Meisenheimer-type Adducts from Thiophene Derivatives. Part 6.[1] A Kinetic and Thermodynamic Study of Substituent Effects on the Formation of Some non-*gem* Adducts

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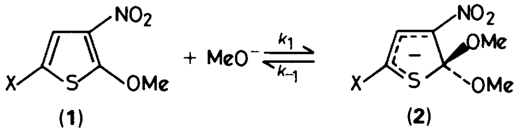
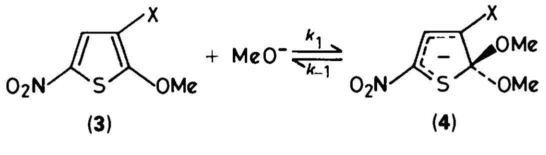
The rate and equilibrium constants for the formation of the Meisenheimer-type adducts [(**6**) and (**8**)] from some 4-nitro-2-X- (**5**) or some 2-nitro-4-X-thiophenes (**7**) and sodium methoxide have been measured at 25 °C in methanol or methanol–dimethyl sulphoxide mixtures. The observed stability and reactivity patterns have been interpreted in the light of the hyper-*ortho* relation in the thiophene ring and the special ability of the nitro group to stabilize effectively the adducts from a *para*-like position also.

Previous studies of the formation of the Meisenheimer-type adducts from some 2-methoxy-3-nitro-5-X-thiophenes (**1a–g**)[2] or 2-methoxy-3-X-5-nitrothiophenes (**3b–f**)[3] and sodium methoxide in methanol showed that the rate of formation and the stability of the thiophene adducts are generally more affected by a substituent variation in the *para* than in the *ortho* position. In fact in 2-methoxy-3,5-dinitrothiophene, common to the two series, the replacement of the nitro group at C-5 with a less electron-withdrawing substituent generally causes a larger lowering in both K and k_1 than that observed for the corresponding substitution of the nitro group at C-3.



(1)



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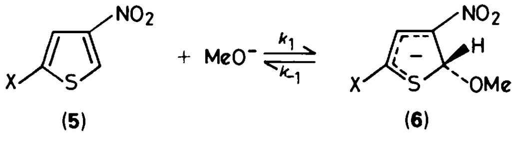

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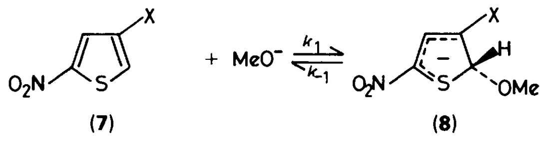


(4)

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 observed stability and reactivity patterns have been interpreted on the basis of a major role played by the hyper-*ortho* relation[4] in the 3-nitro-substituted substrates (**1a–g**), at variance with (**3b–f**); thus, the greater stability and rate of formation of adducts (**4**) with respect to the corresponding adducts (**2**) would result from the preferential conjugative interaction between the 2 and 3 positions which renders substrates (**1**) more stable than substrates (**3**) [compare (**A**)–(**C**) with (**D**)–(**F**)].

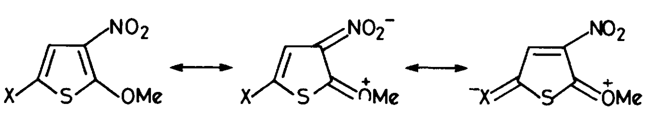
In order to make a comparison between rate and equilibrium data for methoxide attack at an unsubstituted position of the thiophene ring and those for attack at a methoxy-substituted position, we have carried out a kinetic and thermodynamic study of the formation of the Meisenheimer-type adducts from some 4-nitro-2-X-thiophenes (**5c–g**) or 2-nitro-4-X-thiophenes (**7b–g**) and sodium methoxide in methanol or methanol–dimethyl sulphoxide (DMSO) mixtures.

Indeed, the absence of a methoxy group conjugated to a nitro group in compounds (**5**) and (**7**) should bring about very different behaviour in the formation of the corresponding Meisenheimer adducts (**6**) and (**8**).

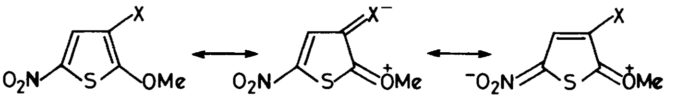
Results

Spectroscopic Evidence for the Formation of Adducts (**6c–f**) *and* (**8b–f**).—^1H *N.m.r. spectra.* The spectra (Table 1 of compounds (**5c–f**) and (**7b–f**) in [$^2H_6$]DMSO show, in addition to the signals of the X group (for X ≠ CN), two doublets of relative intensity 1:1 at δ 8.5–9.1 and 8.2–8.6 (J 1.7–2.0 Hz), attributed to the two ring protons. The addition of concentrated methanolic sodium methoxide results in the appearance of three singlets of relative intensity 1:1:3, at δ 7.1–7.6, 6.1–6.4, and 3.1–3.2; concomitantly the signals relative to the X group, if any, undergo additional shielding (when X = $CONH_2$, coalescence of the two signals is also observed). Therefore, the ^1H n.m.r. pattern supports the formation of Meisenheimer adducts.

Kinetic and Equilibrium Measurements.—By the use of the stopped-flow method as well as conventional methods, we have investigated the kinetics of the formation and decomposition of



(A) (B) (C)



(D) (E) (F)

Table 1. ^1H N.m.r. chemical shifts [δ(ppm)] and J values[a]/Hz in DMSO for some 4-nitro-2-X-thiophenes (**5c–f**) and 2-nitro-4-X-thiophenes (**7b–f**) and the corresponding adducts (**6c, e, f**) and (**8b–f**).

Compound	$\delta(H_\alpha)$	$\delta(H_\beta)$	δ(OMe)	δ(X)	$J(H_\alpha H_\beta)$
(**5c**)	9.05	8.17	—	3.89	1.7
(**6c**)	6.23	7.27	3.09	3.63	—
(**5d**)[b]	9.11	8.51	—	2.62	1.5
(**5e**)	9.12	8.41	—	3.49	1.8
(**6e**)	6.40	7.07	3.13	3.02	—
(**5f**)	9.10	8.62	—	—	1.8
(**6f**)	6.31	7.19	3.13	—	—
(**7b**)	8.51[c]	8.46[c]	—	8.10; 7.61	1.9
(**8b**)	6.17	7.45	3.14	6.93	—
(**7c**)	8.67	8.22	—	3.85	2.0
(**8c**)	6.06	7.48	3.14	3.62	—
(**7d**)	8.75	8.34	—	2.55	2.0
(**8d**)[d]	6.11	7.55	3.11	2.17	—
(**7e**)	8.68	8.52	—	3.37	2.0
(**8e**)	6.17	7.36	3.14	3.00	—
(**7f**)	8.89	8.62	—	—	1.8
(**8f**)	6.17	7.41	3.16	—	—

[a] Varian FT-80 spectrometer. Spectra of adducts were obtained within 15 min of methoxide addition. [b] Addition of sodium methoxide to (**5d**) gives rise, in the following 15 min, to a large number of ^1H n.m.r. absorptions; only when acidification with CF_3CO_2H took place just after methoxide addition, could the starting compound be substantially recovered. [c] These assignments could be reversed. [d] Additional absorption ascribed to decomposition products were detected, while in CD_3OH only the signals of the adducts appeared in the n.m.r. spectrum.

Table 2. Kinetic and equilibrium constants for the formation and for decomposition of adducts (**6c–e**) and (**8b–e**) in MeOH and/or MeOH–DMSO mixtures, at 25 °C.

Adduct	DMSO(%) (v/v)	k_1/dm^3 mol^{-1} s^{-1}	k_{-1}/s^{-1}	K_e/dm^3 mol^{-1}
(**6c**)	30	1.11	0.305	3.64
	50	3.50	0.160	21.9
(**6d**)	30	1.42	0.320	4.43
	50	6.73	0.150	44.9
(**6e**)	0	0.630	0.240	2.60
(**8b**)	50	0.418	7.70×10^{-3}	54.3
	70	3.87	3.00×10^{-3}	1 290
(**8c**)	30	0.445	8.15×10^{-3}	54.6
	50	2.53		
(**8d**)	0	0.0900	0.0120	7.50
	30	0.876	5.50×10^{-3}	159
	50	3.71		
(**8e**)	0	0.310	1.45×10^{-3}	213

Table 3. Kinetic and equilibrium constants for the reactions of some 4-nitro-2-X-thiophenes (**5c–g**) with sodium methoxide in methanol, at 25 °C.

Compound	(**5c**)	(**5d**)	(**5e**)[c]	(**5f**)[d]	(**5g**)[d]
k_1/dm^3 mol^{-1} s^{-1}	0.114[a]	0.146[a]	0.630	2.38	14.9
k_{-1}/s^{-1}	0.665[a]	0.700[a]	0.240	0.350	0.0175
K_e/dm^{3}mol^{-1}	0.170[b]	0.210[b]	2.60	6.80	850

[a] Values extrapolated from data obtained in 30 and 50% DMSO; see Table 1. [b] Calculated from $K_e = k_1/k_{-1}$. [c] At 20 °C, k_1 0.362 dm^3 mol^{-1} s^{-1}, k_{-1} 0.157 s^{-1}, K_e 2.28 dm^3 mol^{-1} [P. Hurtel, B. Decroix, J. Morel, and F. Terrier, *J. Chem. Res.*, 1983, (*S*) 58, (*M*) 725]. [d] See ref. 10.

the adducts (**6**)* and (**8**),† in MeOH or MeOH–DMSO, at various temperatures. The reactions were monitored spectrophotometrically at the wavelengths corresponding to the absorption maxima of the adducts. All experiments were carried out under pseudo-first order conditions with a large excess of the methoxide reagent (10^{-3}–0.6 mol dm^{-3}) over the substrate concentration (*ca.* 5×10^{-5} mol dm^{-3}). Under these experimental conditions, the observed first-order rate constant k_{obs} for equilibrium attainment is given by equation (5).

$$k_{obs} = k_1[MeO^-] + k_{-1} \qquad (5)$$

Based on equation (5), values of the rate constants for formation (k_1) and decomposition (k_{-1}) of the adducts (**6**) and (**8**) according to equations (3) and (4) were readily obtained from plots of k_{obs} *vs.* [MeO$^-$] which were linear. These, together with the values of the equilibrium constants $K_e = k_1/k_{-1}$, are summarized in Table 2

Discussion

A number of studies have shown[6–10] that the addition of DMSO to methanolic solutions increases the stability of all methoxy σ adducts as a result of an increase in k_1 and a decrease in k_{-1}. More significantly, good linear and parallel relationships have been obtained on plotting log k_1 as well as log k_{-1} *vs.* the molar fraction of DMSO, implying that the effect of solvent composition on k_1 and k_{-1} and, therefore, on K_e is approximately independent of the nature of the aromatic electrophile which undergoes the nucleophilic addition.[6,8] This observation has proved to be useful to estimate safely rate and equilibrium constants not directly measureable in a given solvent.[6,7] On this basis, we have estimated the rate constants k_1 and k_{-1} for formation and decomposition of the less stable σ adducts (**6**) (X = CO_2Me, Ac) and (**8**) (X = $CONH_2$, CO_2Me) in methanol by extrapolation of the data obtained in MeOH–DMSO mixtures. The parameters thus calculated together with those directly measured for the most stable adducts (**6**) (X = SO_2Me) and (**8**) (X = Ac, SO_2Me) are summarized in Tables 3 and 4. These Tables also present the corresponding data previously reported for the adducts (**6f**) (X = CN), (**8f**) (X = CN) and (**6g**)–(**8g**) (X = NO_2).[11]

An examination of the data in Tables 3 and 4 indicates that both kinetic (k_1) and equilibrium (K_e) constants for the formation of adducts (**6**) and (**8**) increase, as expected, with increasing electron-withdrawing ability of the X substituent.

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* Since in basic solutions compound (**5b**) was rapidly decomposed, it was not possible to measure kinetic and equilibrium constants for the reaction of this substrate with sodium methoxide.

† The attempts to measure the kinetics of the reaction of 2-nitrothiophene in MeOH or MeOH–DMSO mixtures were unsuccessful since we were not able to duplicate the experiments reported by Doddi *et al.*[5] However, the values reported in ref. 5 appear exceedingly high and do not agree well with those calculated from equations in Table 5.

Table 4. Kinetic and equilibrium constants for the reactions of some 2-nitro-4-X-thiophenes (**7b–g**) with sodium methoxide in methanol, at 25 °C.

Compound	(**7b**)	(**7c**)	(**7d**)	(**7e**)[d]	(**7f**)[e]	(**7g**)[e]
k_1/dm^3 mol^{-1} s^{-1}	0.0100[a]	0.0450[c]	0.900	0.310	0.630	14.9
k_{-1}/s^{-1}	0.0350[a]	0.0180[c]	0.0120	1.45×10^{-3}	5×10^{-3}	0.0175
K_e/dm^3 mol^{-1}	0.285[b]	2.50[b]	7.50	213	126	850

[a] Calculated from data in 50% DMSO assuming the same solvent dependence as for the adducts (**6e**), (**6d**), and (**8d**); see Table 2. [b] Calculated from $K_e = k_1/k_{-1}$. [c] Calculated from data in 30% DMSO assuming the same solvent dependence as for the adduct (**8d**); see Table 2. [d] At 20 °C, k_1 0.220 dm^3 mol^{-1} s^{-1}, k_{-1} 0.001 s^{-1}, K_e 220 dm^3 mol^{-1} [P. Hurtel, B. Decroix, J. Morel, and F. Terrier, *J. Chem. Res.*, 1983, (*S*) 58, (*M*) 725]. [e] See ref. 10.

Table 5. Linear free-energy relationships[a] for the reaction of some 4-nitro-2-X-thiophenes (**5c–g**) or some 2-nitro-4-X-thiophenes (**7b–g**) with sodium methoxide in methanol, at 25 °C.

Relationship	$\rho \pm s_\rho$ (or $\beta \pm s_\beta$)	*R*	*n*	CL
$\log k_1$ (**5**) $= \rho\sigma_p^-$	4.61 ± 0.60	0.983	4	98.0%
$\log K_e$ (**5**) $= \rho\sigma_p^-$	7.91 ± 0.77	0.991	4	99.0%
$\log k_1$ (**5**) $= \beta \log k_e$ (**5**)	0.58 ± 0.07	0.981	5	99.0%
$\log k_1$ (**7**) $= \rho\sigma_p^-$	5.15 ± 0.16	0.999	5	99.9%
$\log k_e$ (**7**) $= \rho\sigma_p^-$	5.72 ± 0.55	0.987	5	99.0%
$\log k_1$ (**7**) $= \beta \log K_e$ (**7**)	0.87 ± 0.11	0.979	5	99.0%

[a] ρ and β, susceptibility constants; s_ρ, standard deviation of ρ; s_β, standard deviation of β; *R*, correlation coefficient; *n*, number of points; CL, confidence level for significance of the correlation.

The logarithmic equilibrium and/or kinetic constants give fair to excellent linear correlations with the σ_p^- constants[12] of X substituents (Table 5, lines 1–4)* and the values of the Hammett reaction constants are consistent with the necessity of delocalizing a greater negative charge in the adducts [ρ_e (**6**) 7.9, ρ_e (**8**) 5.7] than in the corresponding transition states [ρ_1 (**6**) 4.6, ρ_1 (**8**) 5.1]. On the other hand, the 'direct' correlations between log K_e and log k_1 give straight lines (Table 5, lines 3 and 6) with slopes (0.58 and 0.87) practically coincident with the relevant ρ_1/ρ_e ratios.

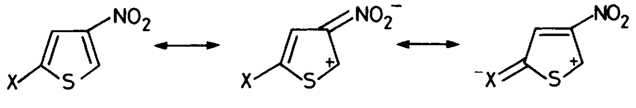
The variations in K_e which accompany the substitution of the nitro group by a less strong electron-withdrawing group (for example, K_e (**6g**)/K_e (**6c**) 5 000 and K_e (**8g**)/K_e (**8b**) 2 980) are mainly caused by the changes in the rate of formation rather than in that of decomposition, suggesting a somewhat complex-like transition state.[13]

In addition, we note that decreasing the electron-withdrawing ability of the X-substituent results in a much larger decrease in the equilibrium constant K_e for adduct formation in the 4-NO_2-2-X series than in the 2-NO_2-4-X series. This confirms previous conclusions reached in comparing the stabilities of the corresponding *gem*-dimethoxy adducts (**2**) and (**4**) and is consistent with the general observation that the presence of a nitro group in a *para*-like position to the sp^3 carbon plays a determining role in delocalizing the negative charge of a σ adduct.[2,3]

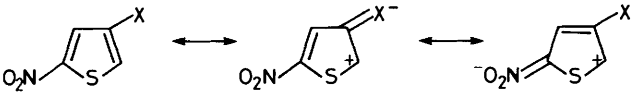
The adducts (**6**) and (**8**) are much less stable than the corresponding adducts (**2**) and (**4**), respectively, on account of both a greater rate of formation and a much lower rate of decomposition of the *gem*-dimethoxy adducts. This behaviour can be explained with reference to the stabilizing effect of the geminal substitution.[14]

A careful analysis of the data reveals, however, a major difference in the substituent effects on the reactions involving MeO$^-$ attack at unsubstituted carbon compared with those involving MeO$^-$ attack at a methoxy-bearing carbon. Thus, we note that the k_1 values for a given X-substituent are greater in the 4-NO_2-2-X series than in the 2-NO_2-4-X series despite the fact that the K_e values are lower in the former than in the latter series.

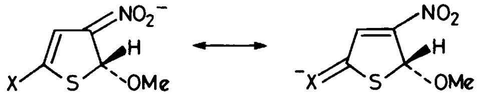
The reactivity sequence k_1 (**8**) < k_1 (**6**) is in agreement with the results of piperidino debromination of 3,5-disubstituted 2-bromothiophenes in methanol, which occurs faster with substituted 2-bromo-3-nitro-5-X derivatives[15] than with the corresponding substituted 2-bromo-5-nitro-3-X derivatives.[16] This is consistent with the general observation that a nitro group in an *ortho*-like position to the reacton centre (hyper-*ortho* relationship) brings about a greater activation than it does in a *para*-like position [compare the major resonance contributors (**B′**) and (**E′**)].



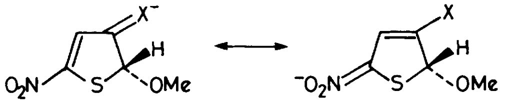
(**A′**) (**B′**) (**C′**)



(**D′**) (**E′**) (**F′**)



(**G′**) (**H′**)



(**I′**) (**L′**)

On the other hand, adducts (**6**) are less stable than adducts (**8**) because in the former the negative charge is predominantly stabilized by the 3-nitro group (**G′**), whereas in the latter compounds both nitro and X substituents concur in delocalizing the charge (**I′** and **L′**).

The contrasting behaviour of the reactions leading to adducts (**2**) and (**4**) on the one hand and (**6**) and (**8**) on the other hand is a significant result in that it adds to the evidence favouring the efficiency of the hyper-*ortho* relationship in the 2-methoxy-3-nitrothiophenes.

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* Since the σ_p^- substituent 'constant' for the methylsulphonyl group appears to be dependent on the reaction in which the relevant substrate is involved, we have excluded data for X = SO_2Me from some calculations.

Conclusions

In conclusion, all of the results obtained imply that when there is no methoxy group at the reaction site and the starting compound is consequently not stabilized by through-conjugation with the nitro group, the Meisenheimer adducts are formed faster than the corresponding *gem*-adducts. On the other hand, the attack of methoxide ion at C-2 is faster and the Meisenheimer adduct is less stabilized when the nitro group is at C-3 and the X-substituent is at C-5 than *vice versa*.

These findings confirm the role of the hyper-*ortho* relation in the thiophene compounds.

Experimental

Synthesis and Purification of Compounds.—Compounds (**5c**),[17] (**5d**),[18] (**5e**),[19] (**7c**),[20] (**7d**),[21] (**7e**),[15] methanol,[22] and stock solutions of sodium methoxide[23] were prepared and/or purified according to the literature methods. Compounds (**5b**) and (**7b**) were prepared as follows and exhibited correct elemental analyses.

4-*Nitrothiophene*-2-*carboxamide* (**5b**). 4-Nitrothiophene-2-carboxylic acid[17] was converted into the acyl chloride (by thionyl chloride) and then into the *amide* (**5b**) by treatment with aqueous ammonia. The solid obtained was crystallized from methanol, m.p. 152–3 °C (lit.,[24] m.p. 149–151.5 °C).

5-*Nitrothiophene*-3-*carboxamide* (**7b**). Compound (**7b**) was obtained from 5-nitrothiophene-3-carboxylic acid[19] as above and crystallized from methanol, m.p. 161–162 °C (lit.,[24] m.p. 163–164 °C).

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