

Table 1. Equilibrium optical density measurements at 20 °C for the reaction of 2-methoxy-5-methyl-3-nitrothiophene (**1a**) with sodium methoxide in methanol at constant ionic strength (μ)^a

		$\mu = 0.05 \text{ M}$								
[MeONa]/M		0.001 02	0.002 04	0.006 11	0.008 15	0.0102	0.0204	0.0306	0.0408	0.0509
D_e at 330 nm		0.560	0.650	0.910	0.990	1.050	1.230	1.330	1.380	1.424
		$\mu = 0.10 \text{ M}$								
[MeONa]/M		0.005 09	0.0100	0.0200	0.0303	0.0404	0.0504	0.0606	0.0815	
D_e at 330 nm		0.916	1.100	1.296	1.365	1.405	1.430	1.460	1.480	

^a Solutions made up to constant ionic strength with sodium perchlorate; $[(\mathbf{1a})] = 9.99 \times 10^{-5} \text{ M}$.

Table 2. Kinetic and equilibrium constants at 20 °C for the reaction of 2-methoxy-5-methyl-3-nitrothiophene (**1a**) with sodium methoxide in methanol at constant ionic strength (μ)^a

[MeONa]/M	K_e^b /l mol ⁻¹	[MeONa]/M	K_e^c /l mol ⁻¹	$10^4 k_{\text{obs}}/s^{-1}$	$10^3 k_1^d$ /l mol ⁻¹ s ⁻¹
0.001 02	99.1	0.005 09	134	0.547	4.36
0.002 04	101	0.0100	130	0.780	4.41
0.006 11	109	0.0200	139	1.19	4.38
0.008 15	108	0.0303	129	1.72	4.52
0.0102	107	0.0404	122	2.20	4.53
0.0204	103	0.0504	115	2.68	4.54
0.0306	107	0.0606	120	3.17	4.60
0.0408	104	0.0815	106	4.07	4.48
0.0509	109				

^a At 330 nm; ϵ_a 16 000, ϵ_s 4565. ^b At μ 0.05M; average value 105 l mol⁻¹, standard deviation 3 l mol⁻¹. ^c At μ 0.10M; average value 124 l mol⁻¹; standard deviation 10 l mol⁻¹. ^d At μ 0.10M; average value 4.48 l mol⁻¹ s⁻¹, standard deviation 0.08 l mol⁻¹ s⁻¹.

Results and Discussion

Spectroscopic Evidence for the Formation of the Adduct (**2a**).—

The n.m.r. spectrum of 2-methoxy-5-methyl-3-nitrothiophene (**1a**) in deuteriated methanol (CD₃OD) shows three absorptions, at δ 2.38 (3 H), 4.17 (3 H), and 7.10 (1 H), attributed to the methyl, methoxy, and aromatic protons, respectively. The addition of concentrated methanolic sodium methoxide results in the appearance of three new absorptions, at δ 2.13 (3 H), 3.98 (6 H), and 6.23 (1 H). As the amount of methoxide added is increased, the intensity of the signals relating to (**1a**) diminishes, while that of the new signals increases; this implies that the extent of the interaction depends on sodium methoxide concentration. The upfield shift of the n.m.r. signals on going from the substrate to the corresponding adduct is consistent with the different charge distribution in the two compounds. This shift, as well as the equivalence of the two methoxy groups, constitutes definite evidence in favour of a Meisenheimer-type adduct structure (σ -complex) for (**2a**).

The u.v. spectrum of (**1a**) in methanol shows an absorption maximum at 338 nm (log ϵ 3.70). The addition of increasing amounts of sodium methoxide caused a progressive increase in absorption and a change in the shape of the spectrum. Finally, at a sodium methoxide concentration in the range 0.3–0.5M, $\{[(\mathbf{1a})] 10^{-4}\text{M}\}$ the substrate was completely converted into adduct, the absorption maximum being now at 328 nm (log ϵ 4.20); further increase in base concentration caused no further spectral change.

It is noteworthy that the shift of the absorption maximum on going from substrate to adduct is not only extremely small but also in the opposite direction (hypsochromic shift) from those observed for the other adducts (**2**).^{3a,c-e}

Determination of the Equilibrium Constant.—The equilibrium constant for the formation of (**2a**), $K_e = [(\mathbf{2a})]/[(\mathbf{1a})][\text{MeONa}]$, can be determined from spectral measurements on methanolic solutions of (**1a**) and sodium methoxide, provided

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

[MeONa]/M	D_e^a	K_e /l mol ⁻¹	$10^3 k_{\text{obs}}/\text{min}^{-1}$	$10^3 k_1$ /l mol ⁻¹ s ⁻¹
0.002 05	0.580	57.3		
0.003 08	0.640	60.7		
0.005 12	0.750	66.4		
0.007 69	0.860	69.9	4.62	3.50
0.0107	0.970	75.1	5.09	3.53
0.0205	1.190	85.6	7.03	3.64
0.0308	1.320	97.4	9.36	3.80
0.0410	1.390	105	12.1	4.01
0.0512	1.430	107	14.7	4.05
0.0615	1.460	110	17.7	4.19
0.0820	1.500	118	24.4	4.50
0.102	1.522	122	31.9	4.82

^a At 330 nm.

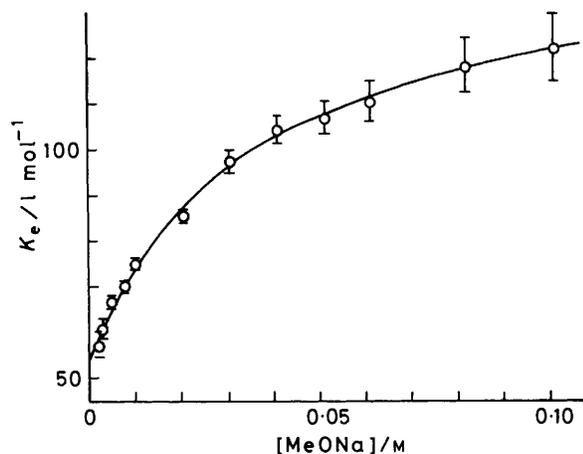
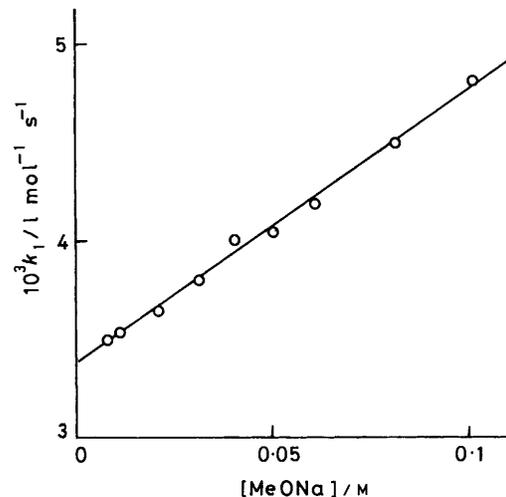
that the extinction coefficient of substrate (ϵ_s) and adduct (ϵ_a) is known. In fact, $[(\mathbf{2a})] = (D_e/l - \epsilon_s c_s)/(\epsilon_a - \epsilon_s)$ and $[(\mathbf{1a})] = c_s - [(\mathbf{2a})]$, where D_e represents the optical density of the solution at equilibrium, c_s the substrate concentration [the sodium methoxide concentration, in large excess over that of (**2a**), is assumed to be constant], and l the thickness of the cuvette in cm.

Preliminary measurements showed that, as previously observed for (**1b**),^{3d} the stoichiometric equilibrium constant, K_e , increased with increasing sodium methoxide concentration. This effect has been ascribed to ion pair formation.^{7,8} In order to confirm this interpretation we have measured the equilibrium optical densities of a series of solutions containing various amounts of the two reagents, at two different ionic strengths (Table 1). By using the values of ϵ_s and ϵ_a obtained from the spectra recorded in the absence of sodium methoxide and at high sodium methoxide concentrations, respectively, we calculated the K_e values shown in Table 2. In view of the high

Table 4. N.m.r. chemical shifts^a of compounds (**1a** and **b**) [0.4M in (CD₃)₂SO] and the corresponding Meisenheimer adducts (**2a** and **b**)^b

Compound	¹ H N.m.r.				¹³ C N.m.r.					
	H(4)	H(5)	H(5-Me)	H(OMe)	C(2)	C(3)	C(4)	C(5)	C(5-Me)	C(OMe)
(1a)	7.11		2.34	4.11	166.50	127.50	118.76	122.66	14.81	63.04
(2a)	6.08		1.90	3.24	126.77	117.32	117.56	121.50	17.68	51.64
Δ[(2a) - (1a)]	-1.03		-0.44	-0.87	-39.73	-10.18	-1.20	-1.16	2.87	-11.40
(1b) ^c	7.29	6.93		4.15	168.42	128.49	121.61	110.17		63.16
(2b) ^c	6.33	5.71		3.25	126.26	117.07	120.50	109.86		51.76
Δ[(2b) - (1b) ^c	-0.96	-1.22		-0.90	-42.16	-11.42	-1.11	-0.31		-11.40

^a δ in p.p.m. from Me₄Si; Varian FT-80 and XL-200 spectrometers. ^b Generated *in situ* by addition of 5M-MeONa in MeOH. ^c Refs. 3b and e.

**Figure 1.** Plot of K_e vs. [MeONa]**Figure 2.** Plot of k_1 vs. [MeONa]

sensitivity of K_e to the experimental uncertainty of D_e (see Experimental section) the agreement between the single values of Table 2, at each ionic strength, is considered satisfactory.

Since it has been shown that the increase in the apparent equilibrium constant, K_e , with increasing sodium methoxide concentration depends on association phenomena, it is possible to obtain a 'thermodynamic' value of K_e by measuring a number of K_e values at various sodium methoxide concentrations (Table 3) and by extrapolating to [MeONa] = 0 the curve of K_e versus [MeONa] (Figure 1). Indeed, graphic extrapolation to [MeONa] = 0 gives $K_e = 54$ l mol⁻¹.

Kinetic Constants for the Formation of (2a).—The kinetic constants for the formation of (**2a**) have been obtained as previously described^{3d} in the presence of a large excess of sodium methoxide and are reported in Tables 2 and 3. The apparent second-order kinetic constant, k_1 , increases linearly with increasing [MeONa] (Figure 2). Extrapolation to infinite dilution gives $k_1 = 3.4 \times 10^{-3}$ l mol⁻¹ s⁻¹. On the other hand, at constant ionic strength, k_1 does not change with changing sodium methoxide concentration (Table 2).

¹H and ¹³C N.m.r. Spectra.—In Table 4 are reported the ¹H and ¹³C n.m.r. chemical shifts of (**1a**) and (**2a**) in (CD₃)₂SO, together, for comparison, with the previously reported^{3b,e} data for (**1b**) and (**2b**). The ¹³C chemical shift variations on going from (**1a**) to (**2a**), when compared with those observed on going from (**1b**) to (**2b**), show a slightly lower increase in shielding at C-3 and a slightly larger increase in shielding at C-5. Moreover, the formation of the adduct (**2a**) appears to be accompanied by a marked deshielding of the 5-Me carbon atom and a significant shielding of the 5-Me protons.

Caution is necessary in interpreting these results, as chemical shifts are due to a variety of effects and because in this case some of the values obtained are of only moderate size. However all the observed results are consistent with the hypothesis that the formation of the adduct (**2a**) is accompanied by a change in the polarity of the C-H bonds of the methyl group (the electron cloud shifting towards the methyl protons),* contributing to the stabilization of the negative charge on the ring; as a consequence a slightly larger fraction of the latter would be spread over C-5, so that a slightly better delocalization of the negative charge among the ring carbon atoms can be achieved.

Thus the n.m.r. data appear to be consistent with the hypothesis that the stabilizing effect of the 5-methyl group on the present adduct is connected with the polarizability of the C-H bonds of the methyl group itself and with its consequent ability to exert a -I effect when demanded by the structural moiety to which it is bonded (see later).

Discussion of Kinetic and Thermodynamic Results.—The equilibrium and kinetic constants for the formation of the adduct (**2b**) from 2-methoxy-3-nitrothiophene (**1b**) and sodium methoxide in methanol, at infinite dilution, are 6 l mol⁻¹ and 1.3×10^{-3} l mol⁻¹ s⁻¹, respectively, at 20 °C. Thus the adduct (**2a**) is nine times more stable and is formed about three times faster than (**2b**). This result confirms the unusual role played by the methyl substituent in reactions where the rate-determining

* In neutral compounds the polarity of the C-H bonds points towards the more electronegative carbon atom, as shown *inter alia* by the shielding effect exerted by the methyl group on C-1 in propene, on C-4 in toluene, and on C-5 in 2-methylthiophene.⁹

transition state (r.d.t.s) bears a fractional negative charge in the aromatic ring. In the reaction under investigation, where the transition state is anionic, the 'activating' effect of methyl group is obviously greater than in the piperidino-substitution of 2-bromo-3-nitro-5-methylthiophene (see before), which involves a zwitterionic r.d.t.s.

Consistent with this interpretation is the observation that the methyl group has a greater effect on the stability than on the rate of formation of the adduct. In fact, since in the adduct the negative charge is a unit, and not fractional as in the transition state, the difference in behaviour between hydrogen and methyl substituents is accordingly greater.

A comparison of the stability and the rate of formation of the adduct (**2a**) with the corresponding values for the other adducts (**2**) studied shows, somewhat surprisingly, that the methyl substituent has a stabilizing effect greater than that of carbamoyl group (K_{CONH_2} , 34); however, the adduct (**2c**) is formed about ten times faster (k_1 $2.78 \times 10^{-2} \text{ l mol}^{-1} \text{ s}^{-1}$) than (**2a**).

We consider that this interesting stability-reactivity pattern must be related to the difference in electronic demands which the methyl group is prompted to satisfy in the transition state and in the adduct. The structural reorganization which the methyl-substituted substrate undergoes on passing from the ground to the transition state is certainly greater than that which involves the carbamoyl group, and one observes a lesser reactivity (k_1) for X = Me than for X = CONH₂; however, the methyl group is significantly polarized in an attractive way with respect to the aromatic ring. In the adduct, where the negative charge to be delocalized is unity, the methyl group suffers a much stronger polarization and indeed appears more efficient than the carbamoyl group in stabilizing the adduct.

Experimental

Synthesis and Purification of Compounds.—Methanol¹⁰ and stock solutions of sodium methoxide¹¹ were prepared and/or purified according to literature methods. Compound (**1a**) was prepared as follows and exhibited correct elemental analytical figures.

2-Methoxy-5-methyl-3-nitrothiophene (1a).—Nitric acid (d 1.5; 2.7 ml) in acetic anhydride (18 ml) was slowly added with stirring to a solution of 2-methoxy-5-methylthiophene¹² (5.6 g) in acetic anhydride (27 ml), at -20°C . The temperature was allowed to rise to 0°C and then the mixture was poured onto crushed ice and extracted with ether. The ether phase was washed with aqueous sodium hydrogen carbonate and water, and dried (Na_2SO_4), and the ether was distilled off. The oily residue was chromatographed on a column of silica gel with benzene as eluant. The compound was crystallized from light petroleum—benzene; m.p. $78\text{--}79^\circ\text{C}$.

Uncertainty of K_e and k_1 Values.—Owing to the substantial contribution of the substrate to the total absorption of the

various solutions, the K_e values are particularly sensitive to errors in optical density measurements. The error in the K_e values, dK_e , depends on the error in the optical density at equilibrium, dD_e , according to equation (i). The vertical

$$dK_e = (1 + K_e[\text{MeONa}]^2)dD_e/[\text{MeONa}](D_e - \epsilon_e c_e) \quad (i)$$

segments of Figure 1 represent the errors in K_e corresponding to $D_e = \pm 0.005$. The corresponding uncertainty in k_1 is considerably lower than the experimental reproducibility, estimated as $\pm 3\%$.

Acknowledgements

We thank the C.N.R. for support.

References

- Part 3, G. Consiglio, C. Arnone, D. Spinelli, F. Sancassan, C. Dell'Erba, G. Leandri, and F. Terrier, *Gazz. Chim. Ital.*, 1987, **117**, 267.
- (a) E. Buncl, A. R. Norris, and K. E. Russell, *Quart. Rev. Chem. Soc.*, 1968, **22**, 123; M. R. Crampton, *Adv. Phys. Org. Chem.*, 1969, **7**, 211; M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667; *Acc. Chem. Res.*, 1974, **7**, 181; J. A. Zoltewicz, *MTP Int. Rev. Sci., Org. Chem. Ser. 2*, 1976, **3**, 63; C. F. Bernasconi, *Acc. Chem. Res.*, 1978, **11**, 147; S. S. Gitis and A. Ya. Kaminskii, *Russ. Chem. Rev. (Engl. Transl.)*, 1978, **47**, 1061; (b) F. Terrier, *Chem. Rev.*, 1982, **82**, 77, and references therein; (c) G. Illuminati and F. Stegel, *Adv. Heterocycl. Chem.*, 1983, **34**, 305, and references therein.
- (a) G. Doddi, G. Illuminati, and F. Stegel, *J. Chem. Soc., Chem. Commun.*, 1969, 953; G. Doddi, G. Illuminati, and F. Stegel, *J. Org. Chem.*, 1971, **36**, 1918; (b) D. Spinelli, V. Armanino, and A. Corrao, *J. Heterocycl. Chem.*, 1970, **7**, 1441; (c) G. Baldini, G. Doddi, G. Illuminati, and F. Stegel, *J. Org. Chem.*, 1976, **41**, 2153; (d) D. Spinelli, G. Consiglio, and R. Noto, *J. Chem. Res.*, 1978, (S), 242; (M), 2984; (e) G. Consiglio, D. Spinelli, C. Arnone, F. Sancassan, C. Dell'Erba, R. Noto, and F. Terrier, *J. Chem. Soc., Perkin Trans. 2*, 1984, 317.
- F. Sancassan, M. Novi, G. Guanti, and C. Dell'Erba, *J. Heterocycl. Chem.*, 1975, **12**, 1083.
- (a) D. Spinelli, G. Consiglio, and A. Corrao, *Tetrahedron Lett.*, 1972, 4021; (b) G. Consiglio, C. Arnone, D. Spinelli, R. Noto, and V. Frenna, *J. Chem. Soc., Perkin Trans. 2*, 1981, 621; (c) G. Consiglio, D. Spinelli, S. Gronowitz, A.-B. Hörnfeldt, B. Maltesson, and R. Noto, *ibid.*, p. 625.
- J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968, 204.
- F. Terrier, *Ann. Chim. (Paris)*, 1969, **4**, 153; C. F. Bernasconi, *J. Am. Chem. Soc.*, 1968, **90**, 4982.
- M. R. Crampton and H. A. Khan, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1173.
- E. Breitmaier and W. Voelter, '¹³C NMR Spectroscopy,' 2nd edn., Verlag Chemie, Berlin, 1978.
- A. Weissberger, 'Technique of Organic Chemistry,' Interscience, 2nd edn., vol. 7, 1963, p. 333.
- J. H. Fendler, *J. Am. Chem. Soc.*, 1966, **88**, 1237.
- S. Gronowitz, P. Moses, A.-B. Hörnfeldt, and R. Håkansson, *Arkiv Kemi*, 1961, **17**, 165.

Received 3rd August 1987; Paper 7/1421