

KINETIC STUDY OF THE REACTIONS OF SOME 5-NITRO-2-(4-NITROPHENOXY)-3-X-THIOPHENES WITH ANILINE AND 4-METHOXYANILINE IN METHANOL

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Dedicated to Professor Otto Exner on the occasion of his 75th birthday in recognition of his outstanding contributions to physical organic chemistry and chemometrics.

The rate constants of the title reactions have been measured at various amine concentrations. The second-order kinetic constant for the amino substitution increases in a hyperbolic way as a function of the nucleophile concentration. The k_3^{Am}/k_{-1} ratio for each catalysed system is not a monotonic function of the X substituent. This result has been rationalized in the framework of the SB-GA (Specific Base-General Acid) mechanism of base catalysis.

Key words: Aromatic nucleophilic substitutions; Thiophenes; Base catalysis; SB-GA mechanism; Reaction kinetics.

In recent years we have thoroughly investigated the mechanism of base catalysis in aromatic nucleophilic substitutions of nitro-activated thiophene derivatives with primary and secondary amines as nucleophiles, both in methanol and in benzene¹.

We now report on a kinetic study of the reactions of some 5-nitro-2-(4-nitrophenoxy)-3-X-thiophenes with aniline and 4-methoxyaniline in methanol, at 20 °C. The substrates used here as "chemical observers" have an activating nitro group fixed at C-5 and a variable substituent at C-3, which represents an *ortho*-like position with respect to the reaction centre located at C-2.

The 3-X substituents chosen, apart from X = H, are (i) the sp² groups CONH₂, CO₂Me and COMe with the same geometry around the carbonyl carbon atom but with different "internal" and "external" conjugative inter-

actions and different steric hindrance; (ii) the methylsulfonyl group (SO₂Me), a group with electronic effects comparable with those of the COMe group but with a tetrahedral geometry much more compressive with respect to the adjacent reaction centre; (iii) the cyano group (CN), a strong electron-withdrawing substituent with a linear geometry; and (iv) the 3-nitro group which has a planar geometry but whose coplanarity with the aromatic ring could be more or less prevented by the steric compressions occurring in the reaction area.

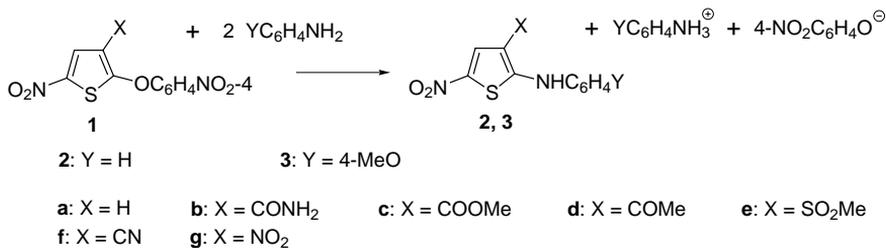
The presence of an *ortho*-like substituent near the reaction centre can determine a different reaction pathway in dependence on three main factors: (a) the activation degree of substrate; (b) the primary and/or secondary kinetic steric effects, as also related to the structures of nucleophile and nucleofugal group; and (c) the possible anchimeric assistance in decomposition of the reaction intermediate.

RESULTS AND DISCUSSION

Reaction Products

5-Nitro-2-(4-nitrophenoxy)-3-X-thiophenes **1**, on treatment with anilines in methanol, gave the corresponding anilino derivatives **2** and **3** in high yields.

The relevant physical data are shown in Tables I-III.



Kinetic Data

The apparent second-order kinetic constants, k_A , for the amine substitution reactions of **1** in methanol at 20 °C, at various amine concentrations, in the presence of amine hydrochloride and at constant ionic strength (0.05 mol dm⁻³) are given in Tables IV and V.

Inspection of the data shows that for both anilines, with the exception of the reactions involving the substrates with X = COMe and X = NO₂, k_A in-

TABLE I
Characterisation data for 5-nitro-2-(4-nitrophenoxy)-3-X-thiophenes **1**

X	Crystallization/ Solvent	M.p., °C	δ (DMSO- d_6 , 200 MHz)	HMRS		
				Calculated/Found	Calculated/Found	
				% C	% H	% N
H ^a	Ligroine/PhH	103				
CONH ₂ ^b	MeOH/DIOX	210				
CO ₂ Me ^b	MeOH/DIOX	167				
COMe	Ligroine/PhH	99	8.37 (H-4); 8.33 (ArH) ^d ; 7.63 (ArH) ^e ; 2.49 (CH ₃)	308.01031	46.75	2.62
				308.01029	46.90	2.60
SO ₂ Me	MeOH/DIOX	197	8.41 (ArH) ^d ; 8.26 (H-4); 7.72 (ArH) ^e ; 3.42 (CH ₃)	343.97729	38.37	2.34
				343.97704	38.50	2.30
CN	MeOH/DIOX	137	8.68 (H-4); 8.43 (ArH) ^d ; 7.79 (ArH) ^e	290.99499	45.36	1.73
				290.99439	45.50	1.80
NO ₂ ^c	Ligroine/PhH	160				

^a Ref.¹²; ^b ref.¹³; ^c ref.¹⁴; ^d AA' part of AA'XX'; ^e XX' part of AA'XX'.

TABLE II
Characterisation data for N-(5-nitro-3-X-2-thienyl)anilines **2**

X	Crystallization/ Solvent	M.p. λ_{max} , nm ^a (log ϵ)	δ (DMSO-d ₆ , 200 MHz)	HMRS		Calculated/Found						
				Calculated/Found	Calculated/Found	% C	% H	% N				
H ^b	MeOH	180 (4.42)	448 (4.42)									
CONH ₂	EtOH	145	432 (4.24)	12.2 (NH) ^c ; 11.89 (NH) ^c ; 8.66 (H-4); 7.45 (ArH) ^d	263.03646 263.03609	50.18 50.30	3.45 3.60	15.96 16.10				
CO ₂ Me	MeOH DIOX	139	416 (4.31)	10.39 (NH) ^c ; 8.08 (H-4); 7.51 (Ar-H) ^d ; 3.85 (CH ₃)	278.03613 278.03599	51.79 51.90	3.62 3.60	10.07 10.20				
COMe	EtOH DIOX	177	418 (4.30)	11.47 (NH) ^c ; 8.53 (H-4); 7.50 (Ar-H) ^d ; 2.49 (CH ₃)	262.04121 262.04102	54.95 55.10	3.84 3.90	10.68 10.80				
SO ₂ Me	MeOH DIOX	160	414 (4.36)	9.97 (NH) ^c ; 8.11 (H-4); 7.51 (Ar-H) ^d ; 3.41 (CH ₃)	298.00820 298.00847	44.29 44.40	3.38 3.30	9.39 9.50				
CN	MeOH DIOX	203	418 (4.23)	11.18 (NH) ^c ; 8.41 (H-4); 7.48 (Ar-H) ^d	245.02590 245.02527	53.87 54.00	2.88 2.90	17.13 17.20				
NO ₂ ^c	EtOH	163	402 (4.34)									

^a In methanol; ^b ref.¹⁵; ^c broad signal (exchangeable protons); ^d multiplet; ^e see ref.¹⁰

TABLE III
Characterisation data for 4-Methoxy-N-(5-nitro-3-X-2-thienyl)anilines 3

X	Crystallization/ Solvent	M.p. λ_{\max} , nm ^a (log ϵ)	δ (DMSO-d ₆ , 200 MHz)	HMRS			
				Calculated/Found	Calculated/Found		
				% C	% H	% N	
H	MeOH	108 455 (4.03)	10.6 (NH) ^c ; 7.88 (H-4); 7.25 (Ar-H) ^d ; 6.99 (Ar-H) ^e ; 6.33 (H-3); 3.74 (CH ₃)	250.04121 250.04087	52.79 52.90	4.03 4.00	11.19 11.40
CONH ₂	MeOH DIOX	187 434 (4.28)	11.6 (NH ₂) ^c ; 11.48 (NH) ^c ; 8.61 (H-4); 7.39 (Ar-H) ^d ; 6.99 (Ar-H) ^e ; 3.79 (CH ₃)	293.04703 293.04689	49.14 49.30	3.78 3.90	14.33 14.40
CO ₂ Me	MeOH DIOX	165 420 (4.28)	10.24 (NH) ^c ; 8.05 (H-4) ^c ; 7.42 (Ar-H) ^d ; 7.07 (Ar-H) ^e ; 3.85 (OCH ₃); 3.80 (CO ₂ CH ₃)	308.04669 308.04616	50.64 50.80	3.92 3.90	9.09 9.20
COMe	EtOH DIOX	192 424 (4.27)	11.40 (NH) ^c ; 8.29 (H-4); 7.33 (Ar-H) ^d ; 6.99 (Ar-H) ^e ; 3.76 (OCH ₃); 2.55 (CH ₃)	292.05177 292.05135	53.42 53.50	4.14 4.10	9.58 9.70
SO ₂ Me	MeOH	118 409 (4.16)	9.88 (NH) ^c ; 8.06 (H-4); 7.43 (Ar-H) ^c ; 7.07 (Ar-H) ^d ; 3.80 (OCH ₃); 3.38 (SO ₂ CH ₃)	328.01876 328.01834	43.89 43.90	3.68 3.70	8.53 8.60
CN	MeOH DIOX	212 422 (4.16)	11.07 (NH) ^c ; 8.38 (H-4); 7.40 (Ar-H) ^c ; 7.05 (Ar-H) ^d ; 3.79 (CH ₃)	275.03646 275.03612	52.36 52.50	3.30 3.40	15.26 15.40
NO ₂ ^b	EtOH DIOX	164 406 (4.20)					

^a In methanol; ^b ref.⁸; ^c broad signal (exchangeable protons). ^d AA' part of AA'XX'. ^e XX' part of AA'XX'.

TABLE IV
Apparent kinetic constants for the reactions of 5-nitro-2-(4-nitrophenoxy)-3-X-thiophenes with aniline^a in methanol at 20 °C

	X = H					
[Aniline], mol dm ⁻³	0.00505	0.0101	0.0253	0.0505	0.0758	0.101
k _A , 10 ⁻⁶ dm ³ mol ⁻¹ s ⁻¹	0.232	0.318	0.409	0.687	0.891	1.05
[Aniline], mol dm ⁻³	0.202	0.404	0.606	0.808	1.01	
k _A , 10 ⁻⁶ dm ³ mol ⁻¹ s ⁻¹	1.30	1.53	1.64	1.71	1.73	
	X = CONH ₂					
[Aniline], mol dm ⁻³	0.000606	0.00101	0.00152	0.00202	0.00306	0.00612
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	1.60	1.65	1.70	1.76	1.84	1.91
[Aniline], mol dm ⁻³	0.00756	0.00918	0.0122	0.0163	0.0204	0.0306
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	2.00	2.07	2.15	2.19	2.25	2.32
[Aniline], mol dm ⁻³	0.0510	0.102	0.204	0.306	0.408	0.510
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	2.38	2.44	2.47	2.48	2.49	2.49
	X = CO ₂ Me					
[Aniline], mol dm ⁻³	0.000606	0.00101	0.00152	0.00202	0.00303	
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	5.61	5.83	5.96	6.09	6.37	
[Aniline], mol dm ⁻³	0.00606	0.00909	0.0121	0.0162	0.0202	
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	6.70	7.02	7.36	7.78	8.22	
[Aniline], mol dm ⁻³	0.0303	0.0505	0.101	0.202	0.303	
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	8.71	9.27	10.00	10.5	10.7	
[Aniline], mol dm ⁻³	0.404	0.505				
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	10.8	10.8				
	X = CN					
[Aniline], mol dm ⁻³	0.000606	0.00101	0.00152	0.00198	0.00297	
k _A , 10 ⁻³ dm ³ mol ⁻¹ s ⁻¹	1.48	1.52	1.55	1.61	1.66	
[Aniline], mol dm ⁻³	0.00446	0.00594	0.00743	0.00891	0.0119	
k _A , 10 ⁻³ dm ³ mol ⁻¹ s ⁻¹	1.72	1.78	1.84	1.91	1.94	
[Aniline], mol dm ⁻³	0.0158	0.0198	0.0297	0.0495	0.0990	
k _A , 10 ⁻³ dm ³ mol ⁻¹ s ⁻¹	1.97	2.00	2.04	2.06	2.09	
[Aniline], mol dm ⁻³	0.198	0.297	0.396			
k _A , 10 ⁻³ dm ³ mol ⁻¹ s ⁻¹	2.11	2.11	2.11			
	X = SO ₂ Me					
[Aniline], mol dm ⁻³	0.00122	0.00204	0.00300	0.00459	0.00600	
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	0.636	0.961	1.35	1.64	1.82	
[Aniline], mol dm ⁻³	0.00765	0.00900	0.0107	0.0120	0.0160	
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	2.17	2.34	2.52	2.70	2.95	
[Aniline], mol dm ⁻³	0.0200	0.0300	0.0500	0.100	0.200	
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	3.13	3.37	3.66	3.90	4.04	
[Aniline], mol dm ⁻³	0.300	0.400	0.500			
k _A , 10 ⁻⁴ dm ³ mol ⁻¹ s ⁻¹	4.10	4.10	4.12			

TABLE IV
(Continued)

X = COMe					
[Aniline], mol dm ⁻³	0.00202	0.00303	0.00404	0.00606	0.00808
k_A , 10 ⁻³ dm ³ mol ⁻¹ s ⁻¹	2.28	2.25	2.30	2.26	2.28
[Aniline], mol dm ⁻³	0.0101	0.0152	0.0202	0.0303	0.0505
k_A , 10 ⁻³ dm ³ mol ⁻¹ s ⁻¹	2.28	2.26	2.31	2.25	2.28
[Aniline], mol dm ⁻³	0.101	0.202			
k_A , 10 ⁻³ dm ³ mol ⁻¹ s ⁻¹	2.29	2.31			
X = NO ₂					
[Aniline], mol dm ⁻³	0.000408	0.000612	0.000816	0.00102	0.00153
k_A , dm ³ mol ⁻¹ s ⁻¹	0.475	0.480	0.480	0.478	0.482
[Aniline], mol dm ⁻³	0.00204				
k_A , dm ³ mol ⁻¹ s ⁻¹	0.480				

^a [Aniline·HCl] + [NaCl] = 0.05 mol dm⁻³.

creases in a curvilinear (hyperbolic) way as a function of the nucleophile concentration, at a constant buffer ratio, according to Eq. (1).

$$k_A = (k_1 k_2 + k_1 k_{Am} [Am]) / (k_{-1} + k_2 + k_{Am} [Am]) \quad (1)$$

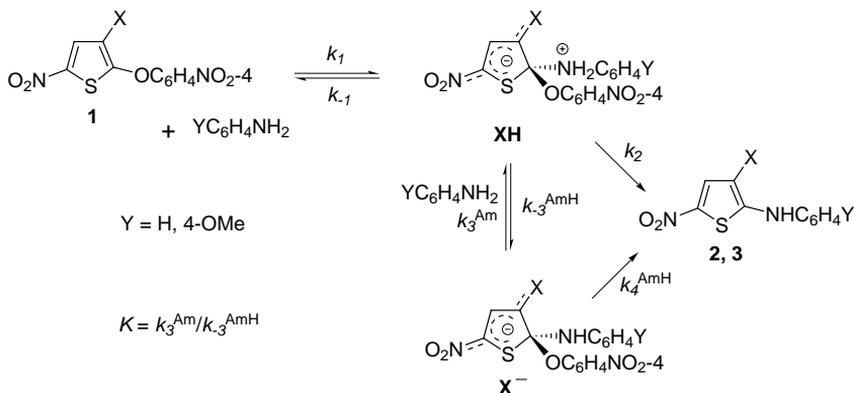
Depending on the catalysis mechanism followed, k_{Am} is equal to k_3^{Am} / k_{-1} or to $k_3^{Am} k_4^{AmH} / k_{-3}^{Am} k_{-1}$ (Scheme 1).

We will show later on that the reactions here investigated are general base-catalysed. Indeed, due to the ionization equilibrium of the amines in methanol (Eq. (2)), two general bases are in solution and also catalysis with the methoxide ion should indeed be observed.



As a matter of fact, since the ionization constants of aniline and 4-methoxyaniline in methanol are very low, the methoxide ion concentration, under the experimental conditions used, is too low to yield any appreciable contribution to catalysis. The kinetic measurements carried out at a constant aniline concentration and a variable buffer ratio (Table VI) support this conclusion.

Equation (1) describes a dependence of k_A on $[Am]$ which is linear at low concentrations $\{(k_{-1} + k_2) \gg k_{Am}[Am]; k_A = k_1k_2/(k_{-1} + k_2) + k_1k_{Am}[Am]/(k_{-1} + k_2)\}$; then curvilinear (hyperbolic) and finally shows a plateau corresponding to the asymptote of the hyperbola, *i.e.*, $k_A = k_1$, due to the condition $k_{Am}[Am] \gg (k_{-1} + k_2)$.



SCHEME 1

A non-linear regression treatment of kinetic data by the least-squares method, according to Eq. (1) has allowed to calculate the values of k_1 , k_2 and of k_3^{Am}/k_{-1} ratio for each catalysed system; the values are reported in Table VII.

A plot of the logarithmic relative kinetic constants, $\log(k_{1,X}/k_{1,H})$ for the reactions of compounds **1** with a given amine *versus* σ^- constants of X substituents (Table VIII)² shows an excellent linear free energy correlation (Table IX). The greater ρ value calculated for the aniline as compared with the 4-methoxyaniline reactions apparently agrees with the reactivity-selectivity principle³ but the difference between the ρ values is not statistically significant.

The greater reactivity of 4-methoxyaniline with respect to aniline reflects, although only qualitatively, the greater basicity of the former. In the reaction of decomposition of the zwitterionic intermediate giving the products, the k_{-1} reactivity order will be, of course, inverted, *i.e.*, 4-methoxyaniline < aniline. In other words, according to the Hammond postulate, for a given substrate, the transition state will be "early" for the more reactive amine.

Let us consider the structure of the reaction intermediate. On account of the different geometry of the groups bonded to tetrahedral carbon 2-atom, the interaction by hydrogen bonding between the ammonium nitrogen

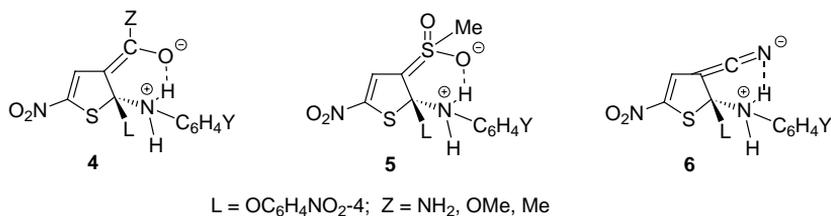
TABLE V

Apparent kinetic constants for the reactions of 5-nitro-2-(4-nitrophenoxy)-3-X-thiophenes with 4-methoxyaniline^a (concentration in mol dm⁻³) in methanol at 20 °C

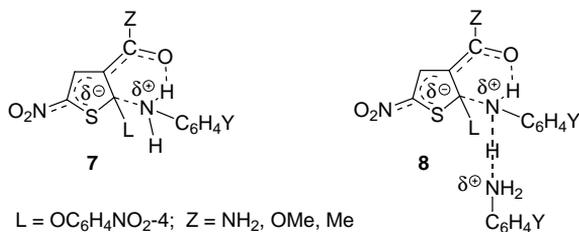
X = H						
[4-Methoxyaniline]	0.00495	0.00990	0.0248	0.0495	0.0743	0.0990
$k_x, 10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	0.651	0.730	0.899	1.25	1.52	1.87
[4-Methoxyaniline]	0.149	0.198	0.297	0.396	0.495	0.594
$k_x, 10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	2.09	2.33	2.60	2.80	2.91	3.00
[4-Methoxyaniline]	0.792	0.990				
$k_x, 10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	3.11	3.18				
X = CONH ₂						
[4-Methoxyaniline]	0.00312	0.00520	0.00832	0.0125	0.0208	0.0312
$k_x, 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	1.68	1.73	1.80	1.86	1.92	1.97
[4-Methoxyaniline]	0.0416	0.0541	0.0666	0.0790	0.0915	0.104
$k_x, 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	2.00	2.02	2.04	2.05	2.05	2.06
X = CO ₂ Me						
[4-Methoxyaniline]	0.00510	0.0102	0.0163	0.0265	0.0326	0.0418
$k_x, 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	5.61	6.09	6.56	7.09	7.30	7.54
[4-Methoxyaniline]	0.0510	0.0673	0.0816	0.102		
$k_x, 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	7.75	7.98	8.11	8.25		
X = CN						
[4-Methoxyaniline]	0.00125	0.00312	0.00520	0.00832	0.0125	0.0208
$k_x, \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	0.0173	0.0174	0.0175	0.0176	0.0178	0.0182
[4-Methoxyaniline]	0.0312	0.0416	0.0541	0.0666	0.0790	0.120
$k_x, \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	0.0186	0.0190	0.0196	0.0201	0.0206	0.0208
[4-Methoxyaniline]	0.160	0.200	0.240	0.300		
$k_x, \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	0.0207	0.0209	0.0209	0.0210		
X = SO ₂ Me						
[4-Methoxyaniline]	0.00312	0.00520	0.00832	0.0125	0.0208	0.0312
$k_x, 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	1.82	1.87	1.94	2.00	2.14	2.29
[4-Methoxyaniline]	0.0416	0.0541	0.0666	0.0790	0.0915	0.104
$k_x, 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	2.42	2.55	2.66	2.75	2.83	2.90
X = COMe						
[4-Methoxyaniline]	0.00204	0.00306	0.00510	0.00734	0.0102	0.0143
$k_x, 10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	1.84	1.80	1.79	1.80	1.84	1.87
[4-Methoxyaniline]	0.0204	0.0306				
$k_x, 10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	1.87	1.87				
X = NO ₂						
[4-Methoxyaniline]	0.000400	0.000500	0.000600	0.000700	0.000800	
$k_x, \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	3.16	3.18	3.15	3.14	3.17	

^a [4-Methoxyaniline-HCl] + [NaCl] = 0.05 mol dm⁻³.

and the 3-X substituent, the so-called “built-in solvation” (ref.⁴) presents three typologies (4–6).



In the decomposition of the reaction intermediate into the reactants, both the intramolecular hydrogen bonding between the ammonium proton and 3-X group and the bond between the nucleophile nitrogen atom and the aromatic carbon atom are broken, as shown, for example, in 7. The more nucleophilic the amine is, the stronger the nitrogen carbon bond, the less acidic the ammonium hydrogen and thus the weaker the hydrogen bonding. As far as this latter bond is concerned, the transition state would be “later” with the more basic aniline. It appears that the effect depending on the nitrogen nucleophilicity, which, according to Hammond’s postulate, would cause a given sequence of the positions of transition state along the reaction co-ordinate, is counterbalanced by the hydrogen bonding effect. If it were the only effect operating, it would give rise to the exactly opposite sequence. Thus, for each substrate, the nucleophile variation does not involve a significant variation of the position of the transition state. In other words, the range of transition states corresponding to various substituted thiophene compounds does not change position on the reaction co-ordinate with the changing nucleophile. This implies that the selectivity, as measured by ρ , is virtually constant whatever the used amine is.



We have seen above that, at variance with the situation where X = H, CONH₂, CO₂Me, CN and SO₂Me, the reactions of compounds with X = COMe and NO₂ are not catalysed. Since on going from X = CO₂Me to X =

CN, both k_2/k_{-1} and k_{Am}/k_{-1} ratios increase in parallel with k_1 values (Table VII), it is possible to estimate these ratios for the two substituents COCH_3 and NO_2 . Such estimates show that the condition $k_{Am}[\text{Am}] \gg (k_{-1} + k_2)$ is fulfilled even for the lowest nucleophile concentration used and thus the relevant k_A measured represent plateau values.

TABLE VI

Apparent second-order kinetic constants, k_A , for the reactions of methyl 5-nitro-2-(4-nitro-phenoxy)thiophene-3-carboxylate with aniline in methanol at 20 °C, as a function of aniline hydrochloride concentration^a

[Aniline·HCl]	0.00100	0.00250	0.00500	0.0100	0.0200
$k_A, 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	7.14	7.15	7.13	7.16	7.15

^a [Aniline·HCl] + [NaCl] = 0.05 dm³ mol⁻¹.

TABLE VII

Linear regression analysis of apparent second-order kinetic constants, k_A , for the reactions of 5-nitro-2-(4-nitrophenoxy)-3-X-thiophenes with aniline and 4-methoxyaniline in methanol at 20 °C, according to Eq. (1)

X	Amine	$k_1, \text{ dm}^3 \text{ mol}^{-2} \text{ s}^{-1}$	k_2/k_1	$k_3^{\text{Am}} k_{-1}, \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$	n^a
H	aniline	$1.90 \cdot 10^{-6}$	0.0868	10.5	11
CONH ₂	aniline	$2.51 \cdot 10^{-4}$	1.60	330	18
SO ₂ Me	aniline	$4.18 \cdot 10^{-4}$	0	144	18
CO ₂ Me	aniline	$1.11 \cdot 10^{-3}$	1.03	84.3	17
CN	aniline	$2.13 \cdot 10^{-3}$	1.83	620	18
COMe	aniline	$2.28 \cdot 10^{-3}$	>>1	>>>1	12
NO ₂	aniline	$4.79 \cdot 10^{-1}$	>>1	>>>1	6
H	4-methoxyaniline	$3.59 \cdot 10^{-5}$	0.162	8.32	14
CONH ₂	4-methoxyaniline	$2.11 \cdot 10^{-3}$	2.74	359	12
SO ₂ Me	4-methoxyaniline	$3.99 \cdot 10^{-3}$	0.786	18.1	12
CO ₂ Me	4-methoxyaniline	$9.05 \cdot 10^{-3}$	1.14	92.4	10
CN	4-methoxyaniline	$2.19 \cdot 10^{-2}$	3.40	97.3	16
COMe	4-methoxyaniline	$1.84 \cdot 10^{-2}$	>>1	>>>1	8
NO ₂	4-methoxyaniline	3.16	>>1	>>>1	5

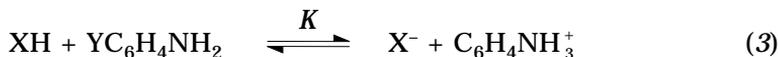
^a Number of data points.

In order to get some insight into the catalysis mechanism, let us consider the various kinetic coefficients involved, *i.e.*, k_{-1} and k_{Am} coefficients, as determined by the various 3-X substituents. As the electron-withdrawing power of the 3-X substituent increases, on one hand the strength of intramolecular hydrogen bonding also increases on account of the higher density of negative charge on the atom which is the acceptor of such a hydrogen bonding; on the other hand, the bond between the nucleophilic nitrogen atom and the aromatic carbon atom becomes more difficult to be broken. Both effects tend to reduce the k_{-1} value; thus ρ_{-1} should be negative.

As far as the k_{Am} step is concerned, it is convenient to take into consideration the two catalysis mechanisms commonly accepted⁵.

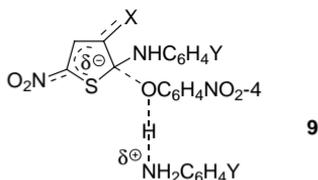
In the first mechanism⁵, the slow step involves the formation of the transition state **8**. With increasing electron-withdrawing power of the X substituent, both the basicity of the oxygen atom(s) of the 3-X group and the acidity of the hydrogen atom involved in the built-in solvation increase. Therefore, the two effects brought about by the X substituent variation increase the strength of the intramolecular hydrogen bond. In the base-catalysed step it is not necessary to break this bond since the primary amine has a second hydrogen atom which can be used to bond the base catalyst. The intervention of a second molecule of amine determines the slow elimination of the non-hydrogen bonded proton. Since an electron-withdrawing X substituent increases the acidity of this proton, as a whole, in this catalysis mechanism, $\rho_3^{Am} > 0$ should be observed. Moreover, since the effect of the X substituent on the rate of proton elimination (k_3^{Am}) is presumably lower than that on the C-N bond breaking (k_{-1}), one should observe $|\rho_3^{Am}| < |\rho_{-1}|$. As a matter of fact, it should be $(\rho_3^{Am} - \rho_{-1}) > 0$ with the implication that k_3^{Am}/k_{-1} should increase with increasing electron-withdrawing power of the X substituent.

In the SB-GA mechanism⁵ (Scheme 1), there is a fast pre-equilibrium with a transition state similar to **8** where a proton transfer from XH, to the amine occurs (Eq. (3)).



For this first reaction of the SB-GA catalysis mechanism, one should observe $\rho_K > 0$. The subsequent step, which involves the general acid-catalysed detachment of the leaving group by the conjugated acid of the

amine (transition state **9**), is disfavoured by electron-withdrawing X substituents and should give $\rho_4 < 0$. An examination of data in Table VII shows that k_{Am}/k_{-1} values are not a monotonic function of the X substituent; they decrease on going from X = CONH₂ to X = CO₂Me and increase on going from X = CO₂Me to X = NO₂. This observation is in contrast with that base catalysis mechanism which involves proton transfer to the base as the rate-determining step (see above).



In contrast, the trend of k_{Am}/k_{-1} values observed can be easily accounted for in the framework of the SB-GA catalysis mechanism⁵. In fact, it is evident that this trend arises from a balance of electronic effects of the X substituent on the two parameters k_{Am} and k_{-1} . In the SB-GA mechanism, the k_{Am} parameter corresponds to Kk_4 . Since the decomposition reaction of XH into the products, controlled by k_4 , and the decomposition of XH into the reactants are very similar processes, it is probable that k_4 and k_{-1} parameters change in a homogeneous and regular way with changing X substituent. Moreover, since it should comply with the condition $k_{-1} \gg Kk_4$ (otherwise no base catalysis would be observed), the relationship $|\rho_{-1}| < |\rho_k + \rho_4|$ has to be satisfied and, because of a much higher mobility of the amine leaving group as compared to 4-nitrophenoxy leaving group ($k_{-1} \gg k_4$), also the relationship $|\rho_{-1}| < |\rho_4|$.

As both ρ_4 and ρ_{-1} are negative (see above), the difference $\rho_4 - \rho_{-1}$ should be negative, too. Therefore, the observation of k_3^{Am}/k_{-1} ratios, which decrease on going from X = CONH₂ to X = CO₂Me, implies that the ρ_K parameter should be less than $|\rho_4 - \rho_{-1}|$. On the other hand, the observation of k_3^{Am}/k_{-1} ratios, which increase on going from X = CO₂Me to X = CN and to X = NO₂, would imply the condition $\rho_K > |\rho_4 - \rho_{-1}|$. In conclusion, two different ρ_K values corresponding to the two substituent ranges would be required.

We think that this dichotomy in the behaviour of the various substrates studied comes from the hyper-*ortho* relation⁶. When the 3-X substituent has a relatively low conjugative effect, a preferential conjugative interaction occurs between the reaction centre and the 5-nitro group. This preferential in-

teraction causes a levelling of electronic effects exerted by the X substituent on the equilibrium $\text{XH} + \text{B} \rightleftharpoons \text{X}^- + \text{BH}^+$ and a relatively low ρ_K value. When the conjugation of the reaction centre with the 3-X substituent becomes important, it interferes successfully with the hyper-*ortho* relation and gives rise to a ρ_K value so much greater than in the preceding case, as to change the sign of the algebraic sum $\rho_4 + \rho_3 - \rho_{-1}$. A positive sum produces k_{Am}/k_{-1} ratios which increase with increasing electron-withdrawing power of the 5-X substituent. This interpretation of the data obtained in the present work leads to strong support for the hypothesis that the catalysis observed occurs *via* the SB-GA mechanism.

The case for X = SO₂Me is worth being considered separately. This substituent has much the same substituent constant as X = COMe (Table VIII) but shows the reactivity with both amines lower than that of substrates with X = CO₂Me. This unexpectedly low reactivity can be accounted for by a strong primary steric effect exerted by this bulky substituent and, in addition, by a greater difficulty than with the sp² groups, to form the hydrogen bonding as shown in 5. Thus data for SO₂Me have to be excluded from the Hammett correlation (Table IX). On the other hand the hyper-*ortho* relation determines a comparatively much lesser value of the k_{-1} constant for this

TABLE VIII
Substituent constants

X	H	CONH ₂	CO ₂ Me	CN	COMe	SO ₂ Me	NO ₂
σ^-	0.00	0.57	0.67	0.79	0.82	0.84	1.23

TABLE IX
Linear regression analysis^a of logarithmic relative kinetic constants [$\log(k_{1,X}/k_{1,H})$] for the reactions of 5-nitro-2-(4-nitrophenoxy)-3-X-thiophenes with aniline and 4-methoxyaniline in methanol at 20 °C, according to the equation $\log(k_{1,X}/k_{1,H}) = \rho\sigma^-$

No.	Amine	$\rho \pm s_\rho$	$i \pm s_i$	r	n^b	CL>(%)
1	Aniline	4.30 ± 0.27	-0.19 ± 0.21	0.992	6	99.9
2	4-Methoxyaniline	3.94 ± 0.31	-0.24 ± 0.24	0.988	6	99.9

^a ρ , reaction constant; i , intercept of the regression line with the ordinate $\sigma = 0$; s_ρ and s_i , standard deviations of ρ and i , respectively; r , correlation coefficient; n , number of data points; CL, confidence level. ^b Data for X = SO₂Me have been excluded from the correlation.

substituent. As a consequence, the k_{Am}/k_{-1} ratio for $X = SO_2Me$ does not lie in the same sequence as that for the other substituents.

For the reactions of 5-nitro-2-(4-nitrophenoxy)thiophene, very low k_2/k_{-1} and k_{Am}/k_{-1} ratios are observed. This occurs because in the transition states pertaining to the reaction of this substrate with the two anilines, there is no built-in solvation (see above). In other words, the powerful anchimeric assistance, which for the other *ortho*-substituted compounds reduces the k_{-1} parameter through stabilisation of the reaction intermediate, is now missing and comparatively lower k_2/k_{-1} and k_{Am}/k_{-1} ratios are, indeed, observed. It is worthwhile to recall that the corresponding reactions⁷ of 3-nitro-2-(4-nitrophenoxy)thiophene are not catalysed suggesting that, the activation being equal, the position of the activating nitro group with respect to the reaction centre is a crucial factor. In this latter compound, in fact, the lack of competition in the conjugation with a 5-substituent and the hyper-*ortho* relation cause a strong conjugative interaction between the reaction centre and the 3-nitro group and the greatest possible electron density on the oxygen atoms of this group. As a matter of fact, the strongest possible hydrogen bonding and the lowest k_{-1} value occur and on the basis of the relationship $k_{-1} \ll (k_2 + k_{Am}[Am])$, the reactions involved are not catalysed.

EXPERIMENTAL

Ethers **1** were prepared by the general method of ref.⁷. Aniline⁸, 4-methoxyaniline⁸ and methanol⁹ were purified by the reported methods. Amino derivatives **2** and **3** were prepared by the general method of ref.¹⁰. The relevant physical data of **1-3** are shown in Tables I-III.

Kinetics measurements. The kinetics were followed spectrophotometrically as previously described¹¹. The concentrations used were $2 \cdot 10^{-4}$ – 10^{-3} mol dm⁻³ for substrates and those reported in Tables IV and V for amines. The wavelength and log ϵ values for UV spectral measurements are shown in Tables II and III. Optical density measurements were carried out after dilution with acidified methanol¹¹.

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