Linear Free Energy Relationships in the Thiophen Series. Part 2.[1] The Kinetics of the Reactions of Some 2-Bromo-3-nitro-5-X-thiophens with Substituted Anilines in Methanol

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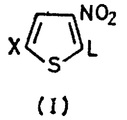
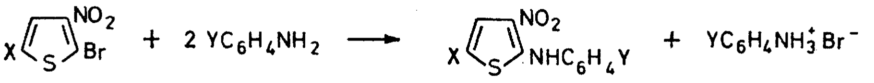
The rate constants for the reactions of 2-bromo-3-nitro-5-X-thiophens (X = H, Br, $CONH_2$, CO_2Me, Ac, SO_2Me, CN, or NO_2) with some substituted anilines $YC_6H_4NH_2$ (Y = *p*-OMe, *p*-Me, H, *m*-Cl, or *p*-CO_2Me) have been measured in methanol at various temperatures. The sensitivity parameters, ρ(Y) and β(X), obtained from Hammett and Brönsted correlations are practically independent of the reactivity of the starting system. The relevance of these results to the reactivity–selectivity principle is discussed.

FROM a study of the piperidino-substitution reactions of some 2-L-3-nitro-5-X-thiophens (I; L = Cl, Br, I, $OC_6H_4NO_2$-*p*, or SO_2Ph, X = H, Br, $CONH_2$, CO_2Me, Ac, SO_2Me, CN, or NO_2), in methanol, we obtained results[1] which were inconsistent with expectations based on the reactivity–selectivity principle.[2]



(I)

In order to extend the scope of linear free-energy relationships in S_NAr reactions of thiophen derivatives,[1] also in connection with recent discussions concerning the reactivity–selectivity relationship, we started a systematic investigation of substituent effects, both in the nucleophile and in the substrate. In this paper we report data for the reaction of some 2-bromo-3-nitro-5-X-thiophens (II; X = H, Br, $CONH_2$, CO_2Me, Ac, SO_2Me, CN, or NO_2) with various substituted anilines $YC_6H_4NH_2$ (Y = *p*-OMe, *p*-Me, H, *m*-Cl, or *p*-CO_2Me) in methanol at 0—40 °C.



(II) (III) (1)

RESULTS AND DISCUSSION

Reaction Products.—2-Bromo-3-nitro-5-X-thiophens (II) give the corresponding 2-anilino-3-nitro-5-X-thiophens (III) on treatment with anilines in methanol [equation (1)]. Except for (III; X = H, Y = *p*-CO_2Me), which was not isolated, the anilino-derivatives (III) were obtained in almost quantitative yield as shown by t.l.c. and u.v.–visible spectral analysis of the reaction mixtures. The relevant physical data are collected in Table 1.

Kinetic Data.—Rate constants and activation parameters for anilino-substitutions of 2-bromo-3-nitro-5-X-thiophens are in Table 2. All the reactions were first order in both substrate and nucleophile. An increase (decrease) of the rate of substitution, for a given substrate, was observed upon introduction of electron-repelling (-attracting) substituents into the nucleophile. On the other hand, for a given nucleophile, a large increase of reactivity was observed upon introduction of electron-withdrawing groups into the aromatic substrate. All the reactions studied were controlled by the enthalpy, and the nearly constant values of their activation entropy agree with the accepted addition–elimination mechanism[3] (bimolecular, with much solvent participation in the transition state).

Linear Free Energy Correlations.—The kinetic data for the reactions of compounds (II) with a given substituted aniline, have been correlated using a monolinear relationship of the Hammett type with σ_p^- constants[4] (Table 3, line 1). The ρ(Y) values at 20° are reported with other statistical data in Table 4 (columns 2—4). To improve the correlation and obtain a set of homogeneous constants for the heteroaromatic system considered, we have utilized the method of Brown[5] to calculate better σ_p^- values (Table 3, line 2). Using these new σ_p^- values we have recalculated ρ(Y) (Table 4, columns 5—7).

A significant test of the correlation can also be obtained by plotting log k_X/k_H for a given aniline against the same ratio for another aniline: thus the influence of the nucleophile in affecting the action of the substituent is more evident. The data obtained are collected in Table 5. In every case the values of *b* (the intercept of the straight line) is near zero (theoretically the straight line should pass through the origin). The values of *a* are practically coincident with the corresponding ratios between the ρ(Y) values (Table 5, column 5).

The Reactivity–Selectivity Principle.—In spite of variations of absolute reactivity with changing Y substituent in aniline and X substituent in the substrate,

TABLE 1

Physical data for Y-substituted *N*-(3-nitro-5-X-2-thienyl)anilines

Y	X	Colour	Crystallization solvent	M.p. (°C)	$\lambda_{max.}$/nm [a]	log ϵ [a]
p-OMe	H	Red	Ethanol	98—99	408	4.04
p-OMe	Br	Orange	Methanol–dioxan	128 (decomp.)	407	4.05
p-OMe	$CONH_2$	Yellow	Methanol–dioxan	214—215	396	3.96
p-OMe	CO_2Me	Orange	Ethanol–dioxan	151—152	388	4.01
p-OMe [b]	Ac [b]	Yellow	Ethanol–dioxan	163—164	340	4.17
p-OMe	SO_2Me	Yellow	Methanol–dioxan	173 (decomp.)	379	3.96
p-OMe	CN	Orange	Ethanol	125—127	384	3.98
p-OMe [c]	NO_2 [c]	Orange	Ethanol–dioxan	164	406	4.20
p-Me	H	Orange	Ethanol	101—102	410	4.06
p-Me	Br	Yellow	Methanol	154 (decomp.)	410	4.07
p-Me	$CONH_2$	Orange	Methanol–dioxan	236—237	397	4.02
p-Me	CO_2Me	Yellow	Ethanol–dioxan	182	390	4.01
p-Me	Ac	Orange	Ethanol–dioxan	167—168	340	4.22
p-Me	SO_2Me	Yellow	Methanol–dioxan	172—173	380	3.98
p-Me	CN	Orange	Ethanol-dioxan	152	384	4.01
p-Me [c]	NO_2 [c]	Orange	Ethanol	146—147	404	4.23
H	H	Orange	Ligroin	70—72	408	4.05
H	Br	Orange	Methanol	103—104	407	4.05
H	$CONH_2$	Yellow	Ethanol	198 (decomp.)	395	3.99
H [d]	CO_2Me [d]	Orange	Methanol–dioxan	160—161 [e]	390	4.00
H [b,f]	Ac [b,f]	Orange	Methanol–dioxan	142—143 [g]	340	4.22
H	SO_2Me	Yellow	Methanol–dioxan	198	380	4.00
H	CN	Yellow	Methanol–dioxan	169—170	384	4.00
H [c]	NO_2 [c]	Orange	Ethanol	162—163	402	4.24
m-Cl	H	Yellow	Ligroin	134	404	4.07
m-Cl	Br	Orange	Methanol–dioxan	154 (decomp.)	405	4.06
m-Cl	$CONH_2$	Yellow	Dioxan–methanol	250 (decomp.)	392	3.97
m-Cl	CO_2Me	Orange	Methanol–dioxan	154—155	385	4.01
m-Cl	Ac	Yellow	Methanol–dioxan	169—170	340	4.24
m-Cl	SO_2Me	Orange	Methanol–dioxan	189—190	376	4.01
m-Cl	CN	Yellow	Ethanol–dioxan	211—212	380	4.02
m-Cl [c]	NO_2 [c]	Yellow	Methanol–dioxan	193	395	4.25
p-CO_2Me [h]	H [h]				412	4.18
p-CO_2Me	Br	Orange	Methanol–dioxan	163 (decomp.)	412	4.18
p-CO_2Me	$CONH_2$	Yellow	Dioxan	266 (decomp.)	398	4.10
p-CO_2Me	CO_2Me	Yellow	Ethanol–dioxan	212—213	390	4.14
p-CO_2Me	Ac	Orange	Ethanol–dioxan	206—208	350	4.26
p-CO_2Me	SO_2Me	Orange	Methanol–dioxan	227—228	382	4.14
p-CO_2Me	CN	Orange	Methanol–dioxan	222 (decomp.)	386	4.13
p-CO_2Me [c]	NO_2 [c]	Yellow	Ethanol–dioxan	189—190	390	4.32

[a] In methanol. [b] V. A. Izmail'skii and P. F. Polevshchikov, *Zhur. Vses. Khim. Obshchetsva im. D. I. Mendeleeva*, 1964, **9**, 707 (*Chem. Abs.*, 1965, **62**, 9089d). [c] D. Spinelli, G. Consiglio, R. Noto, and V. Frenna, *J. Org. Chem.*, 1976, **41**, 968. [d] V. H. Beyer and S. Melde, *J. prakt. Chem.*, 1964, **24**, 100. [e] Lit. m.p. 157 °C. [f] C. D. Hurd and K. L Kreuz, *J. Amer. Chem. Soc.*, 1952, **74**, 2965 [g] See note *f*, m.p. 138.5—139.5 °C. [h] See Experimental section.

TABLE 2

Logarithmic kinetic constants and activation parameters [a] for the reactions of 2-bromo-3-nitro-5-X-thiophens (II) with substituted anilines ($YC_6H_4NH_2$) in methanol at 20 °C

Y	*p*-OMe	*p*-Me	H	*m*-Cl	*p*-CO_2Me
X/(pK_a)[b]	(5.36)	(5.08)	(4.60)	(3.52)	(2.38)
H	−5.348	−5.871	−6.415	−7.352	−8.293
	13.8, −36	14.5, −36	15.6, −35	15.5, −39	17.4, −37
Br	−3.840	−4.401	−4.909	−5.970	−6.924
	11.2, −38	12.9, −35	12.6, −38	13.9, −38	15.5, −37
$CONH_2$	−3.201	−3.813	−4.298	−5.309	−6.262
	10.5, −37	11.6, −36	11.8, −38	13.2, −38	15.0, −36
CO_2Me	−2.746	−3.271	−3.755	−4.800	−5.808
	10.5, −35	11.2, −35	11.3, −37	12.6, −38	13.6, −38
Ac	−2.098	−2.629	−3.135	−4.142	−5.229
	9.5, −36	10.7, −34	10.7, −36	12.2, −36	13.2, −37
SO_2Me	−1.839	−2.365	−2.940	−4.037	−5.085
	8.9, −36	10.0, −35	10.5, −36	11.7, −37	13.8, −35
CN	−1.818	−2.363	−2.901	−4.022	−4.989
	9.0, −36	9.5, −37	10.4, −36	11.6, −37	13.2, −36
NO_2[t]	−0.295	−0.846	−1.380	−2.489	−3.443
	7.6, −34	8.7, −33	9.2, −33	9.9, −36	11.6, −35

[a] For each couple X–Y the number on the first line represents log *k* calculated at 20 °C from activation parameters; the numbers on the second line are, respectively, $\Delta H^‡$/kcal mol^{-1} at 20 °C, and $\Delta S^‡$/cal mol^{-1} K^{-1} at 20 °C. The kinetic constants, *k*/l mol^{-1} s^{-1}, measured in the range 0—40 °C were reproducible to within ±3%; the maximum error of $\Delta H^‡$ is ±0.5 kcal mol^{-1}; the maximum error of $\Delta S^‡$ is ±2 cal mol^{-1} K^{-1}. [b] D. Spinelli, G. Consiglio, R. Noto, and V. Frenna, *J. Org. Chem.*, 1976, **41**, 968

we observe very close reactivity ratios and ρ(Y) values (see Tables 4 and 5). These results can be considered against the background of the Hammond postulate[6] which implies a decreasing selectivity as the energy content of the ground state approaches that of the transition state. This evident failure of the selectivity–reactivity principle is by no means unprecedented. Pross has recently surveyed[7] the literature and reported examples both for and against the applicability of the principle. We agree that, in general, the reactivity–selectivity principle should hold.[7]

TABLE 3

Substituent constants[a]

X	H	Br	CONH$_2$	CO$_2$Me	Ac	SO$_2$Me	CN	NO$_2$
σ_p^-	0.00	0.30	0.62	0.74	0.82	1.05	0.99	1.23
σ_p^-	0.00	0.40	0.58	0.72	0.89	0.95	0.96	1.38

[a] Line 1, σ values from ref. 4; line 2, σ values recalculated by the method of ref. 5.

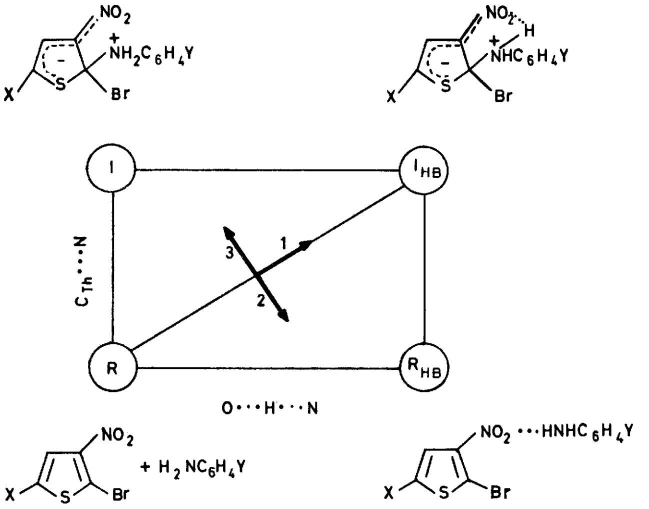
Aromatic nucleophilic substitutions such as those reported here are relatively simple processes in which only a single bond is formed and only a single bond is broken in the transition state; therefore the principle should work. The failure of the principle should imply a more complicated pattern of bond-making and bond-breaking processes. A factor which could play an important role in determining the energy of the first transition state of an addition–elimination mechanism (in the present case the rate-determining transition state) is the hydrogen-bonding interaction between the incipient 'ammonium' hydrogen and oxygen atoms of the 3-nitro-group.

TABLE 4

Reaction constants and other statistical data[a] for the reactions of 2-bromo-3-nitro-5-X-thiophens with Y-substituted anilines in methanol at 20 °C

Y	ρ(Y) ± *s*ρ	*r*	*i*	ρ(Y) ± *s*ρ	*r*	*i*
p-OMe	3.67 ± 0.30	0.9800	0.06	3.66 ± 0.02	0.9999	0.01
p-Me	3.67 ± 0.30	0.9802	0.04	3.66 ± 0.03	0.9998	−0.01
H	3.65 ± 0.31	0.9792	0.07	3.64 ± 0.02	0.9999	0.02
m-Cl	3.53 ± 0.31	0.9779	0.05	3.53 ± 0.04	0.9997	0.00
p-CO$_2$Me	3.48 ± 0.32	0.9757	0.04	3.48 ± 0.04	0.9996	−0.02

[a] ρ(Y) (see text), reaction constants; *s*ρ, standard deviation of ρ; *r*, correlation coefficient; *i*, intercept of the regression line with the ordinate (σ = 0). The number of points is 8 throughout.



More O'Ferrall–Jencks structure–reactivity diagram (see text)

Even if this interaction is less important in protic–polar compared to aprotic–apolar solvents, built-in solvation is a well established phenomenon.[8] A convenient way to visualize structure–reactivity relationships is to consider the transition state to be situated on a More O'Ferrall–Jencks diagram[9] (Figure). The two axes represent the forming of the C_{Th}–N and O · · · H bonds. A decrease in the basicity of aniline (*e.g.* from Y = H to Y = *m*-Cl) will stabilize the R and R_{HB} corners where there is no C_{Th}–N bond-forming. Stabilization of the reactants makes the transition state occur later along the reaction co-ordinate and therefore resemble intermediate (I_{HB}) more closely in accord with the Hammond postulate (Figure, arrow 1). However, stabilizing R_{HB} as well, which represents a perturbation perpendicular to the reaction profile causes the transition state to be displaced perpendicular to the reaction profile and towards the bottom right-hand corner, in an 'anti-Hammond' effect (Figure, arrow 2). These two effects, parallel and perpendicular to the reaction co-ordinate, operate in concert with respect to the oxygen–hydrogen bond distance but oppose each other with respect to the degree of C_{Th}–N bond formation. This implies that while decreasing the basicity of aniline does advance the transition state with respect to hydrogen bonding, the degree of carbon–nitrogen bond formation is expected to show only a slight change. This agrees with the invariance of the ρ(Y) value with changing Y.

*Brönsted-type Correlations.**—The log *k* values relative to the reactions of a given 2-bromo-3-nitro-5-X-thiophen with substituted anilines give a good correlation with the pK_a values of $ArNH_3^+$ in water (Table 6). Even if the comparison is not completely valid because of the difference in the solvent, β values near to unity indicate[11]

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* Concerning the usage of this term, see, for example, S. A. Khan and A. J. Kirby, *J. Chem. Soc. (B)*, 1970, 1172; M. R. Crampton and M. J. Willison, *J.C.S. Perkin II*, 1974, 238.

that the substituents present in aniline cause a similar variation of the position of the rate-determining transition state in the reaction co-ordinates, with respect to Y = H, for these two reactions, whatever the aromatic substrate. The correlations are significantly improved by plotting log k_Y for a given thiophen derivative against the corresponding value for another compound. The data obtained are shown in Table 7.*

TABLE 5

Correlations [a] by the equation $\log(k_X/k_H)_Y = a \log(k_X/k_H)_{Y=H} + b$

Y	$a \pm s_a$ [b]	b	r [c,d]	$\rho_Y/\rho_{Y=H}$
p-OMe	1.00 ± 0.01	−0.01	0.9998	1.01
p-Me	1.00 ± 0.01	−0.03	0.9998	1.01
H	1.00	0.00	1.0000	1.00
m-Cl	0.97 ± 0.01	−0.02	0.9997	0.97
p-CO_2Me	0.96 ± 0.01	−0.04	0.9994	0.96

[a] See text. [b] Standard deviation of *a*. [c] Correlation coefficient. [d] The number of points is 8.

These results allow us to look at the apparent failure of the reactivity–selectivity principle from another viewpoint. Referring again to the Figure, we notice that going from X = H to X = NO_2, *i.e.* decreasing the basicity of the 3-nitro-group, will stabilize the R and I corners where there is no hydrogen bonding. The stabilization of the reactants produces the same Hammond behaviour as before (arrow 1). On the other hand, the stabilization of species I causes the transition state to be shifted, in an anti-Hammond way, towards the top left-hand corner (arrow 3). These two effects add to each other with respect to the carbon–nitrogen bond distance but oppose each other with respect to the degree of O···H bond formation. This involves a later transition state with respect to the C_{Th}–N bond formation but only a slight change in the formation of hydrogen bonding: the insensitivity of the β(X) value to a change in X is accordingly accounted for.

TABLE 6

Brönsted coefficients and other statistical data [a] for the reactions of 2-bromo-3-nitro-5-X-thiophens with Y-substituted anilines in methanol at 20 °C

X	$\beta \pm s_\beta$	r	i
H	0.95 ± 0.06	0.993	−10.6
Br	1.00 ± 0.07	0.994	−9.40
$CONH_2$	0.98 ± 0.07	0.992	−8.69
CO_2Me	1.00 ± 0.05	0.996	−8.24
Ac	1.01 ± 0.06	0.996	−7.68
SO_2Me	1.06 ± 0.05	0.996	−7.69
CN	1.04 ± 0.04	0.994	−7.56
NO_2	1.03 ± 0.05	0.994	−5.99

[a] β, Brönsted coefficient; s_β. standard deviation of β; *r*, correlation coefficient; *i*, intercept of the regression line with the ordinate (log *k* = 0). The number of points is 5 throughout.

Conclusions.—The position of the rate-determining transition state for the reactions of 2-bromo-3-nitro-5-X-thiophens with substituted anilines along the reaction co-ordinate depends on the degree of formation of both C_{Th}–N and O···H bonds. For a given X, a change from Y = H to Y = *m*-Cl implies a later transition state (C_{Th}–N bond) because of the lower nucleophilicity of the aniline: on the other hand, this factor favours hydrogen bonding, *i.e.*, causes the transition state to occur earlier with respect to the O···H bond distance. If the two effects cancel each other exactly, β(X) would appear constant whatever Y.

For a given Y, a change from X = H to X = NO_2 means an earlier transition state (C_{Th}–N bond) because nucleophilic attack on C_{Th} is favoured, but a later transition state with respect to hydrogen bonding due to the lower charge density on the oxygen atoms of the 3-nitro-group. When the two effects balance each other exactly, ρ(Y) appears constant whatever X.

TABLE 7

Correlations [a] by the equation

$\log(k_X)_Y = a\log (k_H)_Y + b$

X	$a \pm s_a$ [b]	b	r [c,d]	β_X/β_H
H	1.00	0.00		1.00
Br	1.05 ± 0.02	1.79	0.9997	1.05
$CONH_2$	1.03 ± 0.00	2.30	0.9997	1.03
CO_2Me	1.04 ± 0.03	2.87	0.9994	1.05
Ac	1.06 ± 0.03	3.61	0.9993	1.06
SO_2Me	1.11 ± 0.02	4.14	0.9997	1.12
CN	1.09 ± 0.02	4.02	0.9996	1.09
NO_2	1.08 ± 0.02	5.49	0.9996	1.08

[a] See text. [b] Standard deviation of *a*. [c] Correlation coefficient. [d] The number of points is 5.

The ρ(Y) values and, consequently, the β(X) values are nearly independent of the substituents either in the aromatic substrate or in the aniline, such variations as there are being in the direction of anti-Hammond behaviour. However, the considerations expressed above maintain the validity of the reactivity–selectivity principle.

EXPERIMENTAL

Synthesis and Purification of Compounds.—Methanol,[10] anilines,[11] and thiophen derivatives (II),[12] were prepared and/or purified as previously reported. The anilino-derivatives (III) were prepared according to the general method reported in ref. 13 and gave correct analyses.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[3b] The concentrations used were 10^{-4}—10^{-2}M for (II) and 6 × 10^{-4}—1M for the anilines as a function of the couple X—Y. The wavelength and log ε values for u.v. spectral measurements are reported in Table 1. The values for (III; X = H, Y = *p*-CO_2Me) were assumed on the basis of a close re-

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* The good quality as well as the slopes near to unity of these ' horizontal ' correlations are a trivial consequence of the ' vertical ' correlations shown in Tables 4 and 5.

semblance (whatever Y) between spectroscopic data for X = H and X = Br (see Table 1).

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