Meisenheimer-type Adducts from Thiophene Derivatives. Part 2.† Kinetic, Thermodynamic, and ^{13}C N.m.r. Studies of Substituent Effects in the Reaction of Sodium Methoxide with Some 2-Methoxy-3-nitro-5-X-thiophenes in Methanol

Giovanni Consiglio, Domenico Spinelli, and Caterina Arnone
Cattedra di Chimica Organica, Faculty of Pharmacy, University of Bologna, Via Zanolini 3, Bologna 40126, Italy
Fernando Sancassan and Carlo Dell'Erba
Institute of Organic Chemistry, Corso Europa, Genova 16132, Italy
Renato Noto
Institute of Organic Chemistry, Via Archirafi 20, Palermo 90123, Italy
François Terrier
Faculté des Sciences et des Techniques, Boite Postale no. 67, Mont Saint-Aignan 76130, France

The rate and equilibrium constants for the formation of the Meisenheimer-type adducts from some 2-methoxy-3-nitro-5-X-thiophenes and sodium methoxide in methanol have been measured at various temperatures. The absence of linear correlation between log K_e or log k_1 and σ_p^- constants has been interpreted in the light of the hyper-*ortho* relation in the thiophene ring. ^{13}C N.m.r. chemical shifts for substrates (1a—g) and related *gem*-dimethoxy adducts (2a—g) have also been determined. The comparison between thermodynamic and ^{13}C n.m.r. data suggests that most of the studied substituents favour the formation of the adducts mainly by stabilizing a fractional negative charge on C-5 of the ring.

Recently [1] we reported kinetic and equilibrium constants for the reaction of 2-methoxy-3-nitrothiophene (1a) with sodium methoxide in methanol. This compound constituted the first example of a methoxy mononitro derivative containing no other activating group (electron-withdrawing substituents, heterocyclic nitrogen atoms, *etc.*) for which the formation of a Meisenheimer-type adduct could be demonstrated.[1,2]

Although the Meisenheimer compounds are considered a good model for intermediates in aromatic nucleophilic substitutions,[3] only a few reports have been published concerning substituent effects on the formation of Meisenheimer adducts.[4] In order to explore the possibility of establishing a linear free energy correlation between logarithmic kinetic and/or equilibrium constants and σ_p^- substituent constants,[5] we have studied the formation of Meisenheimer-type adducts between some 2-methoxy-3-nitrothiophenes (1a—g) and sodium methoxide in methanol.

At the time of the preliminary communication [6] of this work, data concerning the formation of (2f) [7] and (2g) [8] were already available. We will provide additional data regarding the temperature dependence of the formation of (2f) from (1f).

Since ^{13}C chemical shifts were expected to give information concerning substituent effects on charge distribution, we have also carried out a ^{13}C n.m.r. spectroscopic study of both the substrates (1a—g) and the adducts (2a—g).

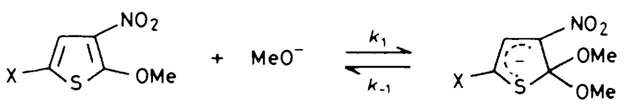
Results and Discussion

Spectroscopic Evidence for the Formation of Adducts (2b—e). —^1H *N.m.r. spectra.* The spectra (Table 1) of compounds (1b—e) in dimethyl sulphoxide show, in addition to the signals of the 5-X group, two singlets of relative intensity 1 : 3 at δ 7.96—8.31 and 5.75—5.80, attributed to the aromatic and methoxy protons, respectively. The addition of concentrated methanolic sodium methoxide results in the appearance of new signals at δ 7.03—7.40 and 3.17—3.20 of relative intensity 1 : 6; concomitantly the signals relative to the 5-X group also move to higher field.

Table 1. Chemical shifts[a] (δ) for some 2-methoxy-3-nitro-5-X-thiophenes (1b—e) and the corresponding adducts (2b—e)

Compound	4-H	OMe	X
(1b)	8.17	4.20	7.55[b]
(2b)	7.21	3.17	6.90[b]
(1c)	7.96	4.24	3.82[c]
(2c)	7.25	3.17	3.58[c]
(1d)	8.31	4.23	2.51[d]
(2d)	7.40	3.16	2.14[d]
(1e)	8.10	4.25	3.40[e]
(2e)	7.03	3.20	2.96[e]

[a] Internal tetramethylsilane, δ 0. [b] $CONH_2$ protons: in (1b), d; in (2b), s. [c] CO_2Me protons. [d] Ac protons. [e] SO_2Me protons.



(1) (2)

a; $X = H$
b; $X = CONH_2$
c; $X = CO_2Me$
d; $X = Ac$
e; $X = SO_2Me$
f; $X = CN$
g; $X = NO_2$

The n.m.r. pattern supports the formation of Meisenheimer adducts (2b—e).

U.v.-visible spectra. The spectra (200—400 nm) of compounds (1b—e) in methanol show the absorption maxima reported in Table 2. 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 depending on the compound, the substrates were completely converted into adducts, the absorption maxima and the extinction coefficients being now

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† Presented in part at a meeting of the Società Chimica Italiana, Catania, 1978; for Part 1, see ref. 1.

Table 2. Spectrophotometric data for substrates (1b—f) and the corresponding adducts (2b—f) in methanol

Compd.	$\lambda_{max.}$/ nm	$\varepsilon_{max.}$/l mol^{-1} cm^{-1}	Compd.	$\lambda_{max.}$/ nm	$\varepsilon_{max.}$/l mol^{-1} cm^{-1}
(1b)	250	14 500	(2b)	294	11 400
	282	9 660		392	19 200
	322	5 340			
(1c)	246	14 200	(2c)	300	6 200
	284	11 300		406	15 700
	315	5 540			
(1d)	248	14 000	(2d)	310	6 100
	300	12 200		436	17 900
(1e)	240	15 200	(2e)	285	4 820
	265	8 310		385	14 800
	310	5 100			
(1f)[a]	278	8 800	(2f)	290	4 900
	313	5 300		399	17 000

[a] Data from ref. 7.

those indicated in columns 5 and 6 of Table 2; further increase in base concentration caused no further spectral change.

The observed spectral changes are reasonably accounted for by the formation of Meisenheimer adducts (2b—e).

Kinetic and Equilibrium Studies.—Equilibrium constants. The equilibrium constant for the formation of compounds (2) can be determined from spectral measurements of methanolic solutions of compounds (1b—e) and sodium methoxide provided that the extinction coefficients of substrates (ε_s) and adducts (ε_a) are known.

Equations (i) apply, where D_e represents the optical density of the solution at equilibrium, b the substrate concentration [the sodium methoxide concentration, being in large excess over that of (2), is assumed to be constant], and l the thickness of the cuvette in cm.

$$[(2)] = \frac{D_e/l - \varepsilon_s b}{\varepsilon_a - \varepsilon_s},\ K_e = \frac{[(2)]}{[(1)][\mathrm{MeONa}]},\ \text{and}\quad [(1)] = b - [(2)] \qquad \text{(i)}$$

Alternatively, the values of K_e and ε_a can be determined simultaneously from the Benesi–Hildebrand equation (ii).[9]

$$b/(D_e - \varepsilon_s b) = 1/(\varepsilon_a - \varepsilon_s) + 1/K_e(\varepsilon_a - \varepsilon_s)[\mathrm{MeONa}] \qquad \text{(ii)}$$

We have measured the equilibrium optical densities of a series of solutions containing various amounts of compounds (1b—d) and sodium methoxide, at various temperatures. Least-squares treatment of equilibrium data according to equation (ii) has furnished the results given in Table 3.

Owing to the relatively high stability of the adducts (2e) and (2f), the equilibrium constants for these two compounds were obtained by rate measurements (see later).

The values of K_e for the formation of adducts (2b—f) at 293.2 K and the thermodynamic parameters are reported in Table 5 together with the data already available for (1a) and (1g).

Rate constant measurements. Kinetic constants for the formation of (2b—f) were determined spectrophotometrically, as previously described,[10] in the presence of a large excess of sodium methoxide.

The second-order constants were obtained by equation (iii).

$$k_{obs.} = k_1([\mathrm{MeONa}] + K_e^{-1}) \qquad \text{(iii)}$$

The plots of $k_{obs.}$ for the formation of adducts (2e) and (2f) *vs.* [MeO$^-$] gave intercepts too small for accurate determination of k_{-1} values. We therefore followed the decomposition of adducts in two buffers, namely 2,6-dichlorophenol–2,6-dichlorophenoxide and 4-cyanophenol–4-cyanophenoxide, at ionic strength 0.01M.

The independence of the observed first-order constant $k_{obs.}$ of pH and of the buffer used (Table 4) showed that we had found the plateau values where $k_{obs.} = k_{-1}$.

The rate coefficients for the formation and/or decomposition of the adducts (2b—f) determined at various temperatures are collected in Table 4. The relevant activation parameters are reported in Table 5.

For comparison we report in Table 6 kinetic and equilibrium data for the Meisenheimer adducts (3) formed in the reaction between methoxide ion and some 2,6-dinitro-4-X-anisoles.[11]

Discussion. The logarithmic kinetic and/or equilibrium constants for the formation of adducts (3) give a good linear correlation with the σ_p^- constants of 4-X substituents (Figure 1).* On the other hand an excellent linear correlation does exist between log K_e and log k_1 (Figure 2). These observations show that the structural modification of the substrate brought about by the 4-X substituent does not alter the nature of the steric interactions in the reaction area. For this reason there is a straightforward linear relationship between the activation and/or reaction free energy and the charge delocalization ability of the electron-withdrawing substituent as measured by σ_p^-.

The adducts (2) differ structurally from the analogous † benzene systems (3) in having one, rather than two, nitro groups flanking the reaction centre and in the presence of the sulphur heteroatom, which is capable, in principle, of participating in charge delocalization.

An examination of rate and equilibrium constants for the formation of adducts in the two series of compounds (Tables 5 and 6) brings out the following points: (i) all the thiophene adducts possess a stability higher than benzene adducts; (ii) the benzene series shows a greater variation in stability than the thiophene series, with increasing electron-withdrawing power of the *para*- (or *para*-like) substituent; (iii) the k_1 values are of the same order of magnitude for corresponding members of each series; differences in stability are mainly caused by differences in k_{-1} values.

Moreover, although both kinetic and equilibrium constants for the formation of adducts (2) increase, as expected, with increasing electron-withdrawing ability of the 5-X substituent, the correlation of log K_e or log k_1 with σ_p^- is not linear, neither is the ' direct ' correlation between log K_e and log k_1 (Figures 3 and 4).

In order to explain the different stability and reactivity patterns observed for the two aromatic systems, it is necessary to consider the role played by the hyper-*ortho* relation [1,13] which is peculiar to thiophene derivatives and can be exemplified with reference to the quinonoid form (4).

The extent to which through-conjugation between the 2-methoxy and 3-nitro groups occurs is a function of the 5-X substituent. In particular, when this substituent is H, or CONH$_2$, CO$_2$Me, or Ac (that is, a ' mild ' electron-withdrawing substituent), there is a significant ' preferential ' through-

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* A similar linear correlation between log K_e and log k_1, for the formation of adducts (3) in water, with σ_p^- has been recently observed by Bernasconi.[12]

† The 2,6-dinitroanisole series presents a degree of activation close to that of 2-methoxy-3-nitrothiophene derivatives. For this reason and because complete data on corresponding 2-nitro-4-X-anisoles are lacking, we have chosen (3) as reference compounds.

Table 3. Linear regression analysis[a] of equilibrium data according to the Benesi–Hildebrand equation: $y = m/a + n$

X	T/K	$m \pm s_m$	$n \pm s_n$	r	n_p	ε_a	K_e
$CONH_2$	289.2	0.148 ± 0.002	5.40 ± 0.13	0.9996	7	18 500	36.5 (1.4)
	293.4	0.156 ± 0.002	5.31 ± 0.18	0.9996	7	18 800	34.0 (1.6)
	298.3	0.166 ± 0.002	5.23 ± 0.16	0.9997	8	19 100	31.5 (1.4)
	302.8	0.177 ± 0.002	5.20 ± 0.15	0.9998	8	19 200	29.4 (1.2)
CO_2Me	288.3	0.0482 ± 0.0005	5.87 ± 0.05	0.9996	8	17 000	122 (2.0)
	296.4	0.0560 ± 0.0007	5.73 ± 0.08	0.9997	6	17 500	102 (3.0)
	303.1	0.0632 ± 0.0010	5.63 ± 0.11	0.9995	6	17 800	89.1 (3.2)
Ac	288.2	0.0317 ± 0.0004	5.12 ± 0.17	0.9994	7	19 500	162 (8.0)
	296.0	0.0345 ± 0.0006	5.12 ± 0.15	0.9993	6	19 500	148 (7.0)
	303.0	0.0382 ± 0.0003	5.03 ± 0.13	0.9997	7	19 900	132 (5.0)

[a] $m = 10^5/K_e\varepsilon$; $n = 10^5/\varepsilon$; s_m and s_n are the standard deviations of m and n, respectively; r is the correlation coefficient; n_p is the number of data points. The values in parentheses represent the maximum estimated error of K_e values.

Table 4. Kinetic constants for the formation and for decomposition of adducts (2b—f) in methanol, at various temperatures[a]

Adduct	10^2k_1/l mol^{-1} s^{-1} (T/K in parentheses)				
(2b)	1.96 (289.1)	2.79 (293.4)	4.23 (298.1)	6.08 (302.9)	
(2c)	7.73 (288.4)	15.2 (296.4)	25.4 (303.2)		
(2d)	20.5 (287.8)	36.4 (295.9)	57.8 (303.0)		
(2e)	34.0 (283.2)	50.7 (288.2)	75.2 (293.2)	110 (298.2)	177 (303.2)
(2f)	60.0 (283.2)	93.0 (288.2)	125 (293.2)	180 (298.2)	275 (303.2)
	10^4k_{-1}/s^{-1} (T/K in parentheses)				
(2e)[b]	2.25 (293.2)	4.11 (298.2)	6.59 (303.2)	9.51 (308.2)	
(2e)[c]	2.56 (293.2)	4.08 (298.2)	6.46 (303.2)	10.0 (308.2)	
(2f)[b]	0.971 (288.2)	1.80 (293.2)	3.15 (298.2)	4.57 (303.2)	
(2f)[c]	0.946 (288.2)	1.64 (293.2)	2.90 (298.2)	4.76 (303.2)	

[a] The rate constants are accurate to within ±4%. [b] 2,6-Dichlorophenol/2,6-dichlorophenoxide buffer. [c] 4-Cyanophenol/4-cyanophenoxide buffer.

Table 5. Kinetic and equilibrium data for the reactions of some 2-methoxy-3-nitrothiophenes (1a—g) with sodium methoxide in methanol

X	K_e[a]/l mol^{-1} s^{-1}	k_1[a]/l mol^{-1} s^{-1}	k_{-1}[b]/s^{-1}	ΔH°[c]/ kJ mol^{-1}	$-\Delta S^\circ$[c]/ J K^{-1} mol^{-1}	$\Delta H_1^\ddagger$[c]/ kJ mol^{-1}	$-\Delta S_1^\ddagger$[c]/ J K^{-1} mol^{-1}	σ_p^-[d]
H	6.0	1.3×10^{-3}[e]	2.17×10^{-4}[e]					0.00
$CONH_2$	34.2	2.78×10^{-2}	8.13×10^{-4}	−11.5	10	57.7	78	0.62
CO_2Me	109	0.116	1.06×10^{-3}	−15.4	14	56.0	72	0.74
Ac	152	0.301	1.98×10^{-3}	−10.0	−8	47.0	94	0.82
SO_2Me	3.13×10^3[f]	0.769	2.46×10^{-4}	−12.1	−26	55.6	57	1.05
CN	7.65×10^3[f]	1.30	1.70×10^{-4}	−2.30	8	50.2	71	0.99
NO_2	3.50×10^5[f]	27.2[g]	7.8×10^{-5}[g]			41.4[g]	75[g]	1.23

[a] Calculated at 293.2 K from thermodynamic (or activation) parameters. [b] Calculated as k_1/K_e. [c] At 293.2 K. [d] Values from ref. 5. [e] Values from ref. 1. [f] Calculated as k_1/k_{-1}. [g] Values from ref. 8.

conjugation between the 2- and 3-positions; when X is SO_2Me, CN, or NO_2 (that is, a strong electron-withdrawing substituent), there is no preferential conjugation; in fact the thiophene derivatives behave like the analogous benzene compounds.*

On account of the more favourable geometry and of the lower aromaticity, the thiophene substrates should be more reactive than the analogous benzene compounds, but the hyper-*ortho* relation, stabilizing the initial state of the thiophene, causes a lowering of reactivity, and thus similar k_1 values are observed for the two aromatic systems.[1,†]

The curvature shown in the plot of log k_1 versus σ_p^- (Figure 4) can be accounted for as follows: when the hyper-*ortho* relation is the prevailing factor, the 5-X substituent possesses a reduced conjugative electron-withdrawing ability (it behaves as having only an inductive effect); the more the conjugation between the 2- and 5-positions gains in relevance (with increasing σ_p^-), the more the preferential conjugation between the 2- and 3-positions is ' interfered with '. Since the transition state benefits more than the starting compound by the increased conjugative ability of the heteroaromatic ring, when X becomes, progressively, SO_2Me, CN, and NO_2, the

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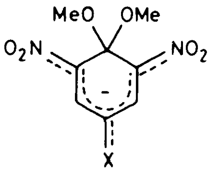
* The hyper-*ortho* relation plays a role not only in the ground state but also in the transition state for the formation of adduct, and in the adduct too.

† In the case of compounds (1e—g), where there is no significant hyper-*ortho* interaction, the stabilization of the initial state is in any case greater than in the analogous benzene derivatives, on account of the greater ' absolute ' conjugation of the methoxy group with the aromatic ring.

Table 6. Kinetic and equilibrium data for the reactions of some 2,6-dinitro-4-X-anisoles with sodium methoxide in methanol, at 293.2 K [a]

X	H	F	Cl	CF_3	SO_2Me	CN	$-N-$ [b]	NO_2	SO_2CF_3
K_e/l mol^{-1}	$7.5-9 \times 10^{-5}$	8.5×10^{-5}	2.5×10^{-3}	5	1.01×10^{2}	1.68×10^{2}	2.87×10^{3}	1.95×10^{4}	1.2×10^{6}
k_1/l mol^{-1} s^{-1}	1.5×10^{-3}	2.5×10^{-3}	1.2×10^{-2}	0.4	1.75	2.82	1.65×10	1.18×10	1.41×10^{2}
k_{-1}/s^{-1}	1.8×10	2.9×10	4.8	8×10^{-2}	1.7×10^{-2}	1.7×10^{-2}	5.7×10^{-3}	6.1×10^{-4}	1.2×10^{-4}

[a] Values from ref. 11. [b] 4-Methoxy-3,5-dinitropyridine.



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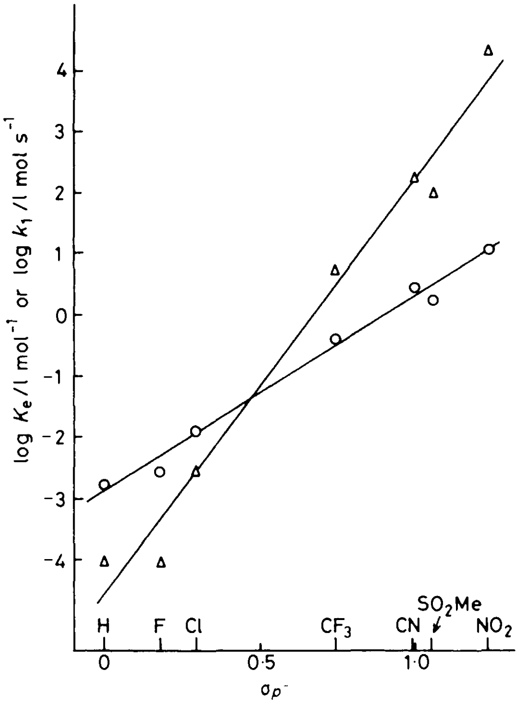

Figure 1. Plot of log K_e (△) or log k_1 (○) for compounds (3) *vs.* σ_p^- constants

function log k_1 (σ_p^-) increases steeply. Of course this effect is more considerable (compare the two curves of Figure 3) with adducts (log K_e *vs.* σ_p^-).

The trend of k_{-1} values with changing 5-X substituent can be rationalized following the same line of reasoning. In particular, on going from X = H to X = Ac, the specific rate of adduct decomposition increases because the relevance of the hyper-*ortho* relation (a factor which stabilizes the adduct more than the initial state) is diminished; as X changes to SO_2Me, CN, or NO_2, 'benzene' behaviour is gradually observed, that is, k_{-1} diminishes in accord with the increased stability of the adduct.

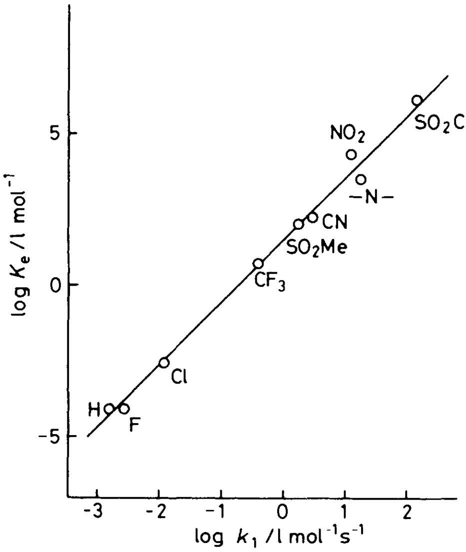

Figure 2. Plot of log K_e values for compounds (3) *vs.* the corresponding log k_1 values

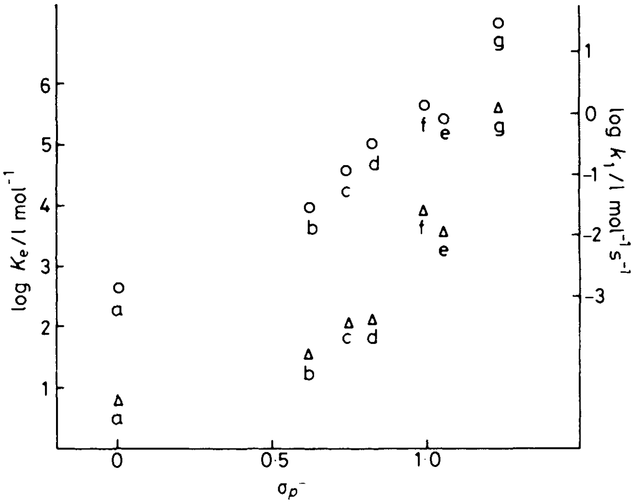

Figure 3. Plot of log K_e (△) or log k_1 (○) for compounds (1) *vs.* σ_p^- constants

^{13}C *N.m.r. Studies.—Spectra.* A more detailed picture of the electronic effects of substituents in stabilizing the substrate and/or the corresponding Meisenheimer complexes would be provided by precise evaluation of charge densities on the carbon atoms. ^{13}C N.m.r. shifts, although sensitive to a variety of other effects,[14] are often claimed to give direct information about this point. However, previous ^{13}C n.m.r. studies of Meisenheimer complexes in the benzene series [15,16] gave results rarely in agreement with expectation. We have carried out an analogous study of Meisenheimer complexes derived from 2-methoxy-3-nitro-5-X-thiophenes to ascertain whether ^{13}C n.m.r. chemical shifts show the same unexpected trends in the thiophene series too. The thiophenes examined have some similarity to the 2,6-dinitro-4-X-anisoles in that the substituent X is far from the ring carbon atom which undergoes methoxide attack, so that steric effects are expected to be constant throughout the series.

Results. ^{13}C N.m.r. chemical shifts of substrates (1a—g) measured in $(CD_3)_2SO$ are reported in Table 7. Assignments were made on the basis of calculated shifts and of the expected larger intensity of the C(4) peak and broadening of the C(3) peak, with respect to the other signals. In parentheses we report for the ring carbon atoms the shifts calculated on the basis of the additivity of substituent effects [17] and for the methoxy and the X carbon atoms the shifts quoted respectively for the corresponding nuclei of 2-methoxythiophene [17] and 2-X-thiophene.[17] Data from ref. 17 refer to acetone solutions. The agreement between observed and expected shifts is not always very good; however, the trends are satisfactory and, in our opinion, no other alternative assignment is reasonable.

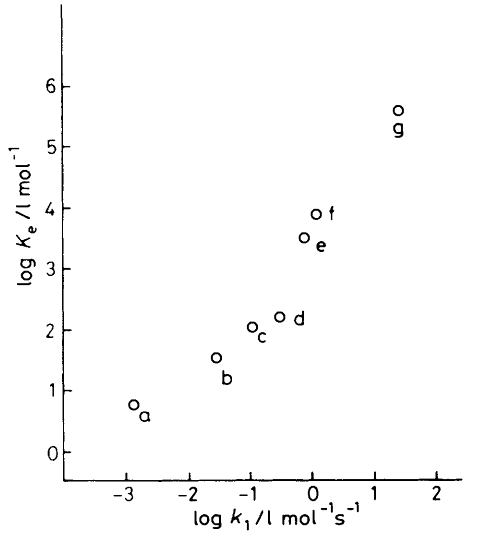

Figure 4. Plot of log K_e values for compounds (1) *vs.* the corresponding log k_1 values

^{13}C N.m.r. chemical shifts of the adducts, formed from compounds (1a—g) [0.4M in $(CD_3)_2SO$] upon addition of 1 equiv. of 5M-MeONa in MeOH, are reported in Table 8. Some of the adducts have short lifetimes (15—20 min) but relaxation of ^{13}C nuclei seems much more effective in the complexes than in the substrates. The intense signal at δ 51—52 was assigned to the methoxy carbon. Assignment of the other peaks was made on the basis of their relative intensities and of the expected low variation of the C(4) chemical shift with respect to the substrate. The assignment of C(3) and C(5) in the compound with X = NO_2 may be reversed; however, this would not appreciably affect our conclusions.

In Table 9 are reported the differences between ^{13}C n.m.r. chemical shifts of Meisenheimer complexes (2a—g) and of the parent substrates (1a—g), together with the measured equilibrium constants.

Discussion. In this kind of study it is generally assumed that the effect of the methoxy group is constant throughout the

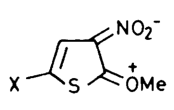

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Table 7. ^{13}C N.m.r. chemical shifts (δ from Me_4Si, Varian XL-200 or FT-80 spectrometers) of substrates (1a—g) [0.4M in $(CD_3)_2SO$]; calculated shifts in parentheses

X	C(2)	C(3)	C(4)	C(5)	C_{OMe}	C_X	
						C_α	C_β or C_γ
H	168.42	128.49	121.61	110.17	63.16		
	(171.6)	(124.9)	(120.4)	(115.7)			
$CONH_2$	170.71	128.46	122.96	122.20	63.58	161.65	
CO_2Me	171.37	129.10	127.96	114.24	64.15	160.68	52.69
	(179.6)	(126.4)	(127.3)	(124.5)		(162.9)	(52.3)
Ac	173.22	129.19	128.69	125.58	64.10	190.26	25.01
	(180.4)	(126.5)	(126.6)	(135.5)		(190.4)	(26.7)
SO_2Me	171.47	128.72	128.12	123.33	64.43		44.70
CN	171.29	128.57	134.71	91.88	64.66	113.19	
	(180.2)	(126.4)	(131.7)	(100.1)		(114.5)	
NO_2	171.28	128.18	125.21	132.92	65.09		
	(180.7)	(126.0)	(123.0)	(141.3)			

Table 8. ^{13}C N.m.r. chemical shifts of Meisenheimer adducts (2a—g)

X	C(2)	C(3)	C(4)	C(5)	C_{OMe}	C_X	
						C_α	C_β or C_γ
H	126.26	117.07	120.50	109.86	51.76		
$CONH_2$	125.87	118.30	125.25	113.37	51.32	164.96	
CO_2Me	127.08	118.63	130.65	104.93	51.74	163.46	51.16
Ac	125.64	120.13	131.91	116.67	51.62	188.26	24.23
SO_2Me	130.61	116.49	129.47	111.95	51.97		43.19
CN	128.78	117.23	134.37	79.62	51.86	117.94	
NO_2 [a]	126.42	118.23 [b]	130.12	119.04 [b]	52.05		

[a] Two additional absorptions at δ 153.23 and 124.64 were ascribed to decomposition products. [b] These assignments could be reversed.

Table 9. Differences between the ^{13}C n.m.r. chemical shifts of Meisenheimer complexes (2a—g) and those of the parent substrates (1a—g)

	$\Delta\delta$						$\Delta\delta_X$		
X	C(2)	C(3)	C(4)	C(5)	$\Sigma\Delta\delta$ [a]	$\Delta\delta_{OMe}$	C_α	C_β or C_γ	K_e
H	−42.2	−11.42	−1.11	−0.31	−12.84	−11.40			6.0
$CONH_2$	−44.8	−10.16	+2.29	−8.83	−16.70	−12.26	+3.31		34.2
CO_2Me	−44.3	−10.47	+2.69	−9.31	−17.09	−12.41	+2.78	−1.53	109
Ac	−47.6	−9.06	+3.22	−8.91	−14.75	−12.48	−2.00	−0.78	152
SO_2Me	−40.8	−12.23	+1.35	−11.38	−22.26	−12.46		−1.51	3 130
CN	−42.5	−11.34	−0.34	−12.26	−23.94	−12.80	+4.75		7 650
NO_2	−44.9	−9.95 [b]	+4.91	−13.88 [b]	−18.92	−13.04			350 000

[a] $\Sigma\Delta\delta$ does not include $\Delta\delta$ for C(2) (*cf.* ref. 15). [b] On reversing the assignment of C(3) and C(5) of the adduct (2g) $\Delta\delta$ for C(3) becomes −9.14 and for C(5) −14.69.

Table 10. Differences between ^{13}C n.m.r. chemical shifts of Meisenheimer compounds derived from 2,6-dinitro-4-X-anisoles and those of the parent substrates, and stability constants

	$\Delta\delta$						$\Delta\delta_X$		
X	C(1)	C(2)	C(3)	C(4)	$\Sigma\Delta\delta$ [a]	$\Delta\delta_{OMe}$	C_α	C_β or C_γ	K_e
CF_3	−44.7	−18.4	+4.8	−30.2	−57.5	−12.6	+3.3		5
COPh	−46.4	−15.6	+5.6	−28.2	−48.2	−12.6	−1.6		45
SO_2Me	−47.0	−17.3	+4.2	−32.0	−58.4	−12.6		+1.6	101
CN	−47.0	−16.5	+2.7	−33.3	−60.8	−12.6	+5.6		168
NO_2	−48.8	−15.2	+4.3	−24.0	−45.8	−12.7			19 500
SO_2CF_3	−51.0	−16.0	+1.4	−36.2	−65.3	−12.7		+1.2	1.2×10^6

[a] $\Sigma\Delta\delta$ does not include $\Delta\delta$ for C(1) (*cf.* ref. 15).

series of substrates examined, so that it can be neglected. This holds strictly for the 2,6-dinitro-4-X-anisoles (X = H, Cl, CF_3, CN, SO_2Me, COC_6H_5, NO_2, or SO_2CF_3) described in ref. 16, where the shift of the methoxy carbon ranged from δ 64.3 (X = H) to 64.8 (X = NO_2 or SO_2CF_3). The assumption is less good in the thiophene series examined here (see Table 7) as the shift of the methoxy carbon ranges from δ 63.16 (X = H) to 65.09 (X = NO_2), showing some sensitivity to the electron-withdrawing power of the 5-X substituent (see before).*

We think that further analysis of ^{13}C n.m.r. chemical shifts of Table 7 is unjustified since the shifts can be markedly influenced by a variety of effects; [14] in fact there is no apparent correlation between the ring carbon chemical shifts and the electron-withdrawing ability of the 5-X substituents.

Inspection of chemical shifts of the Meisenheimer complexes (2a—g) (Table 8) shows, as expected, that only the shifts of C(4) and C(5) vary considerably with X; those of C(3), C(2), and the methoxy carbon are affected only slightly. Analogous results were found in the benzene series.[16]

However, the most interesting data are the shift variations on going from substrates (1a—g) to the corresponding Meisenheimer adducts (2a—g) (Table 9); one might expect that unwanted effects would cancel in these variations,[14] so that they are really indicative of charge density changes around the various carbon nuclei.

The popular belief that substituents stabilize anionic intermediates by taking part of the negative charge leads to the expectations that: (i) the ^{13}C nuclei of the α-carbon atoms of the 5-X substituent are more shielded in the complexes than in the corresponding substrates; (ii) the more stable are the complexes the less additional shielding should be carried by their ring carbon atoms.

However, our findings are roughly opposite to these expectations. Table 9 reveals in fact that the carbon atoms of the substituent directly linked to the ring are generally less shielded in the complexes than in the corresponding substrates, with the exception of the acetyl group. Moreover the observed trend of $\Sigma\Delta\delta$ values for the C(3), C(4), and C(5) ring carbon atoms is opposite to expectation, with the exceptions of compounds where X = Ac or NO_2. Analogous results were found [16] and not interpreted in the benzene series (see the $\Sigma\Delta\delta$ and $\Delta\delta_X$ values of Table 10, taken from ref. 16): here again the only exceptions to the observed trends are the compounds where X is an acyl or a nitro group.

These findings could be explained quite simply by saying that even the differences Δδ examined do not correlate with charge densities. However, it is surprising that the data obtained are not random but show regular trends opposite to expectation in both series and with the same exceptions.

An alternative interpretation would require that most substituents stabilize anionic intermediates not so much by accepting part of their negative charge but mainly by stabilizing the negative fractional charges on ring carbons. Inspection of Δδ values for C(5) (Table 9) shows that they decrease as the thermodynamic stability of the complex increases, with the exception of the compound with X = Ac; however, the value for X = NO_2 may also be regarded as small, in comparison with the marked increase in thermodynamic stability. The main effect of most substituents X should therefore be to stabilize a larger charge density at the carbon atoms to which they are bonded, probably by a charge–dipole interaction,† favoured by an enhanced polarization of the substituent. This has an obvious meaning with regard to substituents like CN; for X = $CONH_2$ or CO_2Me the formation of the adduct would cause the electron reorganization shown in the Scheme, and the CO dipole would stabilize the negative charge on C(5). The observed coalescence of the signals of the amide protons (Z = NH_2) when the adduct is formed (see data in Table 1) can be explained both by the traditional and by the

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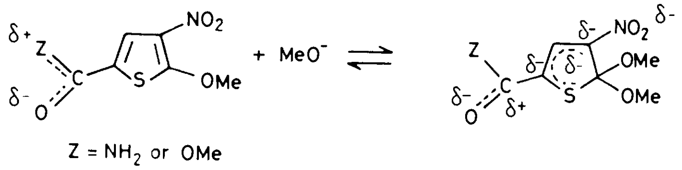
* Indeed, the differences $\Delta\delta_{OMe}$ (Table 9) give a rough linear correlation with σ_p^- substituent constants.

† The importance of charge-dipole interactions *vs.* resonance effects in stabilizing carbanions was stressed recently.[18]



Scheme.

present interpretation. It should be noted that the stabilization of the negative charge density on C(5) also allows a better distribution of the charge among the ring carbons in the complexes.

In addition, the $\Delta\delta$ values for C(4) (Table 10) (ref. 16) decrease on increasing the thermodynamic stability of the complex, with the exception of the compounds where X is an acyl or a nitro-group; thus an analogous interpretation seems to hold also in the benzene series.

Comparison with the study of Olah and Mayr [15] of Meisenheimer complexes obtained from 2,4-dinitro-6-X-anisoles is somewhat hampered by the possibility that steric factors play a role in this series. However, even in this series, among the various compounds examined (corresponding to X = NO_2, CF_3, H, Cl, F, or Me) only that with X = NO_2 could be clearly interpreted on the basis of the current theory.

The hypothesis that the nitro group can really accept part of the negative charge in anionic complexes is not in contrast with the recent findings of Cheng and Brown [19] and of Lipkowitz [20] on *meta*- and *para*-substituted nitrobenzenes, as these studies refer to uncharged molecules.

Another interesting point is that the values of $\Sigma\Delta\delta$ (Table 9) for the three thiophene carbon atoms involved in charge delocalization are dramatically smaller than the values (Table 10) referring to the corresponding five benzene carbons. However, at the moment it is not possible to ascertain which of the various possible effects (*i.e.* the different chemical-shift-variation/charge-unit ratios in the two series, or the different effects of the methoxy group in the substrates of the two series, or the delocalization ability of the sulphur atom, *etc.*) prevails in determining this pattern.

Experimental

Synthesis and Purification of Compounds.—2-Methoxy-3-nitro-5-cyanothiophene,[7] methanol,[21] and stock solutions of sodium methoxide [22] were prepared and/or purified according to the literature methods. Compounds (1b—e) were prepared from the corresponding 2-bromo-3-nitro-5-X-thiophenes [23] as follows, and exhibited correct elemental analytical figures.

Sodium methoxide [from Na (0.5 g) dissolved in dry methanol (25 ml)] was added dropwise, with stirring, to the appropriate 2-bromo-3-nitro-5-X-thiophene (0.02 mol) dissolved in the minimum amount of dry methanol. After 24 h at room temperature, the crystals formed were filtered off.

All the methoxy derivatives were crystallized from methanol or methanol–dioxane and had the following m.p.s (°C): (1b), 240; (1c), 119; (1d), 159; (1e), 178.

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