SUBSTITUENT EFFECTS IN THE REACTIONS OF SOME 2-METHOXY-3-NITRO-5-X-THIOPHENES WITH PYRROLIDINE AND PIPERIDINE IN METHANOL[†]

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Abstract - The kinetics of the title reactions have been studied as a function of amine and methoxide ion concentrations in buffered solutions. All the reactions studied are general base-catalysed. An examination of the catalytic coefficients obtained for each amine-substrate system has showed that the catalysis observed occurs through a SB-GA mechanism and that the general base-catalysed product-forming step is controlled by the ring size of the cyclic amine. The Hammett ρ_1 values calculated are consistent with previous evidence concerning the interactions between the substituent at the C-5 *para*-like carbon atom and the leaving group. Moreover, the results confirm that a methyl group in such a position can behave as a weakly electron-attracting substituent.

Recently[1,2] we have shown that the reactions of 2-methoxy-3-nitro-5-X-thiophenes (**1a-d**) with piperidine in methanol are subjected to general base catalysis. With reference to the reaction mechanism of the Scheme 1 the general expression[3] that relates the apparent second order kinetic constant, k_A, to the concentrations of the various bases present in solution is equation (1),

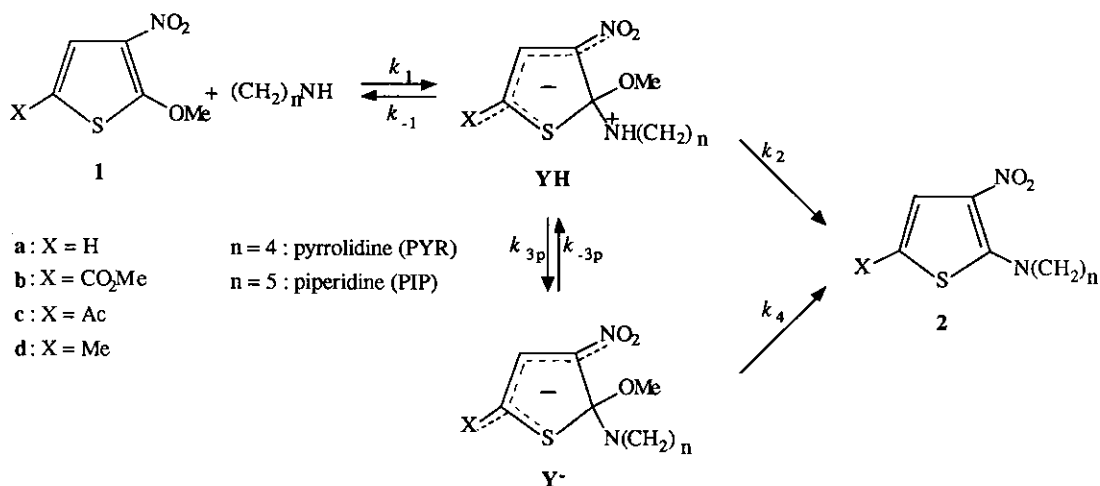$$k_A = [k_1 k_2 (k_{-3p} + k_4) + k_1 k_{3p} k_4]/[(k_{-1} + k_2)(k_{-3p} + k_4) + k_{3p} k_4] \tag{1}$$

where

$$k_{3p} = k_{3p}{}^{MeO}[MeO^-] + k_{3p}{}^{Am}[Am] \tag{2}$$

$$k_{-3p} = k_{-3p}{}^{MeOH} + k_{-3p}{}^{AmH}[AmH^+] \tag{3}$$

$$k_4 = k_4{}^{MeOH} + k_4{}^{AmH}[AmH^+] \tag{4}$$

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a : X = H   n = 4 : pyrrolidine (PYR)

b : X = CO$_2$Me   n = 5 : piperidine (PIP)

c : X = Ac

d : X = Me

Scheme 1

The rate constants k_{3p}^{MeO} and k_{3p}^{Am} refer to the deprotonation of the reaction intermediate **YH** to **Y⁻** by methoxide ion and amine, respectively; k_{-3p}^{MeOH} and k_{-3p}^{AmH} are the rate constants for the reversed process, *i.e.*, the protonation of **Y⁻** to **YH** by MeOH and the conjugate acid of the amine, respectively; k_{4}^{MeOH} represents the rate constant for the methanol assisted leaving group detachment from **Y⁻** ; k_{4}^{AmH} refers to the expulsion of leaving group acid-catalysed by the conjugate acid of the amine and k_2 refers to the 'uncatalysed' (solvent assisted) decomposition of the reaction intermediate **YH** into the reaction products.

The catalysis mechanism implies necessarily the remotion of the 'ammonium' proton from the intermediate **YH** and, in methanol, this can occur substantially in two different ways: *a*) a *slow*, rate-determining detachment by the base to form the deprotonated intermediate **Y⁻**, from which the leaving group breaks off *rapidly*[3] and *b*) a *rapid* deprotonation equilibrium followed by a *slow* detachment of the leaving group general acid-catalysed by the conjugated acid of the amine (SB-GA mechanism).[3]

Assuming $k_4 \gg k_{-3p}$ (mechanism *a*), equation (1) turns into equation (5)

$$k_A = \{k_1 k_2 + k_1 k_{3p}^{MeO}[MeO^-] + k_1 k_{3p}^{Am}[Am]\}/\{k_{-1} + k_2 + k_{3p}^{MeO}[MeO^-] + k_{3p}^{Am}[Am]\} \tag{5}$$

whereas on the assumption $k_4 \ll k_{-3p}$ (mechanism *b*), from equation (1) one can obtain equation (6)

$$k_A = (k_1 k_2 + k_1 K_{3p} k_4)/(k_{-1} + k_2 + K_{3p} k_4) \tag{6}$$

where

$K_{3p} = k_{3p}/k_{-3p} = k_{3p}^{MeO}[MeO^-]/k_{-3p}^{MeOH} = k_{3p}^{Am}[Am]/k_{-3p}^{AmH}[AmH^+] = K_a^{YH}/[MeOH^+_2]$ and K_A^{YH} represents the acid dissociation constant of the reaction intermediate **YH**.

Thus, equation (6) can be, transformed into equation (7)

$$k_A = \{k_1 k_2 + k_1 k_{3p}^{MeO} k_4^{MeOH}[MeO^-]/k_{-3p}^{MeOH} + k_1 k_{3p}^{Am} k_4^{AmH}[Am]/k_{-3p}^{AmH}[AmH^+]\}/ \{k_{-1} + k_2 + $$
$$+ k_{3p}^{MeOH} k_4^{MeOH}[MeO^-]/k_{-3p}^{MeOH} + k_{3p}^{Am} k_4^{AmH}[Am]/ k_{-3p}^{AmH}[AmH^+]\}$$
(7)

Equations (5) and (7) express the same formal dependence of k_A on methoxide ion and amine concentrations; thus, independently of the mechanism followed, the catalysis law has the form

$$y = a \ (b + cx_1 + dx_2)/(1 + b + cx_1 + dx_2)$$
(8)

For the case of 2-methoxy-3-nitro-5-X-thiophenes (**1b, c**) reacting with piperidine in methanol (Am = PIP) k_4 and k_{-3p} coefficients could be estimated and the condition $k_4 << k_{-3p}$ could be demonstrated;[2b] thus, the observed catalysis would occur through the SB - GA mechanism.[3]

In Table 1 are reported the values of a - d parameters obtained by a least squares fitting of experimental k_A values to equation (8). Even though for X = H (**1a**) the piperidine catalysis could not be evidenced on account of the dominance of methoxide catalysis (Table 1, $d/c = \infty$), the SB-GA mechanism probably applies to all the methoxy derivatives studied.

Table 1. Results of least-squares fitting[a] to equation (8) of apparent second-order kinetic constants k_A for the piperidino substitution of compounds (**1a-d**) in methanol at 293.15 K

Compound	$10^3(a \pm s_a)$ dm^3 mol^{-1}s^{-1}	b	$(c \pm s_c)$ dm^3 mol^{-1}	$(d \pm s_d)$ dm^3 mol^{-1}	Ref.
1a	0.815 ± 0.013	0	0	489 ± 20	2a
1b	14.8 ± 0.9	0	1.21 ± 0.08	1850 ± 180	2b
1c	26.5 ± 0.1	0	1.41 ± 0.05	2790 ± 150	2b
1d	1.17 ± 0.14	0	1.28 ± 0.19	1170 ± 190	1

[a] s_a, s_c and s_d are the standard deviations of a, c and d, respectively.

The reaction of 2-methoxy-3-nitrothiophene (**1a**) with pyrrolidine (Am = PYR) in methanol is second order overall;[1] therefore, there is no apparent catalysis and the reaction rate is controlled by the formation of the reaction intermediate **YH**. The change in the size of the amine ring, on going from piperidine to pyrrolidine, would cause, consistently, the variation from $k_2/k_{-1} << 1$ to $k_2/k_{-1} >> 1$. A possible steric factor depending on the ring size, which would markedly reduce k_2 for piperidine with respect to pyrrolidine, would be the steric inhibition of the resonance developing in the reaction product and in the related transition state.[4] However, the apparent absence of base catalysis could also arise from a situation where $k_2/k_{-1} << 1$ but $k_{3p}^{PYR}[PYR] >> k_{-1}$, in the concentration range used and therefore k_A values fall in a 'plateau' region.

With the aim of obtaining further information on this point we were prompted to study the kinetics of the reaction with pyrrolidine in methanol of those 2-methoxy-3-nitro-5-X-thiophenes for which the data for the corresponding reactions with piperidine were already available.[1,2] Since both the absolute reactivity (k_1) and the catalytic coefficients increase with increasing the activation degree of substrate, *i.e.*, with the introduction of electron-withdrawing substituents (Table 1), it was necessary to carry out the kinetics in the presence of

Am-AmH$^+$ buffers. As a matter of fact, due to the ionization equilibrium of the amine in methanol (equation 9), there are two general bases in solution

$$Am + MeOH \rightleftharpoons AmH^+ + MeO^- \qquad (9)$$

and if one wants to study the effect of the concentration of one of the bases on the reaction constant, k_A, the concentration of the other one has to be kept constant.*

Preliminary kinetic runs showed soon that the reaction of methyl 2-methoxy-3-nitrothiophene-5-carboxylate (1b) with pyrrolidine in methanol was catalysed by both bases, pyrrolidine and methoxide. It was necessary, therefore, to use a pyrrolidinium salt and, moreover, to know the ionisation constant of pyrrolidine in methanol in order to calculate the base concentrations. Since this ionization constant has been recently determined at 298.15 K by means of pyrrolidine-pyrrolidinium perchlorate buffers,[5] the reactions investigated in the present work have been studied at this temperature, in the presence of the abovementioned buffers and at a constant ionic strength. For the sake of comparison the corresponding reactions with piperidine have also been studied at 298.15 K in the presence of piperidine-piperidinium perchlorate buffers, at the same ionic strength.

Results and Discussion

The apparent second-order kinetic constants, k_A, for the reactions of 2-methoxy-3-nitro-5-X-thiophenes (1a-d) with pyrrolidine in methanol at 298.15 K at various pyrrolidine and pyrrolidinium (PYRH$^+$) perchlorate concentrations, are reported in Tables 2-5. The corresponding data for the reactions with piperidine in the presence of piperidinium (PIPH$^+$) perchlorate are reported in Tables 6-9.

An examination of kinetic data shows that, at a constant amine concentration, k_A increases with increasing methoxide ion concentration. On the other hand, at a constant buffer ratio, k_A increases with increasing amine concentration. Thus, all the reactions studied are general base-catalysed.

As shown above, independently of the catalysis mechanism, the kinetic constants should obey an equation such as (8), where $x_1 = [Am]_{eff}$ (Am = PYR or PIP) and $x_2 = [MeO^-]$. A least-squares treatment of experimental data according to equation (8) has shown (Table 10) that there is no significant contribution to k_A from the 'uncatalysed' or 'solvent' catalysed reaction pathway (k_2). Moreover, the high value of the d/c ratio calculated for each reaction accounts for our failing to observe amine catalysis in the reactions of 2-methoxy-3-nitrothiophene with either PYR or PIP in methanol which previously had been carried out in the absence of buffers and henceforth at high [MeO$^-$]/[Am] ratios. In such a situation the pyrrolidine catalysis is not observable because, under the experimental conditions adopted, $k_3^{MeO}[MeO^-] \gg k_{-1}$ and the kinetic constants

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* In principle, as in the case of compound (1a),[2a] the effect of methoxide ion concentration could have been studied by adding sodium methoxide from the outside, but for the more reactive substrates (1b-d) this would involve the competitive formation of Meisenheimer-type adducts. The reactions of compounds 1b, c with piperidine in methanol at 293.15 K had been studied without adding a compensating electrolyte.[2b]

Table 2. Apparent kinetic constants[a] for the reaction of 2-methoxy-3-nitrothiophene (**1a**) with PYR in methanol at 298.15 K

$[PYR]_{eff.}$[b]	$[PYRH^+]$	$10^6[MeO^-]$[c]	$10^3 k_A$	$10^3 k_{calc.}$[d]
0.0202	0.0100	4.84	1.48	1.53
0.0202	0.00800	6.05	1.56	1.58
0.0202	0.00600	8.07	1.68	1.67
0.0202	0.00400	12.1	1.86	1.81
0.0202	0.00300	16.1	1.99	1.92
0.0202	0.00200	23.9	2.14	2.08
0.0202	0.00100	46.2	2.38	2.35
0.0200	0.000200	141	2.52	2.67
0.0101	0.0100	2.42	0.972	1.03
0.0152	0.0100	3.65	1.30	1.32
0.0252	0.0100	.6.04	1.67	1.68
0.0303	0.0100	7.26	1.80	1.81
0.0404	0.0100	9.68	1.99	2.00
0.0606	0.0100	14.5	2.18	2.24
0.101	0.0100	2.42	2.42	2.46
0.202	0.0100	4.82	2.64	2.67

[a] Kinetic constants ($dm^3 mol^{-1}s^{-1}$) are accurate to within ±3%. Ionic strength kept constant (0.01 mol dm^{-3}) by addition of $NaClO_4$. [b] The stoicheiometric concentrations have been corrected, when necessary, for the amount consumed in reaction with methanol. [c] Values calculated using K_b^{PYR} 2.40x10^{-6} (see ref. 5). [d] Values calculated by eqn. 8.

Table 3. Apparent kinetic constants[a] for the reaction of methyl 2-methoxy-3-nitrothiophene-5-carboxylate (**1b**) with PYR in methanol at 298.15 K

$[PYR]_{eff.}$[b]	$[PYRH^+]$	$10^6[MeO^-]$[c]	$10^2 k_A$	$10^2 k_{calc.}$[d]
0.0101	0.0101	2.40	3.60	3.64
0.0101	0.00808	3.00	3.95	3.96
0.0101	0.00606	4.00	4.37	4.41
0.0101	0.00404	5.99	5.15	5.10
0.0101	0.00303	7.97	5.66	5.61
0.0101	0.00202	11.9	6.28	6.30
0.0101	0.00101	23.4	7.30	7.28
0.0101	0.000808	28.9	7.50	7.53
0.0101	0.000606	37.5	7.75	7.80
0.0100	0.000404	52.8	8.05	8.08
0.00505	0.0101	1.20	2.19	2.29
0.00606	0.0101	1.44	2.54	2.61
0.00707	0.0101	1.68	2.84	2.90
0.00808	0.0101	1.92	3.14	3.17
0.00909	0.0101	2.16	3.39	3.42
0.0121	0.0101	2.87	4.04	4.03
0.0152	0.0101	3.61	4.64	4.54
0.0202	0.0101	4.80	5.34	5.17

[a-d] As in Table 2.

Table 4. Apparent kinetic constants[a] for the reaction of 5-acetyl-2-methoxy-3-nitrothiophene (**1c**) with PYR in methanol at 298.15 K

$[PYR]_{eff.}$[b]	$[PYRH^+]$	$10^5[MeO^-]$[c]	10^2k_A	$10^2k_{calc.}$[d]
0.00502	0.0101	0.120	5.80	5.79
0.00500	0.00800	0.150	6.01	6.43
0.00500	0.00600	0.200	7.25	7.38
0.00500	0.00400	0.300	8.87	8.95
0.00500	0.00300	0.399	10.2	10.2
0.00498	0.00200	0.596	12.1	11.9
0.00498	0.00100	1.18	14.8	14.7
0.00498	0.000800	1.47	15.5	15.5
0.00496	0.000600	1.92	16.3	16.4
0.00494	0.000400	2.77	17.3	17.3
0.00202	0.0100	0.0485	2.82	2.82
0.00303	0.0100	0.0727	3.96	3.95
0.00404	0.0100	0.0969	5.18	4.94
0.00603	0.0100	0.145	6.68	6.58
0.00800	0.0100	0.192	7.98	7.88

[a-d] As in Table 2.

Table 5. Apparent kinetic constants[a] for the reaction of 2-methoxy-5-methyl-3-nitrothiophene (**1d**) with PYR in methanol at 298.15 K

$[PYR]_{eff.}$[b]	$[PYRH^+]$	$10^6[MeO^-]$[c]	10^2k_A	$10^2k_{calc.}$[d]
0.00400	0.0100	0.960	1.73	1.72
0.00600	0.0100	1.44	2.23	2.25
0.0100	0.0100	2.40	2.92	3.01
0.0150	0.0100	3.60	3.53	3.62
0.0200	0.0100	4.80	3.97	4.03
0.0300	0.0100	7.19	4.46	4.54
0.0400	0.0100	9.59	4.71	4.84
0.0600	0.0100	14.4	5.02	5.19
0.100	0.0100	23.9	5.40	5.51
0.0200	0.00800	5.99	4.12	4.12
0.0200	0.00600	7.99	4.26	4.26
0.0200	0.00400	12.0	4.54	4.49
0.0200	0.00300	15.9	4.69	4.66
0.0200	0.00200	23.7	4.95	4.92
0.0199	0.00100	45.8	4.95	5.31
0.00200	0.0100	0.480	0.957	0.999
0.00300	0.0100	0.720	1.31	1.38
0.00500	0.0100	1.20	1.89	2.02
0.00800	0.0100	1.92	2.54	2.67
0.00200	0.00100	4.77	2.47	2.54
0.00400	0.00100	9.49	3.59	3.57
0.00600	0.00100	14.2	4.15	4.14
0.00998	0.00100	23.4	4.53	4.73
0.00200	0.00200	2.39	1.81	1.82
0.00400	0.00600	1.60	1.96	1.94
0.00600	0.00600	2.40	2.48	2.52
0.00200	0.00600	0.800	1.14	1.16

[a-d] As in Table 2.

Table 6. Apparent kinetic constants[a] for the reaction of 2-methoxy-3-nitrothiophene (**1a**) with PIP in methanol at 298.15 K

$[PIP]_{eff.}$[b]	$[PIPH^+]$	$10^4[MeO^-]$[c]	$10^4 k_A$	$10^4 k_{calc.}$[d]
0.204	0.00994	0.309	1.64	1.71
0.204	0.00745	0.411	1.89	1.93
0.204	0.00497	0.612	2.32	2.32
0.306	0.00994	0.463	2.21	2.32
0.306	0.00745	0.615	2.54	2.58
0.306	0.00497	0.913	3.05	3.03
0.408	0.00994	0.616	2.70	2.82
0.408	0.00745	0.818	3.06	3.11
0.408	0.00497	1.21	3.68	3.58
0.510	0.00994	0.769	3.15	3.24
0.510	0.00745	1.02	3.54	3.54
0.510	0.00497	1.50	4.17	4.02
0.203	0.0100	0.306	1.63	1.70
0.203	0.00800	0.381	1.82	1.87
0.203	0.00600	0.506	2.15	2.12
0.203	0.00400	0.752	2.62	2.56
0.203	0.00300	0.989	2.99	2.92
0.203	0.00200	1.43	3.56	3.49
0.203	0.00100	2.46	4.38	4.42
0.203	0.000800	2.83	4.56	4.67
0.203	0.000600	3.29	4.76	4.94
0.203	0.000400	3.88	4.96	5.22
0.305	0.0100	0.458	2.22	2.31
0.406	0.0100	0.609	2.68	2.81
0.508	0.0100	0.761	3.12	3.23
0.610	0.0100	0.913	3.51	3.58
0.710	0.0100	1.06	3.91	3.89
0.812	0.0100	1.21	4.16	4.16
0.914	0.0100	1.36	4.39	4.39
1.020	0.0100	1.52	4.60	4.60
0.304	0.00300	1.46	3.84	3.68
0.406	0.00400	1.48	4.05	3.85
0.508	0.00500	1.49	4.17	4.01
0.609	0.00600	1.50	4.29	4.14
0.710	0.00700	1.50	4.38	4.26
0.812	0.00800	1.50	4.50	4.38
0.914	0.00900	1.51	4.57	4.49

[a,b,d] As in Table 2. [c] Values calculated using K_b^{PIP} 1.51 x 10^{-6} (see ref. 5).

Table 7. Apparent kinetic constants[a] for the reaction of methyl 2-methoxy-3-nitrothiophene-5-carboxylate (**1b**) with PIP e in methanol at 298.15 K

$[PIP]_{eff.}$[b]	$[PIPH^+]$	$10^6[MeO^-]$[c]	$10^3 k_A$	$10^3 k_{calc.}$[d]
0.0204	0.0102	3.02	1.34	1.34
0.0204	0.00816	3.77	1.55	1.51
0.0204	0.00612	5.03	1.78	1.78
0.0204	0.00408	7.53	2.35	2.31
0.0204	0.00306	10.0	2.84	2.80
0.0204	0.00204	15.0	3.77	3.70
0.0204	0.00102	29.3	5.88	5.77
0.0204	0.000816	36.1	6.65	6.56
0.0204	0.000612	46.7	7.54	7.60
0.0203	0.000408	64.9	8.80	9.02
0.0408	0.0102	6.04	2.35	2.49
0.0612	0.0102	9.05	3.32	3.49
0.0816	0.0102	12.1	4.20	4.37
0.102	0.0102	15.1	5.00	5.15
0.122	0.0102	18.0	5.86	5.83
0.163	0.0102	24.1	7.05	7.03
0.204	0.0102	30.1	8.30	8.01
0.0408	0.00408	15.0	4.25	4.10
0.0612	0.00612	15.1	4.55	4.47
0.0816	0.00816	15.1	4.74	4.82

[a-d] As in Table 6.

Table 8. Apparent kinetic constants[a] for the reaction of 5-acetyl-2-methoxy-3-nitrothiophene (**1c**) with PIP in methanol at 298.15 K

$[PIP]_{eff.}$[b]	$[PIPH^+]$	$10^5[MeO^-]$[c]	$10^3 k_A$	$10^3 k_{calc.}$[d]
0.0204	0.0100	0.308	2.62	2.70
0.0204	0.00800	0.385	3.03	3.19
0.0204	0.00600	0.513	3.98	3.97
0.0204	0.00400	0.768	5.27	5.40
0.0204	0.00300	1.02	6.75	6.70
0.0204	0.00200	1.53	8.96	8.93
0.0204	0.00100	2.99	14.0	13.7
0.0204	0.000800	3.67	15.6	15.3
0.0204	0.000600	4.75	16.7	17.4
0.0203	0.000400	6.59	20.1	20.0
0.0306	0.0100	0.462	3.70	3.89
0.0408	0.0100	0.616	4.82	4.99
0.0510	0.0100	0.769	5.83	6.01
0.0612	0.0100	0.923	6.72	6.96
0.0714	0.0100	1.08	7.81	7.84
0.0816	0.0100	1.23	8.83	8.66
0.0918	0.0100	1.38	9.45	9.43
0.102	0.0100	1.54	10.6	10.2

[a-d] As in Table 6.

Table 9. Apparent kinetic constants[a] for the reaction of 2-methoxy-5-methyl-3-nitrothiophene (**1d**) with PIP in methanol at 298.15 K

$[PIP]_{eff.}$[b]	$[PIPH^+]$	$10^4[MeO^-]$[c]	$10^4 k_A$	$10^4 k_{calc.}$[d]
0.0707	0.00717	0.149	2.43	2.44
0.0808	0.00819	0.149	2.50	2.57
0.0909	0.00922	0.149	2.58	2.69
0.101	0.0102	0.149	2.67	2.82
0.0707	0.0102	0.105	2.03	2.09
0.0808	0.0102	0.119	2.25	2.34
0.0909	0.0102	0.134	2.44	2.58
0.0404	0.00410	0.148	2.17	2.04
0.0505	0.00512	0.148	2.22	2.18
0.0606	0.00614	0.149	2.33	2.31
0.0404	0.0102	0.0598	1.26	1.27
0.0505	0.0102	0.0747	1.49	1.56
0.0606	0.0102	0.0896	1.75	1.83
0.103	0.00800	0.194	3.10	3.16
0.103	0.00600	0.258	3.58	3.59
0.103	0.00400	0.385	4.45	4.33
0.103	0.00300	0.510	5.21	4.98
0.103	0.00200	0.749	6.35	6.02
0.103	0.00100	1.37	7.97	7.92
0.103	0.000800	1.62	8.53	8.47
0.103	0.000600	1.95	9.05	9.08
0.103	0.000400	2.42	9.57	9.77
0.103	0.000200	3.06	10.1	10.5
0.154	0.0102	0.227	3.83	3.90
0.206	0.0102	0.304	4.68	4.80
0.258	0.0102	0.380	5.45	5.55
0.309	0.0100	0.464	6.24	6.22
0.412	0.0100	0.618	7.24	7.28
0.515	0.0100	0.772	8.04	8.10
0.618	0.0100	0.924	8.83	8.76
0.721	0.0100	1.08	9.44	9.30
0.824	0.0100	1.23	9.89	9.75
0.927	0.0100	1.38	10.2	10.1
1.03	0.0100	1.53	10.6	10.5

[a-d] As in Table 6.

obtained pertain to the 'plateau' region. On the other hand, the piperidine catalysis is not detectable owing to the numerical dominance of the methoxide ion catalysis.

According to the catalysis mechanism followed the c and d parameters of equation (8) could correspond either to k_{3p}^{Am}/k_{-1} and k_{3p}^{MeO}/k_{-1}, respectively [equation (5)], or to $k_{3p}^{Am}k_4^{AmH}/k_{-3p}^{AmH}k_{-1}$ and $k_{3p}^{MeO}k_4^{MeOH}/k_{-3p}^{MeOH}k_{-1}$, respectively [equation (7)]. Consistently with what was previously proposed[1-3] for the reactions with piperidine in methanol of compounds (**1a-d**), it is possible to show that all the reactions considered in this work are catalysed through the SB-GA mechanism.

In fact, equation (3) can be transformed[3] into equation (10)

$$k_{-3p} = k_{3p}^{MeO}K_s/K_a^{YH} + k_{3p}^{Am}K_a^{AmH}[AmH^+]/K_a^{YH} \tag{10}$$

Table 10. Results of least-squares fitting[a,b] to equation 8 of apparent second-order kinetic constants (k_A) for the piperidino- and pyrrolidino- substitution of **1a-d** in methanol at 298.15 K

Compound	Amine	$10^3(a \pm s_a)$ $dm^3mol^{-1}s^{-1}$	$c \pm s_c$ dm^3mol^{-1}	$d \pm s_d$ dm^3mol^{-1}	d/c
1a	PYR	2.91 ± 0.05	36.7 ± 1.4	74000 ± 9000	2000
1b	PYR	89.1 ± 0.9	25.5 ± 1.9	181000 ± 11000	7100
1c	PYR	200 ± 2	27.4 ± 2.2	22300 ± 11000	8100
1d	PYR	6.07 ± 0.11	69.3 ± 4.8	122000 ± 11000	1800
1a	PIP	0.803 ± 0.023	0.658 ± 0.031	4440 ± 300	6700
1b	PIP	18.0 ± 0.7	1.72 ± 0.11	14900 ± 1000	8700
1c	PIP	32.8 ± 1.2	0.878 ± 0.117	23300 ± 1800	27000
1d	PIP	1.48 ± 0.02	1.22 ± 0.04	7460 ± 260	6100

[a] As in Table 1. [b] The data were computer-optimized by the constraint $b = 0$; without this constraint the program did not converge or gave unacceptable regression parameters.

where K_s represents the autoprotolysis constant of methanol (at 298.15 K, pK_s 16.92),[6] K_a^{YH} is the acid dissociation constant of **YH** (Scheme 1) and K_a^{AmH} is the acid dissociation constant of the conjugate acid of the amine. Since the deprotonation of **YH** by MeO⁻ is diffusion controlled or nearly so (lower limit for k_{3p}^{MeO} 10^9) and assuming $pK_a^{YH} \cong 8^*$ for both the amines, we have

$$k_{3p}^{MeO}K_s/K_a^{YH} = 10^{-16.92} \, 10^9/10^{-8} = 1.20 \text{ and } k_{-3p} > 1.20$$

An upper limit for k_4 can be estimated from the decomposition rate constants, k_r, of Meisenheimer-type adducts (3) obtained by reacting compounds (**1a-d**) with sodium methoxide in methanol[7] (Scheme 2: at 293.15 K, k_1 2.2×10^{-4}, 1.06×10^{-3}, 1.98×10^{-3} and 6.3×10^{-5}, for X = H, CO$_2$Me, Ac and Me, respectively).

3
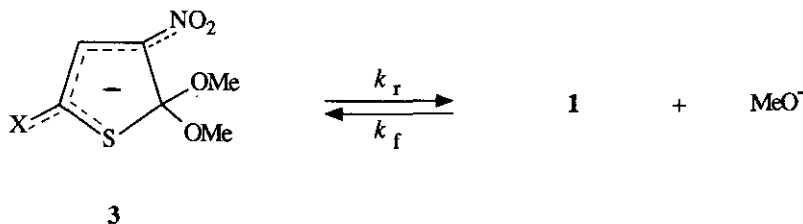
Scheme 2

Since the developing resonance between the aminogroup and the aromatic ring in the reaction pathway leading to (2) (Scheme 1) is presumably greater than that developing on going from (3) to (2) we assume for the k_4/k_r ratio the upper limit of 20. It is evident that within the limits established for k_4 and k_{-3p}, $k_4 \ll k_{-3p}$, for all the

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* Estimated by taking into accounts the acidifying effect[3] of the nitroaryl moiety of **YH** on pK_a of piperidinium or of pyrrolidinium ion.

compounds studied and as a consequence the catalysis observed occurs through the SB-GA mechanism: moreover, the d parameter of equation (8) corresponds to $k_{3p}^{MeO}k_4^{MeOH}/k_{-3p}^{MeOH}k_{-1} = K_a^{YH}k_4^{MeOH}/K_sk_{-1}$.

If one assumes that the decomposition rates of **YH** into reactants, k_{-1}, and the dissociation constants, K_a^{YH}, are not very different for the two amines, the $(k_4^{MeOH})_{PYR}/(k_4^{MeOH})_{PIP}$ ratios can be calculated as 17, 12, 9.6 and 16, for X = H, CO_2Me, Ac and Me, respectively. The corresponding k_4^{PYRH}/k_4^{PIPH} are 56, 15, 31 and 57, respectively. These results suggest that the general base-catalysed product-forming step is controlled by the ring size of the cyclic amine. As also shown by molecular models this effect arises from conformational factors which apparently produce an additional steric compression in the reaction area for the bulkier amine.

The Hammett-type correlation of logarithmic kinetic constants pertaining to the various steps of the reaction mechanism with σ_x^- substituent constants,[8] gave for compounds **1a-c** the following results

$$\begin{aligned}
(\log k_1)_{PYR} &= -2.54 + 2.14\,\sigma_x^- & (r\ 0.9996) \\
(\log k_1)_{PIP} &= -3.00 + 1.90\,\sigma_x^- & (r\ 1.000) \\
\log (k_4^{MeOH}K_a^{YH}/K_sk_{-1})_{PYR} &= 4.87 + 0.558\,\sigma_x^- & (r\ 0.9997) \\
\log (k_4^{MeOH}K_a^{YH}/K_sk_{-1})_{PIR} &= 3.64 + 0.813\,\sigma_x^- & (r\ 0.9940)
\end{aligned}$$

The ρ_1 values calculated (2.14 and 1.90) are consistent with previous evidence[8] concerning the interactions between the substituent at the C-5 carbon atom (a *para*-like position) and the leaving group (here, OMe); however, the small number of data points and the statistical uncertainty of d and c parameters prevents a deeper analysis of regression parameters.

The case of compound (**1d**) with a methyl substituent at C-5 is worth of a separate discussion. The reactivity ratios $(k_1)_{1d}/(k_1)_{1a}$, 2.0 and 1.8, for pyrrolidine and piperidine, respectively, confirm that actually a methyl group in a *para*-like position with respect to the reaction centre can exert a weakly activating effect in a S_NAr reaction.[7b,9] As a matter of fact, because of the polarizability of carbon-hydrogen bonds the methyl group satisfies the electronic demand of the reaction and behaves as a weakly electron-attracting group! Therefore this substituent can not be included in the Hammett-type correlations where traditionally it is considered to be an electron-repelling substituent and thus it would require a negative Hammett substituent constant.

EXPERIMENTAL

Synthesis and Purification of Compounds.- Compounds (**1a**,[10] **1b**,[2b] **1c**,[10] **1d**[7b]), piperidine,[11] pyrrolidine,[4] piperidinium perchlorate,[5] pyrrolidinium perchlorate[5] and methanol[12] were prepared and/or purified according to the methods reported.

Kinetic Measurements.- The kinetics were followed spectrophotometrically as previously described.[13] The concentrations used were 10^{-4} - 4×10^{-4} mol dm^{-3} for substrates and those reported in Tables for piperidine, pyrrolidine, piperidinium perchlorate and pyrrolidinium perchlorate.

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