formation by decreasing the electronic density of the carbonyl group and by decreasing the electronic density of the hydroxy group. This makes the phenolic group a stronger acid, and consequently leads to a strong hydrogen bond. The electron-donating R substituents exert an opposite effect.

The log k_O values were then correlated by a modified Hammett equation (eq 6) that gives rise to the values in eq 7. The values show a positive contribution of σ_m and a positive contribution of σ_p. The contribution of σ_p is higher than the contribution of σ_m.

Acknowledgment. The author is indebted to Dr. Luiz Juliano Neto for helpful comments concerning this work.

Registry No.—Phenylhydrazine, 100-63-0; *p*-cyanophenyl acetate, 13031-41-9; 2′-hydroxy-5′-chloroacetophenone phenylhydrazone, 67338-35-6; 2′-hydroxy-5′-cyanoacetophenone phenylhydrazone, 67338-36-7.

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Catalysis in Aromatic Nucleophilic Substitution. 3.[1] Reactions of Piperidine with 2-Methoxy-3-nitrothiophene and 2-Methoxy-5-nitrothiophene in Methanol

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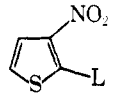
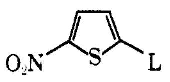
The kinetics of piperidino substitution of 2-methoxy-3-nitrothiophene (If) and of 2-methoxy-5-nitrothiophene (IIf) have been studied in methanol as a function of amine concentration. The reaction of IIf is second order overall, whereas that of If is base catalyzed. Kinetic data are presented which show that sodium methoxide (added or deriving from the reaction of piperidine with methanol) is the only effective catalyst. The complex kinetic system resulting from the competition, at high sodium methoxide concentrations, between the reactions of If respectively with piperidine and with sodium methoxide (Meisenheimer-type adduct formation) has been computer analyzed and the rate coefficients for the single reactions have been estimated. The whole of the data obtained shows that acid catalysis of leaving-group departure by the conjugated acid of piperidine does not occur or is insignificant. The special role of the activating nitro group is discussed.

A recent study[1] of piperidino substitutions of some 2-L-3-nitro- (Ia–e) and 2-L-5-nitrothiophenes (IIa–e), in benzene and in methanol, has shown that only the reactions of compounds IId,e in benzene are piperidine catalyzed due to the poor nucleofugicity of *p*-nitrophenoxy and phenylsulfonyl groups in this solvent; while in compounds Ia–e the *o*-nitro group can assist the intermediate decomposition in both solvents.[2]

For piperidino substitutions in methanol, we now wish to report straightforward second-order kinetic behavior for 2-methoxy-5-nitrothiophene (IIf) but base catalysis for 2-methoxy-3-nitrothiophene (If). The role played by the position of activating nitro group (hyper-ortho or quasi-para) in determining the occurrence of base catalysis will be discussed.



I



II

a, L = Cl
b, L = Br
c, L = I

d, L = $OC_6H_4NO_2$-*p*
e, L = SO_2Ph
f, L = OMe

Results and Discussion

Products. Compounds If and IIf gave the corresponding substitution products with piperidine in high yields (>95%) as shown by TLC and/or UV–visible spectral analysis of the reaction mixtures at infinity.

Reaction of IIf with Piperidine. The apparent second-order kinetic constant, k_A, for the piperidino substitution of IIf in methanol at 20 °C (Table I) is independent of the initial piperidine concentration over a tenfold change.

There can be little doubt that this reaction is second order overall, first order both in substrate and in nucleophile, and that there is no measurable catalysis by the amine acting as a base. This corresponds to the situation where $k_A = k_1$ (see below).

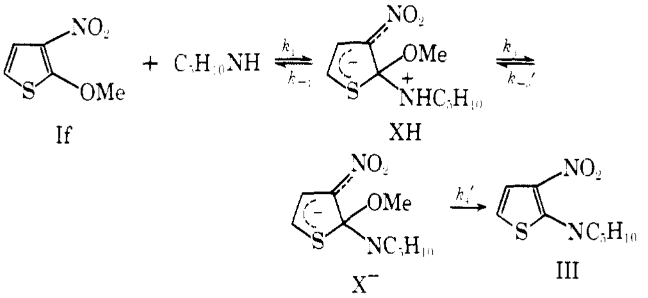
Reaction of If with Piperidine. Items 1–6, 8–10, 12, 14, and 16 in Table II show that k_A increases in a curvilinear

Table I. Kinetic and Activation Parameters[a] for the Reaction of 2-Methoxy-5-nitrothiophene (IIf) with Piperidine in Methanol

[pip], M	0.0203	0.0203	0.0203	0.102	0.203
10^3k, M^{-1} s^{-1}	1.12[b]	2.19[c]	4.02[d]	1.11[b]	1.11[b]

[a] $\Delta H^{\ddagger}$ = 11.1 kcal/mol at 20 °C (maximum error 0.5 kcal/mol); $\Delta S^{\ddagger}$ = −34 eu at 20 °C. [b] At 20.1 °C. [c] At 30.1 °C. [d] At 40.1 °C.

Scheme I



fashion with increasing piperidine concentration (Figure 1). On the other hand, k_A is much lower in the presence of piperidine hydrochloride (items 25–29).

Since a principal effect of this salt is to reduce the concentration of methoxide ion, the increase in k_A with piperidine concentration could be due mainly to catalysis by methoxide ion, a catalyst much more efficient than piperidine.

$$C_5H_{10}NH + MeOH \overset{K_b}{\rightleftharpoons} C_5H_{10}NH_2^+ + MeO^- \qquad (1)$$

Kinetic runs performed in the presence of added sodium methoxide (items 7, 11, 13, 15, 17–24) show that, at constant piperidine concentration, k_A increases with increasing methoxide ion concentration. Moreover, items 7 and 8, 10 and 11, 12 and 13, and 20 and 21 point out that piperidine catalysis is unlikely to occur in any great extent. Finally, items 26 and 29–31 show that the reaction is influenced by the ionic strength.

With reference to Scheme I, the general expression for k_A, in terms of rate coefficients for specific steps, is[3]

$$k_A = k_1k_3'k_4'/(k_{-1}k_{-3}' + k_{-1}k_4' + k_3'k_4') \qquad (2)$$

with

$$k_3' = k_3 + \sum_{i=1}^{n} k_3^{B_i}[B_i] \qquad (3)$$

$$k_{-3}' = k_{-3} + \sum_{i=1}^{n} k_{-3}^{B_i}[BH_i] \qquad (4)$$

where k_3 and $k_3^{B_i}$ refer to the deprotonation of XH by the solvent and by any general base, B_i, and k_{-3}, $k_{-3}^{B_i}$ refer to the protonation of X^- by the solvent and by any general acid, BH_i, respectively. Assuming $k_{-3}' \gg k_4'$ (SB-GA mechanism)[4] leads to the following simplification of eq 2

$$k_A = k_1K_3'k_4'/(k_{-1} + K_3'k_4') \qquad (5)$$

where

$$\begin{aligned} K_3' = k_3'/k_{-3}' &= k_3^{MeO}[MeO^-]/k_{-3}^{MeO} \\ &= k_3^{pip}[pip]/k_{-3}^{pip}[pipH^+] \\ &= k_3/k_{-3}[MeOH_2^+] = K_X/[MeOH_2^+] \qquad (6) \end{aligned}$$

If, on the contrary, one assumes $k_{-3} \ll k_4'$, eq 2 reduces to

$$\begin{aligned} k_A = k_1k_3'/(k_{-1} + k_3') = k_1\,(k_3 + k_3^{MeO}[MeO^-] \\ + k_3^{pip}[pip])/(k_{-1} + k_3 + k_3^{MeO}[MeO^-] + k_3^{pip}[pip]) \qquad (7) \end{aligned}$$

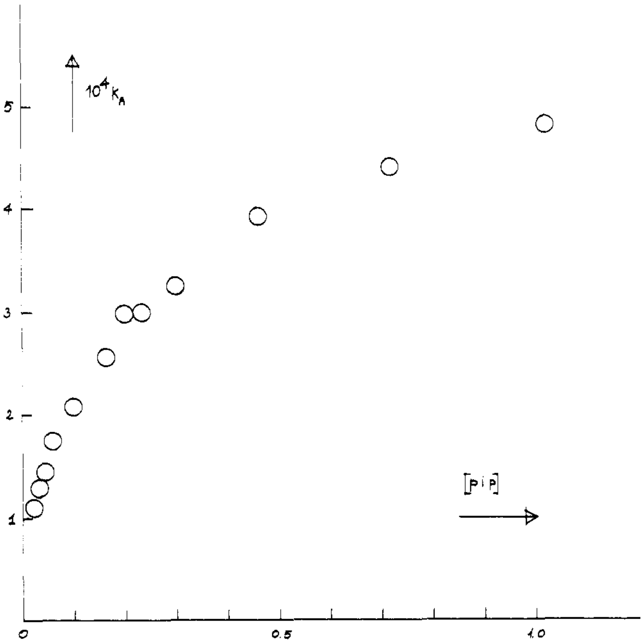
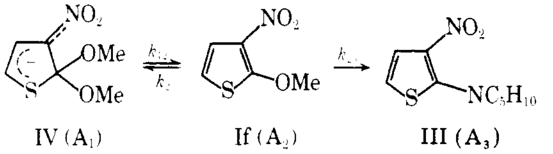


Figure 1. Plot of apparent second-order kinetic constants (k_A) for the piperidino substitution of If in methanol at 20 °C vs. piperidine concentration.

Scheme II



With respect to the dependence of k_A on $[B_i]$, eq 5 and 7 are formally identical. As a consequence, one can write

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

where x_1 = [pip] and x_2 = [MeO⁻].

We have fitted our kinetic data to eq 8 using a least-squares method[5] and the results of the correlation are reported in Table III. It is evident that there is no significant contribution to k_A from the solvent- and/or the piperidine-catalyzed pathway. Thus, the reaction of If with piperidine is catalyzed by methoxide ion in methanol at 20 °C according to the catalysis law

$$k_A = k_1k^*[MeO^-]/(1 + k^*[MeO^-]) \qquad (9)$$

with $k_1 = 8.15 \times 10^{-4}\ M^{-1}\ s^{-1}$ and $k^* = 489\ M^{-1}$ (Table III, line five).[6]

Kinetic Measurements at High Sodium Methoxide Concentrations. Recently[8] we have studied the kinetics and equilibrium for combination of sodium methoxide with If to form the Meisenheimer-type adduct IV.

At methoxide ion concentrations as high as 0.1 M, the piperidino substitution reaction of If has to be treated according to Scheme II.[9] Assuming that each step behaves as a first-order reaction, the differential eq 10–12 are obtained.

$$dA_1/dt = k_{21}A_2 - k_{12}A_1 \qquad (10)$$

$$-dA_2/dt = k_{21}A_2 + k_{23}A_2 - k_{12}A_1 \qquad (11)$$

$$dA_3/dt = k_{23}A_2 \qquad (12)$$

Integration according to a general method[10] gives

$$A_1 = A_2^0k_{21}(e^{-\lambda_3t} - e^{-\lambda_2t})/(\lambda_2 - \lambda_3) \qquad (13)$$

Table II. Kinetic and Apparent Activation Parameters for the Reaction of 2-Methoxy-3-nitrothiophene (If) with Piperidine in Methanol[a] at 20 °C

no.	[pip], M	10^3[MeONa],[b] M	$10^3[MeO^-]$,[c] M	10^4k_A, $M^{-1}\,s^{-1}$	$(10^4k_A)_{calcd}$[d] $M^{-1}\,s^{-1}$	$\Delta H^{\ddagger}$,[e] kcal/mol	$-\Delta S^{\ddagger}$,[f] eu
1	0.0206		0.384	1.09			
2	0.0304		0.467	1.29		6.1	56
3	0.0450		0.569	1.45		6.9	53
4	0.0617		0.667	1.76		7.6	50
5	0.101		0.855	2.07		8.2	47
6	0.158		1.07	2.56	2.80	8.4	46
7	0.0298	1.00	1.18	2.83	2.98		
8	0.202		1.21	2.98	3.03		
9	0.234		1.30	2.99	3.17	9.0	44
10	0.298		1.47	3.26	3.41	9.1	43
11	0.102	0.940	1.45	3.39	3.38		
12	0.458		1.82	3.92	3.84	9.8	41
13	0.254	0.940	1.91	4.00	3.93		
14	0.717		2.28	4.40	4.29	10.1	39
15	0.508	0.940	2.45	4.57	4.44		
16	1.02		2.72	4.82	4.65	10.0	39
17	0.0298	3.00	3.07	5.02	4.89		
18	0.0298	4.00	4.05	5.51	5.41		
19	0.0298	5.00	5.04	5.83	5.79		
20	0.0298	5.64	5.70	6.01	6.00		
21	0.202	5.25	5.52	6.06	5.94	12.5	30
22	0.0508	7.52	7.57	6.34	6.41		
23	0.0508	9.40	9.44	6.61	6.70		
24	0.202	10.5	10.6	6.65	6.83	13.0	29
25	0.200[g]		0.0146	0.686			
26	0.200[h]		0.0292	0.750			
27	0.200[i]		0.0730	0.897			
28	0.200[j]		0.146	1.13			
29	0.400[g]		0.0292	1.25			
30	0.202[k]		1.21	5.05			
31	0.202[l]		1.21	5.22			

[a] The apparent activation parameters have been obtained from measurements at three temperatures in the range 20–40 °C. These further kinetic data are given in the microfilm edition of this volume of the journal. See the Supplementary Material available paragraph. [b] Added sodium methoxide. [c] Total methoxide ion; values calculated using $K_b = 7.3 \times 10^{-6}$ [J. R. Schaefgen, M. S. Newman, and F. H. Verhoek, *J. Am. Chem. Soc.*, **66,** 1847 (1944)]. [d] Values calculated by eq 9. [e] At 20 °C, the probable error is ±0.5 kcal/mol. [f] At 20 °C. [g] Piperidine hydrochloride (pipHCl) = 0.1 M. [h] [pipHCl] = 0.05 M. [i] [pipHCl] = 0.02 M. [j] [pipHCl] = 0.01 M. [k] Sodium acetate = 0.1 M. [l] Sodium perchlorate = 0.1 M.

Table III. Results of Least-Squares Fitting to Equation 8 of Apparent Second-Order Kinetic Constants, k_A, for the Piperidino Substitution of If in Methanol, at 20.0 °C[a]

constraints	$10^4 (a \pm s_a)$, $M^{-1}\,s^{-1}$	$b \pm s_b$	$c \pm s_c$, M^{-1}	$d \pm s_d$, M^{-1}	items
none	7.95 ± 0.13	0.00 ± 0.02	0.05 ± 0.08	554 ± 40	1–24
$b = 0$	8.44 ± 0.17		0.14 ± 0.07	423 ± 25	1–24
$c = 0$	7.91 ± 0.11	0.00 ± 0.02		573 ± 30	1–24
$b = 0; c = 0$	8.32 ± 0.15			455 ± 20	1–24
$b = 0; c = 0$	8.15 ± 0.13			489 ± 20	6–24

[a] s_a, s_b, s_c, and s_d are the standard errors of *a*, *b*, *c*, and *d*, respectively.

$$A_2 = A_2^0\{[(k_{12} - \lambda_3)e^{-\lambda_3 t}/(\lambda_2 - \lambda_3)] - [(k_{12} - \lambda_2)e^{-\lambda_2 t}/(\lambda_2 - \lambda_3)]\} \quad (14)$$

$$A_3 = A_2^0\{1 + [k_{23}(k_{12} - \lambda_2)e^{-\lambda_2 t}/(\lambda_2 - \lambda_3)\lambda_2] - [k_{23}(k_{12} - \lambda_3)e^{-\lambda_3 t}/\lambda_3(\lambda_2 - \lambda_3)]\} \quad (15)$$

where $\lambda_2 = (p + q)/2$; $\lambda_3 = (p - q)/2$; $p = k_{12} + k_{21} + k_{23}$; $q = p^2 - [4k_{12}k_{23}]^{1/2}$. By measuring, at different intervals, the optical densities of the reaction mixtures at the wavelengths of the absorption maxima of III and IV, respectively, the concentrations of each compound can be easily determined according to eq 16 and 17

$$D_1 = \epsilon_{11}A_1 + \epsilon_{12}A_2 + \epsilon_{13}A_3 \quad (16)$$

$$D_2 = \epsilon_{21}A_1 + \epsilon_{22}A_2 + \epsilon_{23}A_3 \quad (17)$$

where ϵ_{1j} and ϵ_{2j} (j = 1, 2, 3) are the molar extinction coefficients of A_j, respectively, at 340 and 398 nm.[8,11]

Applying the above curve-fitting method to eq 15[12] gives the results set forth in Table IV. The k_{23} values in Table IV give second-order kinetic constants, k_A, in excellent agreement with k_1 (eq 9) obtained from kinetic measurements at low methoxide ion concentrations and provide a check of the internal consistency of our results. On the other hand, the k_{12} and k_{21} values in Table IV compare well with those previously obtained.[8]

Implications. Catalysis by methoxide ion in the reaction of If with piperidine in methanol is observable as long as k_{-1} is larger than or similar to $K_3'k_4'$ or k_3' (Scheme I). Since piperidino substitution reactions of compounds Ia–e in methanol are not catalyzed,[1] base assistance in the substitution of methoxy leaving group could be, in principle, needed because

Table IV. Results of Least-Squares Fitting to Equation 15 of Experimental A_3 Values[a] at 20 °C

[MeONa]	$10^5 k_{12}$, s^{-1}	$10^4 k_{21}$, s^{-1}	$10^4 k_{23}$, s^{-1}	$10^3 k_f$, $M^{-1} s^{-1}$	$10^4 k_A$, $M^{-1} s^{-1}$	K_e[b], M^{-1}
0.102	9.99 (1.25)	1.55 (0.16)	1.73 (0.07)	1.52	8.40	15
0.205	6.69 (0.13)	3.28 (0.35)	1.66 (0.11)	1.60	8.06	24

[a] [pip] = 0.206 M; the values in parentheses are standard errors; number of data points, 20. [b] $K_e = k_f/k_{12}$.

of a larger k_{-1} and/or a lower $K_3'k_4'$ (or k_3') for methoxy than for the other leaving groups studied.

According to Bernasconi[4] k_{-1} should be little affected by leaving group variation. In our opinion, a particular situation occurs in *o*-nitro activated S_NAr of thiophene compounds. The hyper-ortho relation[13] between substituents linked to 2 and 3 carbon atoms of the thiophene ring makes the first transition state for piperidino substitution of If closely resemble the reaction intermediate.[14] As a consequence, the two transition states involved in the addition–elimination mechanism could be of similar importance in determining the overall reaction rate.

The quasi-para nitro substituted isomer IIf lacks this through-conjugation factor and the absence of catalysis is accordingly accounted for.

Assuming the SB-GA mechanism for base catalysis implies $k_{-1} \gg K_3'k_4'$, indeed, k_4' refers to a bond-breaking process and it is likely to be quite low with the poor methoxy leaving group.[16]

The piperidino substitution of If in methanol is not catalyzed by acetate ion. In fact, the rate-enhancing effect of sodium acetate is comparable with that produced by sodium perchlorate (items 30 and 31, Table II) and undoubtedly represents the medium effect of an "inert" salt. The absence of catalysis by piperidine and acetate ion could be explained on grounds of low k_3^B values (Scheme I) for these bases.[19]

In view of recent discussions on this subject,[21] our results could imply, alternatively, the absence of general base catalysis and the operation of specific base catalysis (SB) by methoxide ion.

Conclusions. The piperidino substitution reaction of 2-methoxy-3-nitrothiophene in methanol constitutes the first exemplum of *o*-mononitro activated S_NAr for which base catalysis is needed. The hyper-ortho relation is the major factor implied. All of the data obtained agree with a SB (SB-GA) mechanism for base catalysis.

Experimental Section

Materials. Compounds If,[22] IIf,[23] piperidine,[11] and methanol[11] were prepared and/or purified according to the methods reported.

Kinetic Measurements. The kinetics were followed spectrophotometrically as previously described.[1,24] The concentrations used were 1×10^{-3} M for substrates and those indicated in the tables for piperidine, sodium methoxide, piperidine hydrochloride, sodium acetate, and sodium perchlorate. The rate constants are accurate to within ±3%.

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Registry No.—If, 30549-14-5; IIf, 30549-16-7; piperidine, 110-89-4.

Supplementary Material Available: Table of rate constants and apparent activation parameters for the reaction of 2-methoxy-3-nitrothiophene (If) with piperidine in methanol (1 page). Ordering information can be found on any current masthead page.

References and Notes

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(6) The agreement of experimental k_A values with those calculated by eq 9 was excellent for all but five (items 1–5) of the kinetic runs in Table II. At *low piperidine concentrations, unavoidable traces of water and carbon* dioxide could interfere with methoxide ion and introduce inaccuracies in the calculated values of its concentration. For this reason items 1–5 have been excluded from the calculation. Equation 9 applied to items 6–24 gives calculated k_A values (Table II) which do not differ from k_A within the experimental error. Since the term containing $[MeO^-]$ is the sole contributor to k_3', it is possible to apply the "inversion plot" treatment[7] to items 6–24. The results ($1/k_1 = 1140 \pm 40$, $1/k_1k^* = 2.67 \pm 0.07$, $r = 0.994$) nicely reproduce those obtained by the curve-fitting method.

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(9) In Scheme II, $k_{23} = k_A[pip]$; $k_{21} = k_f[MeO^-]$; k_f = second-order kinetic constant for the adduct formation; k_{12} = kinetic constant for the adduct decomposition (under the experimental conditions used in the present work, both [pip] and $[MeO^-]$ are to be considered constant); $A_1 = [IV]$; $A_2 = [If]$; $A_3 = [III]$. We estimate that if $(k_{23} + k_{12})/k_{21} > 20$ there is no significant adduct formation; items 6–24 in Table II all meet this condition.

(10) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed, Wiley, New York, N.Y., 1961, Chapter 8.

(11) D. Spinelli, C. Dell'Erba, and G. Guanti, *Ann. Chim.* (*Rome*), **55**, 1260 (1965).

(12) Although the A_1 values calculated as a function of time reaction, *t*, gave the expected trend (i.e., rapid increase, reaching of a maximum, and decrease to zero), the consistent contribution to absorption from If[8] prevented their use for the subsequent treatment.

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(14) In the reaction of If with sodium methoxide in methanol, to form the Meisenheimer-type adduct, k_1 and k_{-1} are of the same order of magnitude.[8] The reaction of the same substrate with a neutral nucleophile should involve a somewhat more like-intermediate transition state.[15]

(15) L. R. Parks, G. S. Hammond, and M. F. Hawthorne, *J. Am. Chem. Soc.*, **77**, 2903 (1955).

(16) The reaction of 2-trifluoroethoxy-3-nitrothiophene with piperidine in methanol is second order overall[17] and has $\Delta H^{\ddagger}$ = 12.5 kcal/mol and $\Delta S^{\ddagger}$ = −26 eu. An estimate of the upper limits of the apparent activation parameters in Table II indicates a similar $\Delta S^{\ddagger}$ value and a higher $\Delta H^{\ddagger}$ value for methoxy leaving group. According to the Hammond postulate[18] this implies a lower k_{-1} value for the trifluoroethoxy leaving group; moreover, this is more nucleofugic than the methoxy group. Thus, the $K_3'k_4'/k_{-1}$ ratio is likely to be greater than unity and the overall reaction rate is controlled by the formation of intermediate.

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