

THE REACTION OF 2-METHOXY-3-NITROTHIOPHENE WITH N-BENZYLMETHYLAMINE IN METHANOL*

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Dedicated to Professor Otto Exner on the occasion of his 65th birthday.

The kinetics of the title reaction has been studied in methanol as a function of amine and methoxide ion concentrations. The kinetic coefficients obtained point out that the reaction is catalysed by methoxide through a SB catalysis mechanism.

We have recently shown that the reactions of some 2-methoxy-3-nitro-5-R-thiophenes (*Ia–Ic*) with piperidine in methanol are subjected to general base catalysis¹. In the absence of bases added from the outside, the methanolic solutions of piperidine contain only the bases piperidine [PIP] and methoxide [MeO⁻], this one derived from the basic ionization of piperidine in methanol; of course the solvent methanol can be considered as a base, too. With reference to Scheme 1, the general expression for the apparent second-order kinetic constant, k_A , for the piperidino-substitution, in terms of rate coefficients for specific steps, is Eq. (1).

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

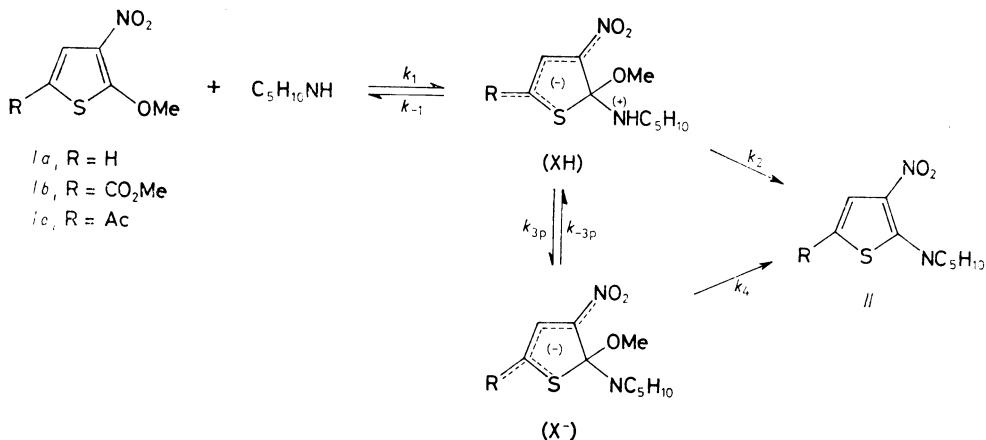
Equations (2)–(4) apply where k_{3p}^{MeO} and k_{3p}^{PIP} refer to deprotonation of (XH) by MeO⁻ and by PIP, respectively, k_{-3p}^{MeOH} and k_{-3p}^{PIPH} refer to the protonation of (X⁻) by the solvent and by PIPH⁺, respectively, and k_4^{MeOH} refers to uncatalyzed or solvent-assisted leaving group expulsion whereas k_4^{PIPH} allows for the possibility of general-acid catalyzed leaving group departure by the protonated amine.

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

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

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

* Part VIII in the series Catalysis in Aromatic Nucleophilic Substitution; Part VII: J. Chem. Soc., Perkin Trans. 2, 1981, 642.



SCHEME 1

Assuming either $k_4 \gg k_{-3p}$ (rate limiting deprotonation of (XH)) or $k_4 \ll k_{-3p}$ (specific base-general acid or SB-GA (ref.²) mechanism) leads to the same formal dependence of k_A on $[MeO^-]$ and $[PIP]$.

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

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

Although previously available evidence² seemed to indicate that the SB-GA mechanism was not a significant pathway in protic solvents, it has been shown¹ that for the piperidino-substitution in methanol of compounds (Ia–Ic) the expulsion of the very sluggish methoxy-leaving group is relatively slow compared with the rapidly established proton transfer equilibrium (i.e., $k_4 \ll k_{-3p}$) and that the k_4 step represents general-acid-catalysed leaving group departure.

The occurrence of SB-GA mechanism for base catalysis is a consequence of the thermodynamically favourable proton transfer from $PIPH^+$ to MeO^- .

We now report the results of a kinetic study of the reaction of 2-methoxy-3-nitrothiophene (Ia) with N-benzylmethylamine (BMA) in methanol, at 20°C. This study was undertaken to investigate the effect of nucleophile variation on the coefficients of the single steps of the overall S_NAr mechanism.

Indeed, depending on the catalysis mechanism, the lower basicity of BMA compared with PIP should reflect not only on k_1 and k_{-1} coefficients but also on the catalytic coefficient(s).

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

RESULTS AND DISCUSSION

Compound *Ia* gave the substitution product, 2-N-benzylmethylamino-3-nitrothiophene, in high yield (>95%) on treatment with BMA in methanol, as indicated by TLC and UV-visible (200–450 nm) spectral analysis of the reaction mixtures at infinity.

The apparent second-order kinetic constants, k_A , for the amino-substitution of *Ia* in methanol at 20°C as a function of BMA and MeO^- concentrations are summarized in Table I.

An analysis of the kinetic data for the reactions carried out in the presence of sodium methoxide added from the outside (items 10–15 in the Table) shows that, at constant BMA 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 BMA concentration in the absence of added sodium methoxide (items 1–9 in the Table).

Owing to the ionization equilibrium of BMA in methanol (Eq. (A)), the catalysis observed for this latter series of reactions could be related, in principle, to both bases, BMA and MeO^- , present in the reaction mixture.

TABLE I
Kinetic constants for the reactions of *Ia* with BMA, in methanol, at 20°C

No.	[BMA] mol l^{-1}	[MeONa] ^a mol l^{-1}	[MeO^-] ^b mol l^{-1}	k_A 10 ^{5c} $\text{l mol}^{-1} \text{s}^{-1}$	k_A 10 ^{5d} $\text{l mol}^{-1} \text{s}^{-1}$
1	0.1	—	2.1	2.14	2.45
2	0.15	—	2.57	2.82	2.90
3	0.2	—	2.96	3.06	3.26
4	0.3	—	3.63	3.7	3.82
5	0.4	—	4.19	4.08	4.25
6	0.485	—	4.66	4.75	4.59
7	0.6	—	5.14	4.9	4.92
8	0.8	—	5.93	5.6	5.42
9	0.99	—	6.6	6.16	5.81
10	0.104	0.00103	10.7	7.6	7.68
11	0.104	0.00154	15.7	9.21	9.21
12	0.104	0.00206	20.8	10.5	10.3
13	0.104	0.00309	31.0	11.6	11.6
14	0.104	0.00412	41.3	12.4	12.5
15	0.104	0.00618	61.9	13.5	13.5

^a Added sodium methoxide; ^b total methoxide ion; ^c kinetic constants are accurate within $\pm 3\%$; ^d values calculated by Eq. (10).



On the analogy with what has been observed in the reactions of piperidino-substitution of the same substrate in methanol³, one can assume, as a first approximation, $b = 0$ and $c = 0$. The catalysis law appropriate to this situation is Eq. (6),

$$k_A = k_1 k^* [\text{MeO}^-] / (1 + k^* [\text{MeO}^-]), \quad (6)$$

where $k^* = k_{3p}^{\text{MeO}}/k_{-1}$ or $k^* = k_{3p}^{\text{MeO}} k_4^{\text{MeOH}}/k_{-1} k_{-3p}^{\text{MeOH}}$ depending on which catalysis mechanism is operating.

In order to ascertain whether or not the experimental data follow Eq. (6), it is necessary to know exactly the concentrations of the methoxide ion derived from equilibrium (A).

Since the basic ionization constant of BMA in methanol is not known, we have used the following procedure to calculate MeO^- concentrations.

Inversion of both sides of Eq. (6) gives

$$1/k_A = 1/k_1 + 1/k_1 k^* [\text{MeO}^-]. \quad (7)$$

By using the kinetic data at constant $[\text{BMA}]$ (items 10–15 in the Table) for which the overall $[\text{MeO}^-]$ concentration can be assumed to be equal to that of the sodium methoxide added from the outside (see below), and by a least-square treatment of data, one obtains $1/k_1 = 6260 \pm 90 \text{ l}^{-1} \text{ mol s}$ and $1/k_1 k^* = 7 \cdot 10 \pm 0 \cdot 16 \text{ l}^{-2} \cdot \text{mol}^2 \text{ s}$, with a correlation coefficient $r = 0 \cdot 999$.

The excellent correlation obtained, besides providing reliable values for k_1 ($1 \cdot 60 \cdot 10^{-4} \text{ l mol}^{-1} \text{ s}^{-1}$) and k^* (882 l mol^{-1}), shows that k_2 and k_{3p}^{BMA} coefficients are really negligible, as assumed.

Equation (7) can be rearranged into Eq. (8)

$$k_A / (k_1 - k_A) = k^* [\text{MeO}^-] \quad (8)$$

and by the k_1 and k^* values previously obtained, it is possible to calculate the "theoretical" MeO^- concentrations corresponding to the k_A values observed for the reactions carried out in the absence of sodium methoxide added (items 1–9 in the Table).

The functional relation between $[\text{MeO}^-]$ and K_b (equilibrium (A)) is Eq. (9).

$$[\text{MeO}^-]^2 + K_b [\text{MeO}^-] - K_b [\text{BMA}] = 0 \quad (9)$$

Thus for a given K_b , one can calculate a series of MeO^- concentrations corresponding to the BMA concentrations used in the reactions of items 1–9 in the Table.

By giving K_b trial values and by using an iterative calculation program, we have obtained for K_b the "best" value of $4.4 \cdot 10^{-7} \text{ l}^{-1} \text{ mol}$ which corresponds to the least standard deviation of $[\text{MeO}^-]$ values calculated by Eq. (9) from those "observed" by means of Eq. (8). The $[\text{MeO}^-]$ values calculated for all the reactions (items 1–15) are reported in the Table (column 4).

Application of Eq. (8) to all the available kinetic data (n 15), with k_1 $1.60 \cdot 10^{-4} \text{ l} \cdot \text{mol}^{-1} \text{ s}^{-1}$, gives an intercept (0.0014 ± 0.0186) statistically not different from zero, a slope (863 ± 8) in excellent agreement with the k^* value calculated above and a very good correlation coefficient (r 0.9994).

As a matter of fact the "best" relationship which fits to our experimental data is Eq. (10).

$$k_A \cdot 10^4 = 1.60 (863 [\text{MeO}^-]) / (1 + 863 [\text{MeO}^-]) \quad (10)$$

The k_A values calculated by Eq. (10) are reported in the Table (column 6) and the corresponding plot is shown in Fig. 1.

In principle the phenomenological k^* parameter could correspond to either $k_{3p}^{\text{MeO}}/k_{-1}$ or $k_{3p}^{\text{MeO}}k_4^{\text{MeOH}}/k_{-3p}^{\text{MeOH}}k_{-1}$ (see above).

The absence of general catalysis ($k_{3p}^{\text{BMA}} = 0$) would allow one to exclude the SB-GA mechanism; however, we suggest that catalysis by amine is not detectable on account of the dominance of catalysis by methoxide ion and that the reaction is catalyzed through a *SB mechanism*.

In fact Eq. (11), analogous to Eq. (3), can be rearranged² into Eq. (12)

$$k_{-3p} = k_{-3p}^{\text{MeOH}} + k_{-3p}^{\text{BMAH}^+} [\text{BMAH}^+], \quad (11)$$

$$k_{-3p} = (k_{3p}^{\text{MeO}}K_s/K_a^{\text{XH}}) + (k_{3p}^{\text{BMA}}K_a^{\text{BMA}}[\text{BMAH}^+]/K_a^{\text{XH}}), \quad (12)$$

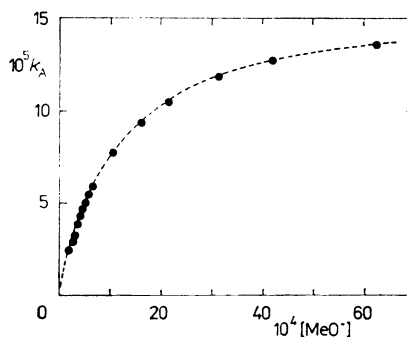
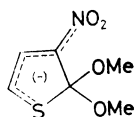


FIG. 1

Plot of apparent second-order kinetic constants k_A for the reaction of *Ia* with BMA in methanol at 20°C: (●) experimental values; dotted line, values calculated by Eq. (10)

where K_s is the autoprotolysis constant of methanol (at 20°C, K_s $1.38 \cdot 10^{-17}$) (ref.⁴) and K_a^{XH} is the acid dissociation constant of (XH). Since the deprotonation of XH by MeO^- is diffusion controlled or nearly so (lower limit for $k_{3p}^{\text{MeO}} \cdot 10^9$) and $\text{p}K_a^{XH}$ can be estimated to be 8*, $k_{-3p} > 10^9 \cdot 10^{-16.86}/10^{-8} = 1.38$

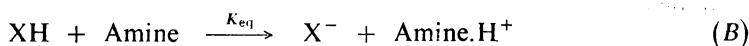
An upper limit of k_4 can be estimated to be $2.2 \cdot 10^{-3} \text{ s}^{-1}$ from k_r value for the decomposition of Meisenheimer-type adduct (III, k_r $2.2 \cdot 10^{-4} \text{ s}^{-1}$ at 20°C) (ref.⁵).



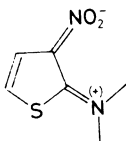
III

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 the SB-GA mechanism with a not detectable contribution from the acid catalysis by BMAH^+ .

Since the position of equilibrium (B) does not depend on the amine used and $(k_{3p}^{\text{MeO}} k_4^{\text{MeOH}} / k_{-1} k_{-3p}^{\text{MeOH}})_{\text{PIP}} = (K_a^{XH} k_4^{\text{MeOH}} / K_s k_{-1})_{\text{PIP}} = 489$ (ref.³) one obtains $(K_a^{XH} k_4^{\text{MeOH}} / K_s k_{-1})_{\text{BMA}} / (K_a^{XH} k_4^{\text{MeOH}} / K_s k_{-1})_{\text{PIP}} = 863/489$ and by assuming $(K_a^{XH})_{\text{BMA}} / (K_a^{XH})_{\text{PIP}} = (K_b)_{\text{PIP}} / (K_b)_{\text{BMA}} = (7.24 \cdot 10^{-6}) / (4.4 \cdot 10^{-7}) = 16.4$, one calculates $(k_4^{\text{MeOH}})_{\text{BMA}} / (k_4^{\text{MeOH}})_{\text{PIP}} = 0.1 \cdot (k_{-1})_{\text{BMA}} / (k_{-1})_{\text{PIP}}$.



The k_4^{MeOH} step represents the methanol assisted leaving group detachment which involves a transition state, where the developing resonance in the structure IV, a canonical form of the product, is more hindered⁶ for BMA reaction than for PIP reaction ($(k_4^{\text{MeOH}})_{\text{BMA}} < (k_4^{\text{MeOH}})_{\text{PIP}}$).



IV

On the other hand, as shown by an examination of molecular models, the conformational and/or stereoelectronic differences between the two amino moieties in the

* Estimated by taking into account the acidifying effect of the nitroaryl moiety on the $\text{p}K_a$ of N-benzylmethylammonium ion².

transition state leading from (XH) to reactants⁷ should bring about a $(k_{-1})_{\text{BMA}} / (k_{-1})_{\text{PIP}}$ ratio lesser than unity.

Thus, the above ratio (0.1) would point out that the amine variation has an effect on the k_{-1} step comparatively lesser than on the k_4 step. Indeed, in the k_4^{MeOH} step the amine is heavily involved in the rearomatization process; in contrast, in the k_{-1} step, this process leads to the same aromatic compound and the amine variation should represent a less critical factor.

EXPERIMENTAL

Compound⁸ *Ia*, N-benzylmethylamine⁹, methanol¹⁰, and stock solutions of sodium methoxide¹¹ were prepared and/or purified according to the methods reported. 2-N-benzylmethylamino-3-nitrothiophene (m.p. 52–3°C, from methanol) was prepared according to the general method reported in ref.¹² and gave satisfactory elemental analyses.

Kinetic measurements. The kinetics were followed spectrophotometrically as previously described¹³. The concentrations used were $5 \cdot 10^{-3} \text{ mol l}^{-1}$ for the substrate and those indicated in Table I for N-benzylmethylamine and sodium methoxide.

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