

Catalysis in Aromatic Nucleophilic Substitution. Part 10.¹ Reactions of Piperidine with 3-Methoxy-5-methyl-2-nitrothiophene in Methanol

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The kinetics of the title reaction has been studied as a function of amine and methoxide-ion concentrations. The reaction is catalysed by methoxide through an SB catalysis mechanism. A comparison with the results previously obtained for 2-methoxy-3-nitrothiophene shows that the mechanistic pattern is not significantly affected by the position of the reaction centre with respect to the sulphur atom of the thiophene ring.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

Although the base catalysis of S_NAr reactions involving amine nucleophiles has been extensively studied,² the detailed mechanism of the base-catalysed product-forming reaction pathway is still an open question.³

A representative situation is shown in Scheme 1 by the reactions of 5-substituted 2-methoxy-3-nitrothiophenes **1a–c** with piperidine in methanol, which are subjected



to base catalysis.⁴ Owing to the basic ionization of piperidine in methanol, the methanolic reaction solutions contain both the bases piperidine (PIP) and methoxide (MeO⁻). With reference to Scheme 1, the general expression for the apparent second-order kinetic constant, k_A ,

in terms of rate coefficients for specific steps, is eqn. (1) with k_{3p} , k_{-3p} and k_4 defined by eqns. (2)–(4).

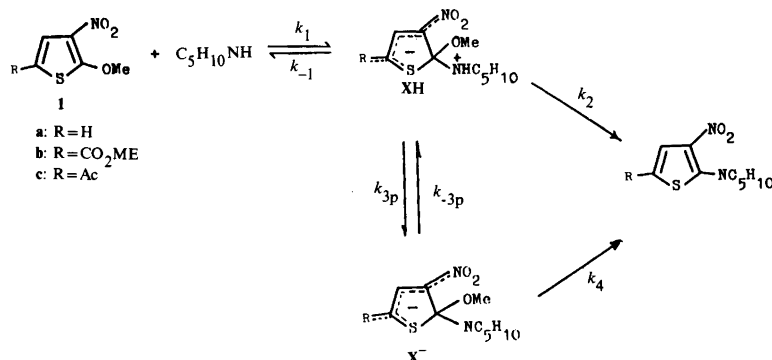
$$k_A = [k_1 k_2 (k_{-3p} + k_4) + k_1 k_{3p} k_4] / [(k_{-1} + k_2) \times (k_{-3p} + k_4) + k_{3p} k_4] \quad (1)$$

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

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

$$k_4 = k_4^{\text{MeOH}} + k_4^{\text{PIPH}^+} [\text{PIPH}^+] \quad (4)$$

The coefficients $k_{3p}^{\text{MeO}^-}$ and k_{3p}^{PIP} refer to the deprotonation of XH by MeO⁻ and by piperidine, respectively, k_{-3p}^{MeOH} and $k_{-3p}^{\text{PIPH}^+}$ refer to the protonation of X⁻ by the solvent and by PIPH⁺, respectively, and k_4^{MeOH} refers to uncatalysed or solvent-assisted leaving-group expulsion whereas $k_4^{\text{PIPH}^+}$ allows for the possibility of general-acid



Scheme 1.

catalysed leaving-group departure by the protonated amine.

Two main interpretations of the base-catalysed step(s) are currently advocated: one is a rate-limiting deprotonation⁵ of XH ($k_4 \gg k_{-3p}$) and the other is the SB-GA mechanism,⁵ that is, a fast equilibrium between XH and X⁻ followed by a rate-limiting general-acid-catalysed detachment of the nucleofuge ($k_4 \ll k_{-3}$).

It can be shown that in both cases the formal dependence of k_A on [MeO⁻] and [PIP] is expressed by a relationship such as eqn. (5), where $x_1 = [\text{PIP}]_{\text{eff.}}$ * and $x_2 = [\text{MeO}^-]$, and that the two mechanisms for base catalysis cannot be distinguished experimentally.

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

For the reactions of compounds **1b** and **1c** it was possible to estimate k_{-3p} and k_4 coefficients and to show^{4b} that is $k_4 \ll k_{-3p}$. Thus, for these compounds, the catalysis observed occurs through the SB-GA mechanism. In the case of **1a**, owing to the dominance of catalysis by methoxide ion, the catalysis by piperidine could not be detected,^{4a} the catalysis mechanism apparently consisting of a rapid equilibrium deprotonation of XH followed by a rate-limiting *non*-catalysed expulsion of the leaving group (SB mechanism⁵).

We now report on the results of a kinetic study of the reaction of 3-methoxy-5-methyl-2-nitrothiophene (**2**) with piperidine in methanol, at 20°C. In this substrate the leaving group (methoxide) and the activating nitro group are hyper-*ortho* related⁶ as in compounds **1a-c**, but here the reaction centre is in a β -position. The aim of this study was to gain information on the catalysis mechanism as well as to investigate the dependence of the mechanistic pattern on the relative position of the heteroatom and of the reaction centre in the thiophene ring. In compound **2** the 5-position, which is quasi-*para*⁶ with respect to the nitro group, is 'occupied' by a methyl group in order to eliminate the possibility of concurrent methoxide attack at this α -position, as observed for 3-methoxy-2-nitrothiophene.⁷

Results and discussion

Compound **2** gave the corresponding substitution product, 5-methyl-2-nitro-3-piperidin-1-ylthiophene in high yield (>95%) on treatment with piperidine in methanol, as indicated by TLC and UV-VIS (200–450 nm) spectral analysis of the reaction mixtures at infinity.

The apparent second-order kinetic constants, k_A , for the piperidino-substitution of **2** in methanol at 20°C as a function of PIP and MeO⁻ concentrations are set forth in Table 1.

* The values of [PIP]_{eff.} represent piperidine concentrations corrected for the amount consumed in reaction with methanol.

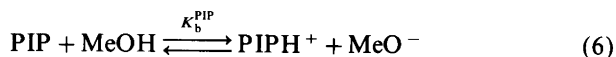
Table 1. Kinetic constants for the reaction of 3-methoxy-5-methyl-2-nitrothiophene (**2**) with piperidine in methanol at 20°C.

No.	[PIP]/ M	[MeONa]/ 10 ⁻³ M	[MeO ⁻]/ 10 ⁻³ M ^a	k_A / 10 ⁻⁴ M ⁻¹ s ⁻¹
1	0.104		0.868	1.28
2	0.156		1.06	1.54
3	0.208		1.23	1.72
4	0.260		1.37	1.83
5	0.312		1.51	1.94
6	0.416		1.74	2.07
7	0.520		1.94	2.19
8	0.624		2.13	2.28
9	0.780		2.38	2.37
10	0.104	1.25	1.70	2.16
11	0.208	1.25	2.00	2.42
12	0.312	1.25	2.26	2.45
13	0.416	1.25	2.47	2.60
14	0.520	1.25	2.67	2.66
15	0.416	2.50	3.39	3.00
16	0.416	3.75	4.43	3.31
17	0.416	6.25	6.70	3.64
18	0.416	12.5	12.7	4.07
19	0.416	25.0	25.1	4.36
20	0.208	1.32	2.06	2.41
21	0.208	2.65	3.13	2.94
22	0.208	5.30	5.57	3.59
23	0.208	7.95	8.13	3.93
24	0.208	10.6	10.7	4.12
25	0.208	15.9	16.0	4.34
26	0.208	21.2	21.3	4.58

^a Total sodium methoxide. Values calculated using K_b^{PIP} 7.3×10^{-6} (cf. Ref. 10).

An analysis of the kinetic data for the reactions carried out in the presence of sodium methoxide (entries 3, 11, 20–26 and 6, 13, 15–19 in Table 1) shows that, at constant PIP concentration, k_A increases with increasing methoxide-ion concentration, indicating base catalysis from this species. On the other hand k_A also increases with increasing PIP concentration in the absence of added sodium methoxide (entries 1–9).

Owing to the ionization equilibrium of PIP in methanol [eqn. (6)], the catalysis observed for this latter series of reactions could be related, in principle, to both bases, PIP and MeO⁻, present in the reaction mixture.



The catalysis law for the reactions studied should have (see above) the form of eqn. (7) where, depending on the

$$k_A = k_1(k_2 + k_{\text{PIP}}[\text{PIP}] + k_{\text{MeO}}[\text{MeO}^-]) / (k_{-1} + k_2 + k_{\text{PIP}}[\text{PIP}] + k_{\text{MeO}}[\text{MeO}^-]) \quad (7)$$

mechanism followed, k_{PIP} is equal to $k_{3p}^{\text{PIP}}/k_{-1}$ or to $k_{3p}^{\text{PIP}}k_4^{\text{PIPH}}/k_{-3p}^{\text{PIPH}}k_{-1}$ and k_{MeO} is equal to $k_{3p}^{\text{MeO}}/k_{-1}$ or to $k_{3p}^{\text{MeO}}k_4^{\text{MeOH}}/k_{-3p}^{\text{MeOH}}k_{-1}$.

We have fitted our kinetic data to eqn. (7) using a least-squares method⁸ and the results have shown that

there is no statistically significant contribution to k_A from either the solvent-assisted pathway for the decomposition of the intermediate (k_2) or from that catalysed by piperidine (k_{PIP}). Indeed, the data are optimized by the following values of the parameters involved: $k_2 = 0$, $k_{PIP} = 0$, $k_1 = (4.95 \pm 0.05) \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and $k_{MeO} = 436 \pm 13 \text{ dm}^3 \text{ mol}^{-1}$.

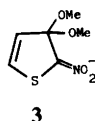
The apparent absence of general catalysis ($k_{PIP} = 0$) would exclude the SB-GA mechanism but would be compatible with an SB mechanism.⁵

Eqn. (3) can be rearranged⁵ as eqn. (8), where K_s is the

$$k_{-3p} = (k_{3p}^{MeO} K_s / K_a^{XH}) + (k_{3p}^{PIP} K_a^{PIPH} [PIPH^+] / K_a^{XH}) \quad (8)$$

autoprotolysis constant of methanol (at 20°C, $K_s = 1.38 \times 10^{-17}$),⁹ K_a^{PIPH} is the acid-dissociation constant of piperidinium ion in methanol ($pK_b^{PIP} = 5.14$)¹⁰ and K_a^{XH} is the acid-dissociation constant of (XH)₂. Since the deprotonation of (XH)₂ by MeO⁻ is diffusion controlled, or nearly so, (lower limit for $k_{3p}^{MeO} = 10^9$) and pK_a^{XH} can be estimated to be 8,* $k_{-3p} > 10^9 \times 1.38 \times 10^{-17} / 10^{-8}$, that is, $k_{-3p} > 1.38$.

An upper limit of k_4 for **2** can be estimated⁵ to be ca. 0.1 s^{-1} from the k_r value for the decomposition of Meisenheimer-type adduct **3** (calculated¹¹ $k_r = 1.32 \times 10^{-2} \text{ s}^{-1}$ at 20°C).



It is clear that k_4 can never approach k_{-3p} , the real situation being $k_4 \ll k_{-3p}$; thus the catalysis observed occurs through an SB-GA mechanism with an undetectable contribution from acid catalysis by PIPH⁺, that is, through an SB mechanism, and k^{MeO} is equal to $k_{3p}^{MeO} k_4^{MeOH} / k_{-3p}^{MeOH} k_{-1}$ (see above).

Since the position of equilibrium (9) does not depend⁵ on the base used and $(k_{3p}^{MeO} k_4^{MeOH} / k_{-3p}^{MeOH} k_{-1})_{1a} =$



$(K_a^{XH} k_4^{MeOH} / K_s k_{-1})_{1a} = 489$,^{4a} one obtains $(K_a^{XH} k_4^{MeOH} / K_s k_{-1})_2 / (K_a^{XH} k_4^{MeOH} / K_s k_{-1})_{1a} = 436 / 489 = 0.9$. As it is reasonable that K_a^{XH} values for the two intermediates (XH)₂ and (XH)_{1a} are very similar, the k_4^{MeOH} / k_{-1} ratios for the two compounds **2** and **1a** should be very similar, too. The k_4^{MeOH} and k_{-1} coefficients refer to the methanol-assisted leaving-group detachment and to the decomposition of intermediate XH to the reactants, respectively. These two processes are very similar to each other in that both imply decomposition of a Meisenheimer-like intermediate (XH or X⁻). Thus, as it is reasonable to assume¹¹

that $(k_{-1})_2 > (k_{-1})_{1a}$, on the same grounds $(k_4)_2$ should be greater than $(k_4)_{1a}$. Owing to a balance between the values of these parameters for each substrate, the mechanistic pattern is not significantly affected by the position of the reaction centre with respect to the sulphur atom.

Experimental

Compound **2** was synthesized by nitration with nitric acid ($d = 1.4$) of 4-methoxy-2-methylthiophene dissolved in acetic anhydride, at -5 to 0°C . The mixture was poured onto crushed ice and extracted with ether. The ethereal extracts were washed with water, dried with sodium sulphate and evaporated. The residue was chromatographed on a column of silica gel (eluant benzene). Compound **2** was crystallized from methanol, m.p. 138 – 139°C (Anal. C₆H₇NO₃S: C, H, N, S). 5-Methyl-2-nitro-3-piperidin-1-ylthiophene (m.p. 47 – 48°C , from ligroin. Anal. C₁₀H₁₄N₂O₂S: C, H, N, S) was prepared according to a general method¹² and had $\lambda_{\text{max}} = 425 \text{ nm}$ ($\log \epsilon = 4.11$) in methanol.

The kinetics were followed as previously described.¹³ The concentrations employed were $3 \times 10^{-4} \text{ M}$ for the substrate and those indicated in Table 1 for piperidine and sodium methoxide. Kinetic constants are accurate to within $\pm 3\%$.

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* Estimated by taking into account the acidifying effect⁵ of the nitroaryl moiety of (XH)₂ on the pK_a of piperidinium ion.