Catalysis in Aromatic Nucleophilic Substitution. Part 4.[1] Reactions of Piperidine with 2-Methoxy-3-nitrothiophen in Benzene

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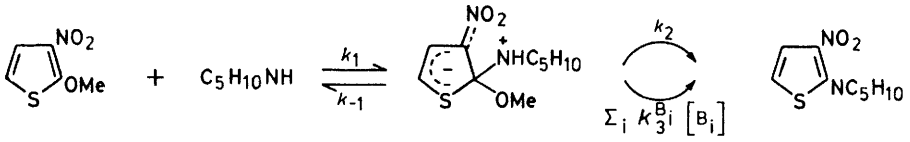
The rate of piperidino-substitution of 2-methoxy-3-nitrothiophen (I) in benzene as a function of amine concentration has been studied. The reaction is strongly catalysed by piperidine, being third-order overall (second-order in amine) and represents the first example of an S_NAr of an *ortho*- or *ortho*-like mononitro-substituted derivative for which base catalysis is needed in benzene. The results obtained have been interpreted by taking into account the properties of the leaving group and its peculiar *ortho*-like relation with the activating nitro group.

S_NAr REACTIONS with amines of substrates containing poor leaving groups are often base catalysed.[2] In a recent study [1] we reported the first example of base catalysis (by methoxide ion) in the piperidino-substitution of an *ortho*-like substituted derivative, 2-methoxy-3-nitrothiophen (I), in a protic solvent (methanol). With reference to the Scheme, base catalysis has been observed [1] in methanol because the product-forming steps designated by k_2 and $k_3^{Bi}[B_i]$ are slower than or as slow as the reversion of the intermediate (II) to reactants. Since this latter reaction leads to charge neutralisation, k_{-1} is expected to increase strongly on going from methanol to benzene, thus reducing the k_2/k_{-1} ratio.



(I) (II) (III)

SCHEME

In this paper we report kinetic results on the piperidino substitution of (I) in benzene, in the temperature range 10—30 °C. We shall show that in a solvent where no lyate ion is present, this reaction is catalysed by piperidine.

RESULTS AND DISCUSSION

Compound (I) gave the substitution product (III) on treatment with piperidine in benzene in high yield as indicated by t.l.c. and/or u.v.–visible (200—450 nm) spectral analysis of the reaction mixtures.

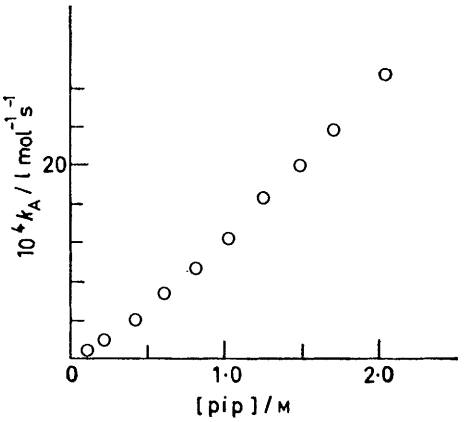
A plot of the apparent second-order rate constants (k_A) of piperidino-substitution *versus* piperidine concentration ([PIP]) shows a more than linear increase of k_A with increasing [PIP] (see Figure and Table 1). There is little doubt that the curves go through the origin; thus the reaction is wholly piperidine-catalysed and no spontaneous decomposition of intermediate into products is detectable ($k_2 = 0$).

A plot (not shown) of $k_A/[PIP]$ *versus* [PIP] is linear in the concentration range 0.1—1.0M and the relation (1)

$$k_A/[PIP] = k_0 + k_{PIP}[PIP] \quad (1)$$

holds with $k_0 = k_1k_3^{PIP}/k_{-1}$. At higher piperidine concentrations one observes a levelling-off in $k_A/[PIP]$ ratios (Table 1).

A more or less slight upward curvature in plots of k_A *versus* amine concentration has been observed in other cases [2c-f] and attributed to a medium effect. We have already shown [3] that the addition of polar substances to the hydrophobic solvent (benzene) can affect the reaction rate by changing the properties of the medium: the slight increase of $k_A/[PIP]$ values with [PIP] and the small kinetic effect of pyridine (Table 2) can be interpreted along similar lines. The levelling-off of third-order kinetic constants beyond [PIP] 1.0M is an interesting consequence of the drastic change introduced in the solvent composition but we are unable, at present, to give a good explanation for it.



Plot of piperidine concentration *versus* apparent second-order rate constant k_A for piperidino substitution of (I) at 20 °C in benzene

The observation that piperidino-substitution of (I) in benzene is third order overall (second order in amine) deserves more comment. The stabilizing interaction

between the ammonium proton and the oxygen of the *ortho*-like nitro group in (II) (built-in solvation) [4] is a factor usually sufficient to assist decomposition of the intermediate.[2g] Thus piperidino-dehalogenation in benzene of 1-halogeno-2-nitrobenzenes [2g,5] and of 2-halogeno-3-nitrothiophens [3b] are not piperidine catalysed and the formation of the intermediate is rate determining.

TABLE 1

Kinetic constants for the piperidino-substitution of 2-methoxy-3-nitrothiophen (I) in benzene at 10—30 °C [a]

	10^4k_A/l mol^{-1} s^{-1}			10^4k_A[PIP]$^{-1}$/l^2 mol^{-2} s^{-1}		
[PIP]/M	10.0 °C	20.0 °C	30.0 °C	10.0 °C	20.0 °C	30.0 °C
0.101	0.657	0.897	1.29	6.50	8.88	12.8
0.202	1.44	1.85	2.44	7.13	9.16	12.1
0.404	3.26	4.03	5.37	8.07	9.98	13.3
0.606	5.20	6.67	8.67	8.58	11.0	14.3
0.808	7.49	9.45	12.0	9.27	11.7	14.8
1.01	9.41	12.3	16.3	9.32	12.2	16.1
1.24	11.8	16.6	19.8	9.52	13.4	16.0
1.47	14.5	20.0	24.4	9.86	13.6	16.6
1.70	16.5	23.6	27.9	9.71	13.9	16.4
2.04	20.3	29.4	34.7	9.95	14.4	17.0

[a] A least-squares treatment of k_A/[PIP] values by equation (1), ([PIP] = 0.101—1.01M) gives, respectively: at 10.0 °C, 10^4 k_0 6.50 ± 0.25, 10^4k_{PIP} 3.16 ± 0.40, r 0.969; at 20.0 °C, 10^4k_0 8.48 ± 0.12, 10^4k_{PIP} 3.81 ± 0.19, r 0.995; at 30.0 °C, 10^4k_0 11.8 ± 0.3, 10^4k_{PIP} 4.02 ± 0.56, r 0.963. From k_0 values one calculates $\Delta H^{\ddagger}$ at 20 °C as 4.5 kcal mol^{-1} and $\Delta S^{\ddagger}$ at 20 °C as −57 cal mol^{-1} K^{-1}.

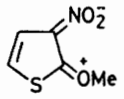
TABLE 2

Kinetic constants for the piperidino-substitution of 2-methoxy-3-nitrothiophen (I), at 20 °C, in the presence of pyridine [a]

[pyridine]/M	0	0.102	0.204	0.306	0.408	0.509
10^4k_A/l mol^{-1} s^{-1}	1.85	1.85	1.89	1.97	1.98	1.99

[a] [PIP] = 0.202M.

The peculiar *ortho*-like relation [6] between the 2-methoxy and the 3-nitro groups in (I) exemplified by the quinonoid structure (IV) causes the first transition state for piperidino-substitution to resemble the reaction intermediate (large k_{-1}): because no compensating effect operates on k_2, and because of the poor nucleofugicity of the methoxy leaving group (low k_3^{PIP}[PIP] values) the overall reaction rate is controlled by decomposition of the intermediate.



(IV)

Consistent with the complexity of the reaction mechanism, a low activation enthalpy and a high absolute activation entropy were observed (Table 1), resulting from a balance of the activation parameters for the single steps (k_1, k_{-1}, and k_3^{PIP}).

As far as the mechanism of catalysis is concerned, our data do not allow us to make any definite choice between the SB-GA mechanism [2a] and bifunctional catalysis,[2h] although the first has been favoured in recent papers.[2e,i]

EXPERIMENTAL

Synthesis and Purification of Compounds.—Compound (I),[7] (III),[8] piperidine,[9] pyridine,[3a] and benzene [9] were prepared and/or purified according to methods previously reported.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[3b,8] The concentrations used were 10^{-3}M for (I) and those indicated in the Tables for piperidine and pyridine. The rate constants are accurate to within ±3%.

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