Catalysis in Aromatic Nucleophilic Substitution. Part 7.[1] Kinetics of the Reactions of Some 5-Substituted 2-Methoxy-3-nitrothiophenes with Piperidine in Benzene

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The kinetics of the reactions of some 2-methoxy-3-nitro-5-X-thiophenes (Ia—g; X = H, $CONH_2$, CO_2Me, Ac, SO_2Me, CN, or NO_2) with piperidine and with n-butylamine in benzene have been measured in the range 20—40 °C. The reactions with piperidine are catalysed by piperidine, being third-order overall (second-order in amine). The electronic effects of the 5-substituent on the 'catalytic' constants are shown to be most consistent with the SB-GA mechanism of base catalysis in benzene.

In previous publications we have shown that the substitution reactions of 2-methoxy-3-nitro-5-X-thiophenes (Ia, c, and d) with piperidine are base-catalysed in methanol.[2,3] With reference to the Scheme, base catalysis has been observed because the product-forming steps designated by k_2 and $k_3^{B_i}[B_i]$ are slower than or as slow as the reversion of the intermediate (XH) to reactants.

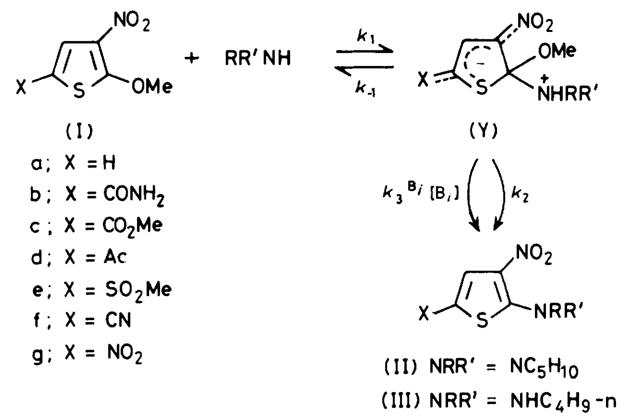
According to equation (1), which is appropriate to the mechanism indicated in the Scheme, this implies a *hyperbolic* dependence of the second-order kinetic constant, k_A, on base concentration.

$$k_A = \frac{k_1k_2 + k_1\Sigma_i k_3^{B_i}[B_i]}{k_{-1} + k_2 + \Sigma_i k_3^{B_i}[B_i]} \qquad (1)$$

Owing to the dominance of catalysis by methoxide ion, catalysis by piperidine was not detectable in the substitution of compound (Ia) by piperidine.[2] The presence of an electron-withdrawing substituent conjugated with the reaction centre, as in (Ic and d), enhances k_3^{OMe}/k_{-1} and k_3^{PIP}/k_{-1} and makes piperidine catalysis detectable. An estimate of the rate coefficients pertaining to the specific steps of mechanism strongly suggested[3] a specific base-general acid (SB–GA) mechanism for the base catalysis.

On going from methanol to benzene k_2/k_{-1} is strongly reduced and the substitution of (Ia) by piperidine responds *linearly* to catalysis by piperidine.[4] Evidence based on the remarkable difference in behaviour between pyrrolidine and piperidine in the reactions of these amines with (Ia) in benzene favours the SB–GA mechanism for base catalysis in benzene also.[1]

In order to obtain information about the role of the 5-substituent in (I) in affecting the catalytic coefficients and to elucidate further the base catalysis mechanism, we have measured the kinetics of substitution in benzene of compounds (Ib—g) by piperidine, in the temperature range 20—40 °C. For comparison we have also measured the kinetic constants for the corresponding reactions with n-butylamine in benzene.



Scheme.

Results and Discussion

Compounds (Ia—g) gave the substitution products (IIa—d and f) and (IIIa—g) on treatment with piperidine and n-butylamine, respectively, in benzene, in high yields (>95%), as indicated by t.l.c. and u.v.-visible (200—450 nm) spectral analysis of the mixtures obtained after complete reaction. The relevant physical data are shown in Table 1. For the reactions of compounds (Ie and g) with piperidine in benzene no well defined kinetic behaviour was observed and the spectra of the completed reaction mixtures indicated that significant decomposition of materials had occurred.

The apparent second-order kinetic constants, k_A, for the substitution of (Ib—d and f) by piperidine in benzene, as a function of piperidine (PIP) concentration, are shown in Table 2. The relevant apparent activation parameters are reported in Table 5. The reactions are catalysed by piperidine and the kinetic data obey equation (2). The third-order kinetic constants, k', are set out in Table 5.

$$k_A = k'[PIP] = k_1k_3^{PIP}[PIP]/k_{-1} \qquad (2)$$

With reference to the Scheme, equation (2) implies that $k_2 = 0$ and $k_{-1} \gg k_3^{PIP}[PIP]$ for all the compounds studied. The 'catalytic' constant, k', increases with increasing electron-withdrawing power of the 5-substituent in (I), but there is no linear correlation between log k' values and the substituent constants, σ_p^- [5] (Figure 1, curve *a*). In principle the failure of kinetic data to follow a linear Hammett-type equation could depend on an inherent inadequacy of the substituent constants used in measuring correctly the electronic effects of 5-substituents in the substitution of compounds (I) by piperidine in benzene.

In order to clarify this point we have studied the reactions of compounds (Ia—g) with n-butylamine (BA) in benzene. The apparent second-order kinetic constant, k_A (Table 3), in-

Table 1. Physical and spectroscopic data [a] for piperidino derivatives (IIa—g) and n-butylamino derivatives (IIIa—g)

Compd.	Crystallization solvent	M.p. (°C)	$\lambda_{max.}$/ [b] nm	log ε [b]
(IIa) [c]			392 [c]	3.76 [c]
(IIb) [d]			390	3.77
(IIc) [d]			388	3.77
(IId) [e]			390	3.81
(IIe) [d]			382	3.74
(IIf) [d]			386	3.77
(IIg) [f]			386 [f]	4.18 [f]
(IIIa) [g]	Light petroleum	50	390	3.99
(IIIb) [g]	Methanol	186	388	4.00
(IIIc) [g]	Light petroleum	78	384	4.00
(IIId) [h]	Hexane	97	388	4.05
(IIIe) [g]	Light petroleum–benzene	94	374	3.96
(IIIf) [g]	Light petroleum–benzene	86	380	3.95
(IIIg) [g]	Light petroleum–benzene	63	410	4.20

[a] All the new substitution products gave correct elemental analyses. [b] In benzene. [c] Ref. 16. [d] Ref. 13. [e] D. Spinelli and G. Consiglio, *J. Chem. Soc., Perkin Trans. 2*, 1975, 989. [f] D. Spinelli, G. Guanti, and C. Dell'Erba, *J. Heterocycl. Chem.*, 1968, **5**, 323. [g] Yellow. [h] C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, 1952, **74**, 2965.

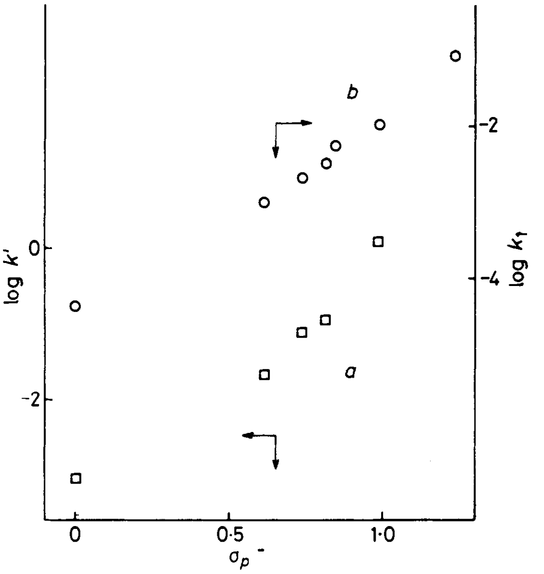


Figure 1. Plot of log k' (□, curve *a*) or log k_1 (○, curve *b*) for compounds (I) *versus* σ_p^-

creases only slightly with increasing n-butylamine concentration, following the equation $k_A = k_0 + k_{BA}[BA]$. The k_{BA}/k_0 values observed (Table 4) are not representative of genuine base catalysis, according to Bunnett's classification,[6] and probably stem from a medium effect. In fact, owing to the low amine concentrations used, the reactivity of (Ig) does not change with [BA] within experimental error. The apparent kinetic constant of (Ie) decreases as the n-butylamine concentration is increased: this behaviour has precedent[7] and can be analogously accounted for by some effect of complexing between the two reagents. Thus, on the whole, the reactions of compounds (Ia—g) with n-butylamine in benzene are not amine-catalysed, and the kinetic constants ' at infinite dilution ' (Table 5) are represented by k_1 in the Scheme. Consistent with this interpretation are the activation parameters shown in Table 5. Whereas the low activation enthalpies and high absolute activation entropies observed for substitutions by piperidine demonstrate a complex reaction mechanism with a balance of activation parameters for the individual steps (k_2, k_{-1}, and k_3^{PIP}), the enthalpy and entropy values calculated for substitutions by n-butylamine give no indication of balance and agree with an addition–elimination mechanism where the formation of the intermediate is rate-limiting.

Table 2. Kinetic constants for the reactions of some 2-methoxy-3-nitro-5-X-thiophenes (Ib—d and f) with piperidine in benzene at various temperatures

(Ib) (X = $CONH_2$)

[PIP]/M	0.119	0.142	0.178	0.237
10^3k_A [a]/l mol^{-1} s^{-1}	2.54	3.05	3.59	4.73
[PIP]/M	0.282	0.119	0.119	
10^3k_A [a]/l mol^{-1} s^{-1}	5.89	3.17 [b]	3.83 [c]	

[a] At 293.2 K. [b] At 303.0 K. [c] At 313.4 K.

(Ic) (X = CO_2Me)

[PIP]/M	0.0205	0.0410	0.0615	0.0820
10^3k_A [a]/l mol^{-1} s^{-1}	1.54	3.17	4.79	6.42
[PIP]/M	0.102	0.0410	0.0410	
10^3k_A [a]/l mol^{-1} s^{-1}	8.22	3.63 [b]	4.23 [c]	

[a] At 293.1 K. [b] At 303.2 K. [c] At 313.2 K.

(Id) (X = Ac)

[PIP]/M	0.0202	0.0405	0.0608	0.0810
10^3k_A [a]/l mol^{-1} s^{-1}	2.29	4.56	6.81	9.21
[PIP]/M	0.101	0.0405	0.0405	
10^3k_A [a]/l mol^{-1} s^{-1}	11.5	5.27 [b]	6.23 [c]	

[a] At 293.0 K. [b] At 303.3 K. [c] At 313.2 K.

(If) (X = CN)

[PIP]/M	0.0102	0.0205	0.0308	0.0410
10^2k_A [a]/l mol^{-1} s^{-1}	1.30	2.66	3.79	4.95
[PIP]/M	0.0478	0.0205	0.0205	
10^2k_A [a]/l mol^{-1} s^{-1}	6.03	2.88 [b]	3.26 [c]	

[a] At 293.1 K. [b] At 303.3 K. [c] At 313.2 K.

The plot of log k_1 *versus* σ_p^- is again curvilinear (Figure 1, curve *b*), but the curvature is less pronounced in this case.* By plotting log $[k'/(k')_H]$ (piperidine reaction) *versus* log $[k_1/(k_1)_H]$ (n-butylamine reaction), as shown in Figure 2, it is possible to ' minimize ' the influence of k_1 on curve *a* of Figure 1. In fact the dependence of the kinetic constant for nucleophilic attack, k_1, on the 5-substituent is presumably the same for the two amines † and the curve of Figure 2 represents the variation of (k_3^{PIP}/k_{-1}) as the 5-substituent is changed.

In aromatic nucleophilic substitution the electronic activation increases with increasing electron-withdrawing power of the substituent. In the case of substitutions of compounds (Ia—d and f) by piperidine in benzene the change from X = H to X = CN, although causing stabilization of the transition state leading to the intermediate (Y), destabilizes the

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* Indeed, a linear correlation does exist between log k_1 and σ_p^- (ρ 2.62 ± 0.16, *r* 0.991, *n* 7) but the intercept (−4.51) is very different from log $(k_1)_H$.

† The log *k* values for the reactions of compounds (Ia—g) with piperidine in methanol at 20 °C give an excellent linear correlation (*s* 0.99 ± 0.01, *i* −0.02 ± 0.04, *r* 1.000, *n* 7) with the corresponding log *k* values for the reactions with n-butylamine in methanol.[8] The slope shows an identical susceptibility of the two reactions to substituent effects.

Table 3. Kinetic constants for the reactions of some 2-methoxy-3-nitro-5-X-thiophenes (Ia—g) with n-butylamine in benzene at various temperatures

(Ia) (X = H)

[BA]/M	0.202	0.404	0.505	0.758
10^5k_A [a]/l mol^{-1} s^{-1}	5.52	6.60	7.45	8.90
[BA]/M	1.01	0.202	0.202	
10^5k_A [a]/l mol^{-1} s^{-1}	10.4	11.2 [b]	22.0 [c]	

[a] At 293.2 K. [b] At 303.2 K. [c] At 313.2 K.

(Ib) (X = CONH$_2$)

[BA]/M	0.101	0.202	0.505	1.01
10^3k_A [a]/l mol^{-1} s^{-1}	1.09	1.14	1.30	1.55
[BA]/M	0.101	0.101		
10^3k_A [a]/l mol^{-1} s^{-1}	2.09 [b]	3.99 [c]		

[a] At 293.2 K. [b] At 303.0 K. [c] At 313.4 K.

(Ic) (X = CO$_2$Me)

[BA]/M	0.0995	0.199	0.498	0.0995
10^3k_A [a]/l mol^{-1} s^{-1}	2.58	2.91	4.10	8.75 [b]

[a] At 293.3 K. [b] At 313.3 K.

(Id) (X = Ac)

[BA]/M	0.0206	0.0514	0.103	0.0206
10^3k_A [a]/l mol^{-1} s^{-1}	3.31	3.58	3.86	6.28 [b]
[BA]/M	0.0206			
10^3k_A [a]/l mol^{-1} s^{-1}	10.8 [c]			

[a] At 293.1 K. [b] At 303.1 K. [c] At 313.1 K.

(Ie) (X = SO$_2$Me)

[BA]/M	0.008 25	0.0165	0.0202	0.0330
10^3k_A [a]/l mol^{-1} s^{-1}	5.45	5.39	5.20	4.95
[BA]/M	0.0505	0.101	0.008 25	
10^3k_A [a]/l mol^{-1} s^{-1}	4.71	4.03	19.3 [b]	

[a] At 293.2 K. [b] At 313.4 K.

(If) (X = CN)

[BA]/M	0.0202	0.0505	0.101	0.0202
10^2k_A [a]/l mol^{-1} s^{-1}	1.17	1.21	1.33	2.18 [b]
[BA]/M	0.0202			
10^2k_A [a]/l mol^{-1} s^{-1}	3.94 [c]			

[a] At 293.2 K. [b] At 303.1 K. [c] At 313.3 K.

(Ig) (X = NO$_2$)

[BA]/M	0.000 505	0.001 01	0.002 02	0.000 505
10^2k_A [a]/l mol^{-1} s^{-1}	8.47	8.81	8.86	13.2 [b]
[BA]/M	0.000 505			
10^2k_A [a]/l mol^{-1} s^{-1}	19.1 [c]			

[a] At 293.0 K. [b] At 303.2 K. [c] At 313.2 K.

Table 4. Values of k_0 and k_{BA} for the reactions of some 2-methoxy-3-nitro-5-X-thiophenes (Ia—d and f) with n-butylamine in benzene at 293.2 K

Compound	10^3k_0	10^3k_{BA}	k_{BA}/k_0
(Ia)	0.0427	0.0609	1.4
(Ib)	1.04	0.507	0.49
(Ic)	2.17	3.85	1.8
(Id)	3.20	6.55	2.0
(If)	11.2	20.2	1.8

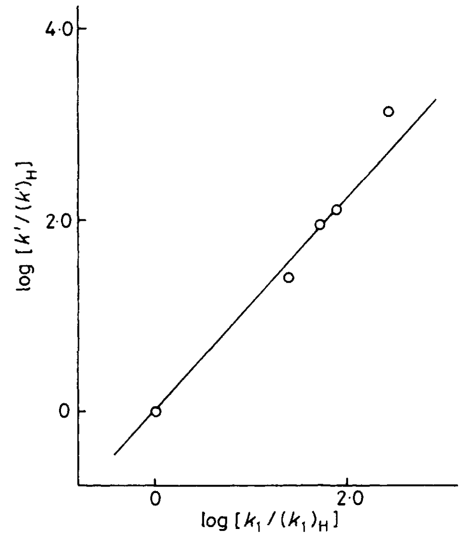

Figure 2. Plot of log [$k'/(k')_H$] *versus* log [$k_1/(k_1)_H$]. The straight line has been calculated by excluding compound (If)

transition state for the reverse reaction (k_{-1}) relative to (Y) and the uncatalysed pathway (k_2): moreover this variation determines a greater acidity of the ammonium proton in the intermediate (Y). In the light of the mechanism proposed for the k_2 step,* this results in a stabilization of the transition state for the ' non-catalysed ' leaving group expulsion. Since the two effects of the 5-substituent are in opposite directions with a net effect which is very small, the increase in electronic activation reduces k_{-1} much more than it does k_2. As a consequence k_2/k_{-1} should increase with increasing electronic activation (Hammett absolute ρ value larger for k_{-1} than for k_2). However, in the case of the very sluggish methoxide leaving group k_2/k_{-1} is expected to be very low irrespective of the 5-substituent; indeed, we observe $k_2/k_{-1} = 0$ for all the methoxy compounds studied.

We have already shown that the substitutions of compounds (Ic and d) by piperidine in methanol are catalysed by the SB–GA mechanism. It is conceivable that the corresponding reactions of compounds (Ia—d and f) in benzene are catalysed by the same mechanism. This hypothesis is supported by the kinetic results of this work shown diagrammatically in Figure 2. The points relative to compounds (Ia—d) show a good adherence to the solid line of slope 1.1 and indicate that in this range of electronic activation k_3^{PIP}/k_{-1} is nearly independent of the 5-substituent and that the Hammett absolute ρ value for k_3^{PIP} is nearly the same as for k_{-1}. *This is consistent with the SB–GA mechanism for the k_3^B step.*

Removal of the ammonium proton from the intermediate (X) could happen in various ways,[10] *e.g.* (*a*) rate-limiting proton abstraction by the base to form a deprotonated intermediate, followed by rapid leaving group expulsion; (*b*) rapid equilibrium deprotonation followed by rate-limiting general acid-catalysed detachment of the nucleofuge (SB–GA mechanism); or (*c*) concerted proton transfer and leaving group detachment with bifunctional catalysis by the amine.

The similar sensitivities of k_3^{PIP} and k_{-1} to the acidifying effect of the electron-withdrawing 5-substituent suggest that the intermediate is deprotonated in an equilibrium reaction

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* The mechanism of the k_2 step involves a transfer of an ammonio proton to the leaving group in concert with leaving group departure.[9]

Table 5. Kinetic constants, apparent activation parameters, and substituent constants for the reactions of some 2-methoxy-3-nitrothiophenes (Ia—g) with piperidine and with n-butylamine in benzene at 293.2 K

Compound	$10^3 k_1 k_3^{\text{PIP}}/k_{-1}$ [a] $\text{l}^2\ \text{mol}^{-2}\ \text{s}^{-1}$	$10^3 k_1$ [b] $\text{l mol}^{-1}\ \text{s}^{-1}$	$(\Delta H^\ddagger)_{\text{PIP}}$ [c] kJ mol^{-1}	$(-\Delta S^\ddagger)_{\text{PIP}}$ [d] $\text{J mol}^{-1}\ \text{K}^{-1}$	$(\Delta H^\ddagger)_{\text{BA}}$ [c] kJ mol^{-1}	$(-\Delta S^\ddagger)_{\text{BA}}$ [d] $\text{J mol}^{-1}\ \text{K}^{-1}$	σ_p^- [e]
(Ia)	0.848 [f]	0.0427 [f]	18.8 [f]	238	50.2	155	0.00
(Ib)	20.8	1.04	13.0	250	46.6	142	0.62
(Ic)	77.8	2.17	8.4	264	44.1	144	0.74
(Id)	113	3.20	9.2	258	42.6	147	0.82
(Ie)		5.70 [g]			45.3	133	0.85 [h]
(If)	1 250	11.2	5.2	257	43.6	133	0.99
(Ig)		87.1 [g]			28.2	169	1.23

[a] Mean value of the kinetic constant k' calculated as $k_A/[\text{PIP}]$ (see text). [b] Second-order kinetic constants for substitutions by n-butylamine. [c] At 293.2 K; the maximum error is 2.1 kJ mol^{-1}. [d] At 293.2 K; the maximum error is 7 J $\text{mol}^{-1}\ \text{K}^{-1}$. [e] Values from ref. 5. [f] Values from ref. 4. [g] Values obtained by extrapolation at [BA] = 0 (see text). [h] 'Thiophenic' σ^- value for methylsulphonyl group (*cf.* ref. *e*, Table 1).

where the variable substituent exerts its full electronic effects, in contrast with the situation in the k_2 step or in mechanisms (*a*) and (*c*) where the proton is only partially transferred in the transition state.

The marked deviation of the point relative to compound (If) from the solid line of Figure 2 is analogous to that observed in the Hammett-type correlation of logarithmic kinetic constants for the reactions of compounds (Ia—g) with methoxide ion to form Meisenheimer adducts.[11] The major factor involved is the hyper-*ortho* relation [12] between 2-methoxy and 3-nitro groups which diminishes in a 'non-linear' fashion with increasing electron-withdrawing power of the 5-substituent.

Experimental

Synthesis and Purification of Compounds.—Compounds (Ia—g),[11] (IIa—g),[13,14] piperidine,[15] and benzene [16] were prepared and/or purified according to the methods reported. Compounds (IIIa—g) were prepared according the general method of ref. 15. The physical data are shown in Table 1.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[7] The concentrations used were 10^{-4} to 2×10^{-3}M for substrates and those indicated in the Tables for the amines. The kinetic constants were reproducible to within ±3%.

Acknowledgements

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