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\(_N\)-Ar 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).

\[
k_A = \left[ k_{1} k_{2} (k_{-3p} + k_4) + k_{3p} k_4 \right] / \left[ (k_{-1} + k_2) \times (k_{-3p} + k_4) \right]
\]

(1)

\[
k_{3p} = k_{3p}^{MeO-} [MeO-] + k_{3p}^{PIP} [PIP]
\]

(2)

\[
k_{-3p} = k_{-3p}^{MeOH} + k_{-3p}^{PIP} [PIPH^+]
\]

(3)

\[
k_4 = k_4^{MeOH} + k_4^{PIP} [PIPH^+]
\]

(4)

The coefficients \(k_{3p}^{MeO-}\) and \(k_{3p}^{PIP}\) refer to the deprotonation of XH by MeO\(^-\) and by piperidine, respectively, \(k_{-3p}^{MeOH}\) and \(k_{-3p}^{PIP}\) 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 \(k_4^{PIP}\) allows for the possibility of general-acid

\[\text{Scheme 1.}\]


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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 deprotonation\(^2\) of XH (\(k_4 \gg k_{-3p}\)) and the other is the SB-GA mechanism,\(^3\) that is, a fast equilibrium between XH and X\(^-\) followed by a rate-limiting general-acid-catalysed detachment of the nucleofuge (\(k_4 \ll k_{-1}\)).

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 \(x_1 = [\text{PIP}]_{av}\) and \(x_2 = [\text{MeO}^-]\), and that the two mechanisms for base catalysis cannot be distinguished experimentally.

\[
k_A = a(b + cx_1 + dx_2)/(1 + b + cx_1 + dx_2)
\]  
(5)

For the reactions of compounds 1b and 1d it was possible to estimate \(k_{-3p}\) and \(k_4\) coefficients and to show,\(^4\) that \(k_4 \ll k_{-3p}\). 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,\(^5\) the catalysis mechanism apparently consisting of a rapid equilibration of XH followed by a rate-limiting non-catalysed expulsion of the leaving group (SB mechanism\(^6\)).

We now report on the results of a kinetic study of the reaction of 3-methoxy-5-methyl-2-nitrophenol (2) with piperidine in methanol at 20°C. In this substrate the leaving group (methoxide) and the activating nitro group are hyper-ortho related\(^6\) 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-nitrophenol.\(^7\)

### Results and discussion

Compound 2 gave the corresponding substitution product, 5-methyl-2-nitro-3-piperidin-1-yli-thiophene 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 piperidine-substitution of 2 in methanol at 20°C as a function of PIP and MeO\(^-\) concentrations are set forth in Table 1.

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

<table>
<thead>
<tr>
<th>No.</th>
<th>[PIP] (\times 10^{-3}) M</th>
<th>[MeONa] (\times 10^{-2}) M</th>
<th>[MeO(^-)] (\times 10^{-2}) M</th>
<th>(k_A) (\times 10^{-4}) M(^{-1}) s(^{-1})</th>
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* Total sodium methoxide. Values calculated using \(K_p\) \(7.3 \times 10^{-8}\) (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.

\[
PIP + MeOH \xrightleftharpoons{\text{K}}^{\text{MeOH}} \text{PIP}^+ + MeO^- \quad (6)
\]

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_{2p}[\text{PIP}] + k_{MeO}[\text{MeO}^-])(k_{-1}

+ k_1 + k_{2p}[\text{PIP}] + k_{MeO}[\text{MeO}^-])\quad (7)

mechanism followed, \(k_{2p}\) is equal to \(k_{2p}^{\text{MeOH}}/k_{2p}\) or to \(k_{2p}^{\text{MeOH}}\) \(+ k_{2p}^{\text{MeOH}}k_{MeO}k_{MeOH}k_{MeOH}\) and \(k_{MeO}\) is equal to \(k_{MeO}^{\text{MeO}}/k_{MeO}\) or to \(k_{MeO}^{\text{MeO}}\) \(+ k_{MeO}^{\text{MeO}}k_{MeO}k_{MeOH}k_{MeOH}\).

We have fitted our kinetic data to eqn. (7) using a least-squares method\(^8\) and the results have shown that

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\(^*\) The values of [PIP]\(_{av}\) represent piperidine concentrations corrected for the amount consumed in reaction with methanol.
there is no statistically significant contribution to \( k_4 \) from either the solvent-assisted pathway for the decomposition of the intermediate (\( k_2 \)) or from that catalysed by piperidine (\( k_{	ext{pip}} \)). Indeed, the data are optimized by the following values of the parameters involved: \( k_2 = 0, k_{	ext{pip}} = 0, k_1 = (4.95 \pm 0.05) \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \) and \( k_{\text{MOE}} = 436 \pm 13 \text{ dm}^3 \text{ mol}^{-1} \).

The apparent absence of general catalysis (\( k_{	ext{pip}} = 0 \)) would exclude the SB–GA mechanism but would be compatible with an SB mechanism.\(^5\)

Eqn. (3) can be rearranged\(^6\) as eqn. (8), where \( K_s \) is the autoxidation constant of methanol (at 20°C, \( K_s = 1.38 \times 10^{-17}, \)) \( K_s \) is the acid dissociation constant of piperidinium ion in methanol (\( pK_s^\text{pip} = 5.14 \))\(^10\) and \( K_{\text{XH}} \) is the acid dissociation constant of \((\text{XH})_2 \). Since the deporationation of \((\text{XH})_2 \) by MeO\(^-\) is diffusion controlled, or nearly so, (lower limit for \( k_{3p} \) = 100) and \( pK_{\text{XH}} \) can be estimated to be \( 8^* \) \( k_{3p} > 10^9 \times 1.38 \times 10^{-17} \times 10^{-4} \), that is, \( k_{3p} > 1.38 \).

An upper limit of \( k_4 \) for 2 can be estimated\(^5\) to be ca. 0.1 s\(^{-1}\) from the \( k_4 \) value for the decomposition of Meisenheimer-type adduct 3 (calculated\(^1\) \( k_4 = 1.32 \times 10^{-2} \text{ s}^{-1} \) at 20°C).

\[ k_{3p} = (K_{\text{MOE}} K_s K_{\text{XH}}) + (K_{3p} K_s K_{\text{PIPH}} P_{\text{PIPH}}^+ / K_s^\text{XH}) \] (8)

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 \( k_{\text{MOE}} \) is equal to \( k_{\text{MOE}}^\text{XH} K_s K_{\text{XH}} \) (see above).

When the position of equilibrium (9) does not depend\(^6\) on the base used and \((k_{\text{MOE}} K_s K_{\text{XH}} k_{-1})\) is = XH + BH\(^+\) \( \rightleftharpoons \) X\(^-\) + BH\(^+\) (9)

\( (K_{\text{XH}} K_s K_{\text{XH}} k_{-1}) = 489, 48 \) one obtains \((K_{\text{XH}} K_s K_{\text{XH}} k_{-1}) = 436/489 = 0.9 \). As it is reasonable that \( K_{\text{XH}} \) values for the two intermediates \((\text{XH})_2 \) and \((\text{XH})_2 \)\(^1\) should be very similar, the \( K_{\text{XH}} k_{-1} \) ratios of the two compounds 2 and 1a should be very similar, too. The \( K_{\text{MOE}} \) 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 assume\(^1\)

that \( \langle k_{-1} \rangle > \langle k_{-1} \rangle \), on the same grounds (\( k_4 \))\(^2\) should be greater than (\( k_4 \)). 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 (eluants benzene). Compound 2 was crystallized from methanol, m.p. 138–139°C (Anal. C\(_8\)H\(_8\)NO\(_3\)S: C, H, N, S). 5-Methyl-2-nitro-3-piperidinyl-1-thiophene (m.p. 47–48°C, from ligroin. Anal. C\(_{10}\)H\(_8\)N\(_2\)O\(_2\)S: C, H, N, S) was prepared according to a general method\(^12\) and had \( \lambda_{\text{max}} \) = 425 nm (log ε 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 ± 3%.

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\( ^* \) Estimated by taking into account the acidifying effect\(^1\) of the nitroaryl moiety of \((\text{XH})_2 \) on the pK\(_s\) of piperidinium ion.

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**References**


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