Catalysis in Aromatic Nucleophilic Substitution. Part 5.† Reactions of Piperidine with Methyl 2-Methoxy-3-nitrothiophen-5-carboxylate and 5-Acetyl-2-methoxy-3-nitrothiophen

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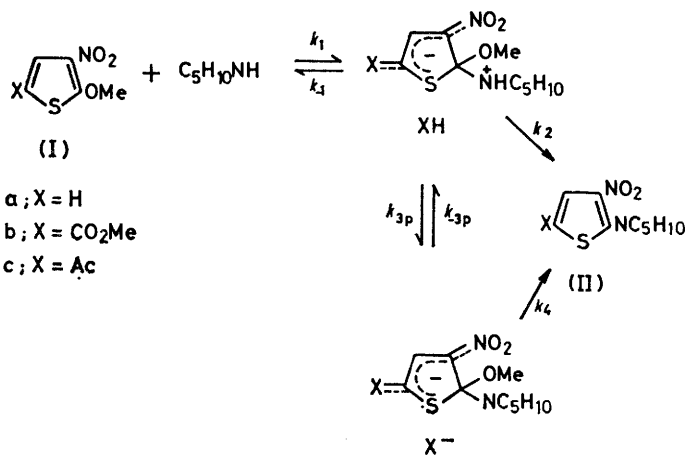
The kinetics of piperidino-substitution of methyl 2-methoxy-3-nitrothiophen-5-carboxylate (Ib) and of 5-acetyl-2-methoxy-3-nitrothiophen (Ic) have been studied in methanol as a function of piperidine and methoxide ion concentrations. The reactions are catalysed by both piperidine and methoxide. Evidence is presented that the departure of the methoxy group is general-acid-catalysed, indicating a specific base-general acid mechanism for base catalysis.

RECENTLY we reported on the peculiar behaviour of 2-methoxy-3-nitrothiophen (Ia), the piperidino-substitution of which is catalysed by methoxide ion in methanol [1] and by piperidine in benzene,[2] respectively. Owing to the dominance of catalysis by methoxide ion, catalysis by piperidine was not detectable in methanol.[1] These results could imply, in principle, either specific base (SB) catalysis or, alternatively, a SB-general acid (GA) mechanism [3] with a weak contribution to catalysis from piperidine. In order to clarify this point, and also in view of recent discussions on this subject,[4] we now report kinetic data for the reactions of methyl 2-methoxy-3-nitrothiophen-5-carboxylate (Ib) and 5-acetyl-2-methoxy-3-nitrothiophen (Ic) with piperidine in methanol. Our results, incidentally, give information about the role played by the 5-substituent in (I) in affecting the various catalytic pathways.

RESULTS AND DISCUSSION

Compounds (Ib and c) gave the substitution products (IIb and c) in high yields (>95%) on treatment with



SCHEME

piperidine in methanol as indicated by t.l.c. and u.v.–visible (200—450 nm) spectral analysis of the reaction mixtures at infinity.

† Part 4, ref. 2.

The apparent second-order kinetic constants k_A for the piperidino-substitutions of (Ib and c) in methanol at 20 °C as a function of piperidine (PIP), piperidine hydrochloride ($PIPH^+$), and methoxide ion concentrations are summarized in Tables 1 and 2.

TABLE 1

Kinetic constants for the reaction of methyl 2-methoxy-3-nitrothiophen-5-carboxylate (Ib) with piperidine in methanol at 20 °C

No.	$[PIP]_{st}$/M	$[PIPH^+]_{st}$/M	$10^6[MeO^-]$ [a]/M	10^3k_A [b]/l mol^{-1} s^{-1}
1	0.0410	0.1	2.99	0.733
2	0.0410	0.04	7.48	0.892
3	0.0415	0.02	15.1	1.14
4	0.0415	0.01	30.2	1.49
5	0.0410	0.008	37.2	1.67
6	0.0410	0.006	49.4	1.91
7	0.0410	0.005	59.1	2.08
8	0.0410	0.004	73.3	2.36
9	0.0415	0.003	97.5	2.76
10	0.0410	0.002	139	3.36
11	0.0410	0.0008	276	5.07
12	0.0415	0.0004	383	6.56
13	0.0205	0.02	7.47	0.593
14	0.0615	0.06	7.48	1.24
15	0.0820	0.08	7.48	1.51
16	0.102	0.1	7.44	1.78
17	0.131	0.128	7.47	2.15
18	0.164	0.16	7.48	2.57
19	0.205	0.2	7.48	3.04

[a] Values calculated using K_b 7.3 × 10^{-6} (J. R. Schaefgen, M. S. Newman, and F. H. Verhoek, *J. Am. Chem. Soc.*, 1944, **66**, 1847). [b] Rate constants are accurate to within ±3%.

The reactions are strongly accelerated by MeO^- with a curvilinear plot of k_A *versus* $[MeO^-]$ (Figure 1). Between the lowest and highest $[MeO^-]$ concentration there is a several-fold increase in k_A, leaving no doubt that both reactions are catalysed by methoxide ion.

The reactions are also catalysed by piperidine with k_A increasing somewhat less than linearly with piperidine concentration (Figure 2). At the low methoxide concentration used in these experiments the relative importance of piperidine catalysis is increased and the acceleration between the lowest and highest [PIP] for (Ib) [(Ic)] amounts to a 5 (7)-fold factor. We are confident that this effect represents genuine base catalysis.

With reference to the Scheme, the general expression for k_A, in terms of rate coefficients for specific steps, is equation (1). Equations (2)—(4) apply where k_{3p}^{MeO}

and k_3^{PIP} refer to deprotonation of XH by MeO^- and by piperidine, respectively, k_{-3p}^{MeO} and k_{-3p}^{PIP} refer to the

$$k_A = \frac{k_1k_2(k_{-3p} + k_4) + k_1k_{3p}k_4}{(k_{-1} + k_2)(k_{-3p} + k_4) + k_{3p}k_4} \quad (1)$$

$$k_{3p} = k_{3p}^{MeO}[MeO^-] + k_{3p}^{PIP}[PIP] \quad (2)$$

$$k_{-3p} = k_{-3p}^{MeO} + k_{-3p}^{PIP}[PIPH^+] \quad (3)$$

$$k_4 = k_4^{MeO} + k_4^{PIP}[PIPH^+] \quad (4)$$

protonation of X^- by the solvent and by $PIPH^+$, respectively and k_4^{MeO} refers to uncatalysed or solvent-assisted leaving group expulsion whereas k_4^{PIP} allows for the possibility of general-acid catalysed leaving group departure by the protonated amine.

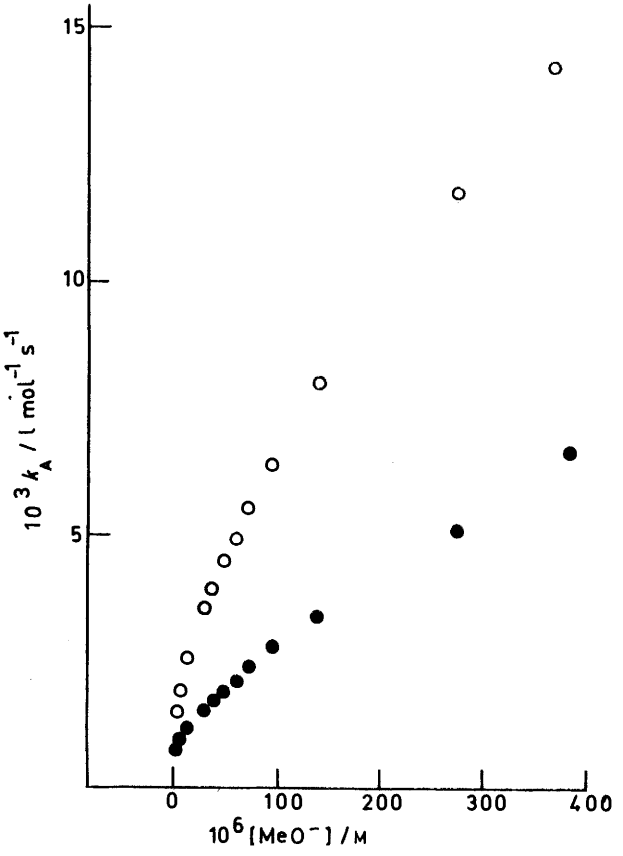


FIGURE 1 Plot of apparent second-order kinetic constants k_A for piperidine-substitution in methanol at 20 °C of (Ib) (●) and (Ic) (○) *versus* [MeO^-]

Assuming either $k_4 \gg k_{-3p}$ (rate limiting deprotonation of XH) or $k_4 \ll k_{-3p}$ (SB-GA mechanism) leads to the same formal dependence of k_A on [MeO^-] and [PIP].

$$k_A = a(b + cx_1 + dx_2)/(1 + b + cx_1 + dx_2) \quad (5)$$

As a consequence one can write equation (5) where $x_1 = [PIP]_{eff.}$* and $x_2 = [MeO^-]$.

We have fitted our kinetic data to equation (5) using a least-squares method [5] and the results of the correlations are reported in Table 3.

* The values of [PIP] have been corrected, when necessary, for the amount consumed in reaction with methanol.

TABLE 2

Kinetic constants for the reaction of 5-acetyl-2-methoxy-3-nitrothiophen (Ic) with piperidine in methanol, at 20 °C

No.	$[PIP]_{st}$/M	$[PIPH^+]_{st}$/M	$10^6[MeO^-]^a$/M	$10^3k_A{}^b$/l mol^{-1} s^{-1}
1	0.0408	0.1	2.98	1.57
2	0.0408	0.04	7.44	1.94
3	0.0408	0.02	14.9	2.54
4	0.0408	0.01	29.7	3.47
5	0.0415	0.008	37.6	3.91
6	0.0408	0.006	49.2	4.44
7	0.0407	0.005	58.8	4.89
8	0.0407	0.004	73.0	5.51
9	0.0407	0.003	95.9	6.40
10	0.0407	0.002	139	7.95
11	0.0405	0.0008	275	11.7
12	0.0404	0.0004	379	14.2
13	0.0104	0.01	7.58	0.883
14	0.0208	0.02	7.58	1.31
15	0.0622	0.06	7.56	2.57
16	0.0830	0.08	7.57	3.23
17	0.104	0.1	7.59	3.71
18	0.133	0.128	7.58	4.48
19	0.166	0.16	7.57	5.28
20	0.208	0.2	7.59	6.41

[a,b] As Table 1.

As in the case for (Ia),[1] we observed very low $k_2 : k_{-1}$ ratios; thus, there is no significant contribution to k_A from the solvent-assisted pathway for the decomposition of the intermediate.

A lower limit of k_4 can be estimated from k_r values for the decomposition of Meisenheimer-type adducts (IIIb) (k_r 1.1×10^{-3}) [6] and (IIIc) (k_r 2.0×10^{-3}).[6] Since

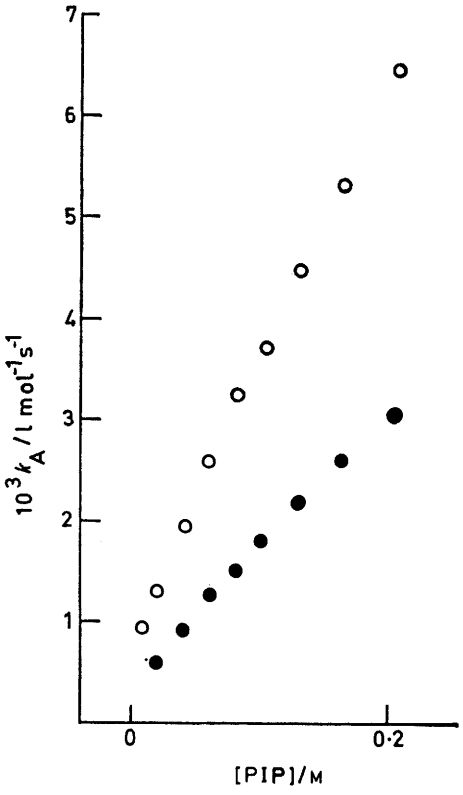
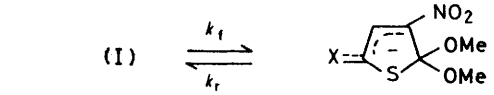


FIGURE 2 Plot of apparent second-order kinetic constants k_A for piperidino-substitution in methanol at 20 °C of (Ib) (●) and (Ic) (○) *versus* [PIP]

$k_{-3p} = k_{3p}^{OMe}K_S/K_a^{XH} + (k_{3p}^{PIP}/k_{3p}^{OMe})K_a^{PIP}$ where K_S is the autoprotolysis constant of the solvent (for methanol, pK_S 16.86),[7] K_a^{PIP} is the basic dissociation constant



(III)

of piperidine in methanol (pK_a^{PIP} 5.14),[8] and K_a^{XH} is the acid dissociation constant of XH (assumed pK_a^{XH} 8),* one obtains k_{-3p} $1.4 \times 10^{-9}k_{3p}^{OMe}(1 + 90[PIPH^+])$ for (Ib) and $1.4 \times 10^{-9}k_{3p}^{OMe}(1 + 70[PIPH^+])$ for (Ic).

It is clear that k_4 values can never approach k_{-3p} values,† the real situation being $k_4 \ll k_{-3p}$: thus, the catalysis observed occurs through the SB-GA mechanism. This is because the pK difference between the methoxy leaving group and the acid catalyst ($PIPH^+$) is large enough to balance the increase in entropy of including another molecule into the transition state.

and that the k_4 step represents general-acid-catalysed leaving group departure. The occurrence of the SB-GA mechanism for base catalysis is a consequence of the thermodynamically favourable proton transfer from $PIPH^+$ (pK 5.14) to MeO^- (pK 16.86). The presence of an electron-withdrawing substituent conjugated with the reaction centre enhances the k_3^{OMe}/k_{-1} and k_3^{PIP}/k_{-1} values and makes piperidine catalysis detectable in methanol.

EXPERIMENTAL

Synthesis and Purification of Compounds.—Compounds (Ic) [10] and (II),[11] piperidine,[12] and methanol [12] were prepared and/or purified according to the methods reported.

Methyl 2-Methoxy-3-nitrothiophen-5-carboxylate (Ib).—To a solution of methyl 2-bromo-3-nitrothiophen-5-carboxylate [11] (1 g) in methanol (10 ml) was added a solution of sodium methoxide (0.09 g Na in 5 ml methanol). The crystals separated after 24 h at room temperature and were filtered and the residue, recrystallized from methanol, had m.p. 118—119 °C.

TABLE 3

Results of least-squares fitting [a] to equation (5) of apparent second-order kinetic constants k_A for the piperidino-substitution of (Ib and c) in methanol at 20 °C

Compound	Constraints [b]	$10^3(a \pm s_a)$/l mol^{-1} s^{-1}	$b \pm s_b$	$c \pm s_c$/l mol^{-1}	$d \pm s_d$/l mol^{-1}
(Ib)	None	16.6 ± 1.5	0.00807 ± 0.00368	0.999 ± 0.130	1520 ± 220
	$b = 0$	14.8 ± 0.9		1.21 ± 0.08	1850 ± 180
(Ic)	None	27.2 ± 1.1	0.00428 ± 0.00355	1.33 ± 0.08	2640 ± 190
	$b = 0$	26.5 ± 0.08		1.41 ± 0.05	2790 ± 150

[a] s_a—s_d are the standard errors of a–d, respectively. [b] With the constraints ($c = 0$) or ($b = 0$ and $c = 0$), the program [5] does not converge or gives regression parameters with unacceptable uncertainties.

The behaviour of (Ib and c) confirms the results previously obtained with (Ia), stressing the peculiarity of 5-substituted 2-methoxy-3-nitrothiophens which represent, up to now, the first and unique example of an *o*-mononitro-activated 'system' requiring base catalysis *in methanol*.

As expected on the grounds of substituent electronic effects, k_1, k_3^{OMe}/k_{-1}, and k_3^{PIP}/k_{-1} increase with increasing electron-withdrawing ability of the 5-substituent.

Logarithmic relative kinetic constants ($\log k_{5-X}/k_{5-H}$) can be tentatively correlated with σ_p^- values for 5-X: the ρ value observed (1.78) agrees with arguments based on interactions between X and the methoxy-leaving group [9] but the limited number of points in the Hammett-type correlation prevents further speculation (concerning, *e.g.* $\rho_3^{OMe} - \rho_{-1}$, $\rho_3^{PIP} - \rho_{-1}$, $\rho_3^{OMe} - \rho_3^{PIP}$, *etc.*) on substituent effects.

Conclusions.—Although previously available evidence [4] seemed to indicate that the SB-GA mechanism was not a significant pathway in protic solvents, we have shown that the expulsion of the very sluggish methoxy-leaving group is relatively slow compared with the rapidly established proton transfer equilibrium (*i.e.* $k_4 \ll k_{-3p}$)

* Lower limit estimated by taking into account the acidifying effect of the nitroaryl moiety [4] on the pK_a of piperidinium ion.

† We assume that deprotonation of XH by MeO^- is diffusion controlled or nearly so with k_{3p}^{MeO} *ca.* 10^9 as a lower limit.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[13] The concentrations used were 5×10^{-4}—10^{-3}M for substrates and those indicated in the Tables for piperidine and piperidine hydrochloride.

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