured spectrophotometrically. A good fit to the Hammett equation was found. The highly positive ρ-value (+3,21) indicates that the substitution of the halogen by the piperidyl group is facilitated by a decreased electronic density at the reaction centre.

THE aromatic nucleophilic substitution between substituted halo-nitrobenzene compounds and nucleophilic reagents (piperidine, sodium methoxide, sodium thiophenoxide, etc) have been studied kinetically[1] and the substitution reaction rate has been correlated with the effect of substituents *meta* or *para* to the leaving halogen.[2] It has been found[2] that a good fit to the Hammett equation[3] may be achieved when the σ^- values[3b] are used as substituent constants. The σ^- parameters may be taken from the compilation by Jaffè.

$$\log \frac{k}{k_0} = \rho\sigma^- \qquad \text{(a)}$$

It has been found also that the nucleophilic substitution reactions of some six-membered heterocyclic compounds may be correlated by the Hammett equation.[4]

In the field of the thiophene compounds Imoto *et al.*[5] extended the Hammett relationship to the dissociation and esterification of thiophene-carboxylic acids, to

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* Part V: D. Spinelli and C. Dell'Erba, *Ann. Chimica* **54**, 281 (1964).

[1] J. F. Bunnett and R. E. Zahler, *Chem. Rev.* **49**, 273 (1951); J. F. Bunnett, *Quart. Rev.* **22**, 3 (1958); *Theoretical Organic Chemistry* (Kekulè Symposium 1958) pp. 144–157. Butterworths, London (1959).

[2] E. Berliner and L. C. Monack, *J. Amer. Chem. Soc.* **74**, 1574 (1952); W. Greizerstein, R. A. Bonelli and J. A. Brieux, *ibid.*, **84**, 1026 (1962); F. Kalberer, *Bull. Soc. Fribourgoise des Sci. Naturelles* **44**, 225 (1954); E. L. Eliel and K. W. Nelson, *J. Org. Chem.* **20**, 1657 (1955); R. L. Heppolette, J. Miller and V. A. Williams, *J. Chem. Soc.* 2929 (1955) and previous papers; J. F. Bunnett, F. Draper, P. R. Ryason, P. Noble, R. G. Tonkyn and R. E. Zahler, *J. Amer. Chem. Soc.* **75**, 642 (1953); J. F. Bunnett, H. Moe and D. Knutson, *Ibid.* **76**, 3936 (1954). C. L. Bevan, *J. Chem. Soc.* 655 (1953); L. R. Parks, G. Hammond and M. E. Hawthorne, *J. Amer. Chem. Soc.* **77**, 2903 (1955); N. B. Chapman and R. E. Parker, *J. Chem. Soc.* 3301 (1957); J. F. Bunnett and G. T. Davis, *J. Amer. Chem. Soc.* **76**, 3011 (1954); J. F. Bunnett and R. F. Snipes, *Ibid.* **77**, 5422 (1955).

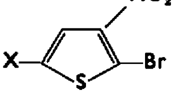
[3a] L. P. Hammett, *Physical Organic Chemistry* McGraw-Hill, N.Y. (1940); [b] H. H. Jaffè, *Chem. Rev.* **53**, 191 (1953).

[4] M. L. Belli, G. Illuminati and G. Marino, *Tetrahedron* **19**, 345 (1963).

[5] E. Imoto and Y. Otsuji, *Bull. of Osaka Prefecture* Series A Vol. 6, 115 (1958).

the saponification and polarographic reduction of esters of thiophene-carboxylic acids, to the bromination of acetylthiophenes and mercuriation of thiophene derivatives. The polarographic reduction of thiophene derivatives and the saponification of esters of thiophene-carboxylic acids have been studied also by Tirouflet *et al.*[6] Data relative to the dissociation of thiophene-carboxylic acids have been reported by Price *et al.*[7]

Continuing our research[8] on the kinetics of the nucleophilic substitution, since in the literature no information was available concerning the validity of the Hammett equation for reactions in which the carbon of the thiophene ring is directly involved, we have measured the rate constants for the reaction between 2-bromo-3-nitro-5-X-thiophenes (in I: $X = H, Br, COOC_2H_5, CONH_2, SO_2CH_3, COCH_3, CN, SO_2OC_6H_5, NO_2$) and piperidine in ethanol at various temperatures.



I

EXPERIMENTAL

(A) *Synthesis and purification of the compounds*

2-Bromo-3-nitro-thiophene,[9] 2,5-dibromo-3-nitro-thiophene,[10] 2-bromo-3-nitro-5-thiophencarboxamide,[11a] 2-bromo-3-nitro-5-acetylthiophene[11b] and 2-bromo-3,5-dinitro-thiophene[11b] were prepared and purified according to the methods reported.

Piperidine was purified by drying over KOH and distillation through a column. The middle fraction, b.p. 106–107° was used.

The other compounds were prepared as reported below.

2-*Bromo*-3-*nitro*-5-*thiophencarboxylic acid ethyl ester*. A mixture of conc. HNO_3 (4·2 ml $d = 1{\cdot}42$) and conc. H_2SO_4 (13 ml) was added with stirring to a solution of 2-bromo-5-thiophene-carboxylic acid ethyl ester (15 g) in conc. H_2SO_4 (40 ml) cooled to −5°–10°. After the addition the mixture was allowed to stand at −5° for 30 min and then poured over crushed ice. The precipitated solid was separated by filtration and crystallized from EtOH in colourless prisms, m.p. 87°. (Found: Br, 28·10; N, 5·08. $C_7H_6BrNO_4S$ requires: Br, 28·57; N, 5·00%.)

2-*Bromo*-3-*nitro*-5-*methylsulphonyl-thiophene*. 2-Bromo-5-methylsulphonyl-thiophene (4 g) were added to a cooled (0°) and stirred mixture of conc. H_2SO_4 (11 ml) and fuming HNO_3 (15 ml) and stirring continued at 0° for 30 min. It was then poured over ice-water. The separated solid was filtered off, washed with water and crystallized from EtOH as colourless needles, m.p. 155–156°. (Found: Br, 28·06; N, 4·97. $C_5H_4BrNO_4S_2$ requires: Br, 27·97; N, 4·89%.)

2-*Bromo*-5-*methylsulphonyl-thiophene*. This product was prepared from 2-bromo-5-thiophene-sulphonyl chloride by reduction with Na_2SO_3 and methylation of the sulphinic acid with MeI, according to Cymerman and Lowe.[12] It crystallized from ligroine as colourless prisms, m.p. 81°. (Found: Br, 33·19; S, 26·55. $C_5H_5BrO_2S_2$ requires: Br, 32·84; S, 27·04%.)

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[6] J. Tirouflet and J. P. Chanè, *C.R. Acad. Sci., Paris* **243**, 500 (1956); J. Tirouflet, P. Fournari and J. P. Chanè, *Bull. Soc. Chim. Fr.* 981 (1957); J. Tirouflet, *Ibid.* 1066 (1958); P. Fournari, *Ibid.*, 1021 (1960).

[7] C. C. Price, E. C. Mertz and J. Wilson, *J. Amer. Chem. Soc.* **76**, 5131 (1954); C. C. Price and E. A. Dudley, *Ibid.* **78**, 68 (1956).

[8] D. Spinelli, C. Dell'Erba and A. Salvemini, *Ann. Chim.* **52**, 1156 (1962).

[9] C. Carpanelli and G. Leandri, *Ann. Chim.* **51**, 181 (1961).

[10] W. Steinkopf, H. Jacob and H. Penz, *Liebigs Ann.* **512**, 136 (1934).

[11] [a] S. Nishimura and E. Imoto, *Nippon Kagaku Zhassi* **82**, 1543 (1961); [b] R. Motoyama, K. Sato and E. Imoto, *Ibid.* **78**, 779 (1957).

[12] J. Cymerman and J. L. Lowe, *J. Chem. Soc.* 6166 (1949).

The IR spectrum is characteristic of compounds with a —SO_2— group

2-Bromo-5-cyano-thiophene. This product was prepared from 2-bromo-5-thiophenaldoxime according to Reynaud and Delaby.[13] The product distilled at 100–102°/6 mm. (Found: N, 7·50; S, 17·09. C_5H_2BrNS requires: N, 7·44; S, 17·02%.)

2-Bromo-5-thiophenaldoxime. This product was prepared from 2-bromo-5-thiophene aldehyde according to Reynaud and Delaby.[13] It crystallized from aqueous EtOH as colourless flakes, m.p. 149°. (Found: N, 6·83. C_5H_4BrNOS requires: N, 6·79%.)

2-Bromo-3-nitro-5-thiophen-sulphonic acid phenyl ester. This product was prepared from 2-bromo-3-nitro-5-thiophen-sulphonyl chloride and sodium phenoxide by a previously described procedure.[14] The product was crystallized from EtOH as colourless needles, m.p. 95°. (Found: Br, 22·27; N, 3·87. $C_{10}H_6BrNO_5S_2$ requires: Br, 21·97; N, 3·84%.)

2-N-*Piperidyl*-3-*nitro*-5-X-*thiophenes* (*see scheme* b). 2-N-piperidyl-3-nitro-5-X-thiophenes were prepared by allowing the corresponding 2-bromo-3-nitro-5-X-thiophenes to react with piperidine. A typical run is reported below:

Piperidine (0·011 mole) was added to a suspension of 2-bromo-3-nitro-5-X-thiophene (0·005 mole) in EtOH (10 ml) and refluxed for 30 min. After cooling, the reaction mixture was evaporated at red. press. The residue was washed with water containing a little EtOH and crystallized. The crystallization details and the analytical data are reported in Table 1.

(B) *Kinetic measurements*

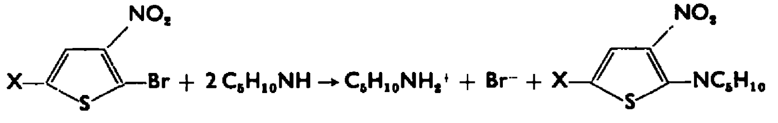
The kinetic technique and method of calculation for the kinetic constants used, have been reported previously.[15] The wavelength (in mμ) and the logarithm of the molar extinction coefficient of the 2-N-piperidyl-3-nitro-5-X-thiophenes used to follow the reaction spectrophotometrically are reported in Table 1.

The rate constants are given in Table 2.

The concentrations used were 1×10^{-4}M for the 2-bromo-3-nitro-5-X-thiophenes and 6×10^{-4}M for the piperidine. The solvent used was purified 95° EtOH.

DISCUSSION OF THE RESULTS

The composition of the reaction products, defined unambiguously from the analytical data, confirms what has been already observed by ourselves[8,16] and by other workers[17] in many other analogous thiophene derivatives, namely that only the activated bromine is involved in the substitution reactions (see Scheme b).



(b)

In Table 2 the rate constants are reported together with the values of the corresponding thermodynamic parameters, while in Fig. 1 the logarithms of the rate constants at 20° are plotted against the Hammett substituent constants. This plot shows that the reaction follows the Hammett equation.

It was found convenient to use the Jaffè σ^- parameters for the series of reactions studied. These are nucleophilic substitutions where the substituents influence the reaction centre with inductive and conjugative effects, the latter being predominant.

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[13] P. Reynaud and R. Delaby, *Bull. Soc. chim. Fr.* 1614 (1955).

[14] G. Leandri, G. Monaco and D. Spinelli, *Ann. Chim.* **49**, 407 (1959).

[15] D. Spinelli, A. Salvemini and C. Dell'Erba, *Ann. Chim.* **54**, 869 (1964).

[16] G. Leandri, D. Spinelli and C. Dell'Erba, *Ann. Chim.* **50**, 1597 (1960); D. Spinelli and C. Dell'Erba, *Ibid.*, **54**, 281 (1964).

[17] C. D. Hurd and K. L. Kreuze, *J. Amer. Chem. Soc.* **74**, 2965 (1952); A. H. Blatt, N. Gross and E. W. Tristran, *J. Org. Chem.* **22**, 1588 (1957); E. B. Towne, W. H. Moore and J. B. Dichey, U.S. Pat. 2825726, *Chem. Abstr.* **52**, 9613 (1958).

TABLE 1. 2-N-PIPERIDIL-3-NITRO-5-X-THIOPHENES

X =	Crystallization solvent	Colour and crystal form	M.P.	Found (%)		Formula	Required (%)		λ_{max} (mμ)	log ε
				N	Br or S		N	Br or S		
H*	ligroin	orange plates	77°						400	3·76
Br	ligroin	orange prisms	98°	9·71	Br, 27·60	$C_9H_{11}BrN_2O_2S$	9·62	Br, 27·49	404	3·78
$CONH_2$	ethanol	orange prisms	216°	16·49		$C_{10}H_{13}N_3O_3S$	16·47		394	3·76
$COOC_2H_5$	ligroin	yellow prisms	90°	9·91	S, 11·42	$C_{12}H_{16}N_2O_4S$	9·86	S, 11·26	390	3·78
SO_2CH_3	ligroin	yellow prisms	104°	9·80		$C_{10}H_{14}N_2O_4S_2$	9·65		384	3·79
CN	ligroin	yellow prisms	118°	17·80		$C_{10}H_{11}N_3O_2S$	17·72		388	3·79
$SO_2OC_6H_5$	ethanol	yellow needles	116°	7·64	S, 17.10	$C_{15}H_{16}N_2O_5S_2$	7·61	S, 17·39	380	3·78
NO_2	ethanol	orange plates	103°						380	4·18
$COCH_3$	methanol	yellow needles	96°	11·11		$C_{11}H_{14}N_2O_3S$	11·02		345	4·22

* D. Spinelli, C. Dell'Erba and A. Salvemini, *Ann. Chimica*, **52**, 1156 (1962).

TABLE 2. KINETIC DATA FOR THE REACTION BETWEEN 2-BROMO-3-NITRO-5-X-THIOPHENES AND PIPERIDINE IN ETHANOL

X =	10^3k, 1 mol^{-1} sec^{-1}, at various temperatures[a]							E_{exp}[b] kcal/ mole	$\Delta H\ddagger$[c] kcal/ mole	$-\Delta S\ddagger$[d] u.e.	σ^-[e]
	10·00°	15·40°	20·00°	29·15°	39·00°	48·75°	60·40°				
H			0·151[f]		0·625	1·473	2·936	14·9	14·3	27·1	0·000
Br			2·53	4·82	10·65			13·8	13·2	25·3	0·289
$CONH_2$			8·69	17·12	35·37			13·5	12·9	24·4	0·552
$COOC_2H_5$			35·6	65·0	119·7			11·6	11·0	27·6	0·678
SO_2CH_3			98·0	190·2	419			13·9	13·3	18·0	1·049
$COCH_3$			116	195	331			10·1	9·5	30·3	0·874
CN			187	361	785			13·8	13·2	16·6	0·997
$SO_2OC_6H_5$			513	940	1706			11·5	10·9	22·6	
NO_2	1980	2580	2950					6·6	6·0	35·8	1·270

[a] The rate constants are accurate to better than ±2%.

[b] The probable error is 0·3 kcal/mole.

[c] At 20°, the probable error is 0·3 kcal/mole.

[d] At 20°.

[e] H. H. Jaffè, *Chem. Rev.*, 53, 191 (1853); L. N. Fergusson, "The Modern Structural Theory of Organic Chemistry", Prentice-Hall, N.Y., p. 415 (1959).

Value calculated from the activation parameters.

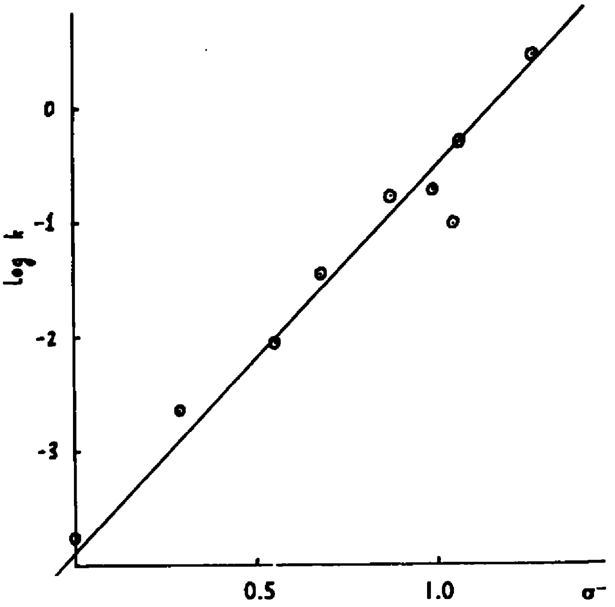

Fig. 1

The position 5 of the thiophene ring in respect to the position 2 must be regarded as a *para*-like position, since it may be subject to a conjugative effect whereas a steric effect cannot influence it.

As Hammett constants for the substituents *p*-Br, *p*-$COCH_3$, *p*-$COOC_2H_5$, *p*-CN and *p*-NO_2, the σ^- values reported by Jaffè[3b] and Fergusson[18] have been used and for *p*-$CONH_2$ the value reported by van Beckum *et al.*[19] When the value for *p*-SO_2CH_3 reported by the previous workers[3b,18] ($\sigma^-_{p\text{-}SO_2CH_3} = 1{\cdot}049$) is used for the reaction

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[18] *The modern structural theory of organic chemistry* p. 415. Prentice-Hall, N.Y. (1963).

[19] H. van Beckum, P. E. Verkade and B. M. Wepster, *Rec. Trav. Chim.* 78, 815 (1959).

between 2-bromo-3-nitro-5-methylsulphonyl-thiophene and piperidine the point deviates from the best $\rho\sigma^-$ line which may be drawn using all the other points.* This value was, therefore, not used in calculating the ρ parameter for the reaction.

As the σ_p^- for the p-$SO_2OC_6H_5$ group is not in the literature, σ_p^- equal to 1·065 was deduced from our experimental data.

The ρ value found for the reaction (b) at 20° (Fig. 1) is 3·21 with an excellent correlation coefficient (r = 0·995). This value is in agreement with the known observation that for aromatic nucleophilic substitutions the positive ρ values are high because of the sensitivity of the reaction centre to the substituent's electronic structure. Furthermore, the ρ value found compares favourably with the ones reported in the literature[2] for analogous reactions.

At 20° the observed kinetic constants show the following reactivity order (Table 1) p-NO_2 > p-$SO_2OC_6H_5$ > p-CN > p-$COCH_3$ > p-$CONH_2$ > p-$COOC_2H_5$ > p-Br > p-H. The substituent polar effect is in agreement with what is to be expected.

The highly positive ρ value and the reactivity order observed, similar to the ones found in the benzene series, show that in thiophene derivatives the reaction rate largely depends upon the facility with which the π electron aromatic sextet is distorted by the substituents present.

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* A better agreement is found using the value 0·840 for the $\sigma^-_{p\text{-}SO_2CH_3}$ which has been determined by F. G. Bordwell and H. M. Andersen [*J. Amer. Chem. Soc.* **75**, 6019 (1953)] who applied the Hammett relationship to the thiophenol dissociation. The necessity of using a σ^- which is lower than the value usually reported in literature for the benzene series may be related to the consideration that the sulphonyl group generally operates more with an inductive than with a mesomeric effect and that the thiophene ring, in which the π electron sextet is more easily delocalized, is more strongly influenced by substituents with a mesomeric effect than by those with an inductive effect. The new ρ value, calculated using $\sigma^-_{p\text{-}SO_2CH_3} = 0{\cdot}840$ is practically equal to the one determined excluding this parameter.