Aromatic nucleophilic substitution reactions of some 3-nitro-2-*p*-nitro-phenoxy-5-X-thiophenes with substituted anilines in methanol

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A series of optimised 'thiophene' sigma constant values has been calculated by using the reactions of some 3-nitro-2-*p*-nitrophenoxy-5-X-thiophenes with some substituted anilines. The susceptibility constants obtained are discussed in the framework of the reactivity–selectivity principle.

Continuing our studies on the application of the Hammett equation to aromatic nucleophilic substitution reactions occurring in thiophene compounds,[15] we now report data for the reactions of some 3-nitro-2-*p*-nitrophenoxy-5-X-thiophenes (**1**: X = H, Br, CONH$_2$, CO$_2$Me, Ac, SO$_2$Me, CN, NO$_2$) with various substituted anilines (**2**: Y = *p*-OMe, *p*-Me, H, *m*-Cl, *p*-Cl) in methanol at 0–40 °C. This study is aimed at verifying the general applicability of 'thiophene' σ-values[15] and to gain information about the influence of the nature of the nucleophilic amine on the susceptibility constant ρ(Y).

All the reactions are first order in both substrate and nucleophile. Therefore, they proceed *via* the generally accepted attachment-detachment mechanism[16] with the formation of the first transition state as rate determining step.

The logarithmic relative kinetic constants [log (k_X/k_H)] for the reactions of **1** with a given Y substituted aniline have been correlated using a monolinear relationship of the Hammett type with the σ_p^- constants[17] defined from acidity constants of anilinium ions. To optimise the statistical results and obtain a homogeneous set of 'thiophene' σ constants pertaining to the reaction system investigated, we have utilised Brown's method (extended selectivity treatment).[18] The scale of optimised 'thiophene' σ_X^- values has been 'anchored' to the σ$^-$ constant for NO$_2$ as the substituent ($\sigma_{NO_2}^-$ 1.23). A comparison of the anchored thiophene σ$^-$ constants, $\sigma_{anc.}^-$, obtained for anilino substitution reaction of **1** with those previously calculated for the reactions of some 2-L-3-nitro-5-X-thiophens with aniline[15] or piperidine[15] in methanol (σ_T^-), confirms the general applicability of the σ_T^- set substituent constants to reactions occurring on thiophene systems. Using $\sigma_{anc.}^-$ values, we have calculated optimised ρ(Y) values (Tables 1 and 2).

In spite of variations of absolute reactivity with changing Y substituent in the aniline and X substituent in the substrate, the reaction selectivity, as measured by ρ(Y), is insensitive to the nucleophile variation, pointing out a failure of the selectivity-reactivity principle.[19]

On the other hand, the general applicability of such relationships as the Hammett-type equations to thiophene compounds shows that by changing the 5-X substituent the

transition state structure changes regularly getting closer to the intermediate σ-complex as the reactivity decreases.

Aromatic nucleophilic substitutions such as those reported here are not simple processes in which only a single bond is formed and only a single bond is broken in the transition state but the pattern of bond making and bond-breaking processes is more complicated. Indeed, the hydrogen-bonding interaction between the incipient 'ammonium hydrogen' and oxygen atoms of the 3-nitro group plays an important role in determining the energy of the first transition state of the attachment-detachment mechanism.[21]

Structure–reactivity relationships have been conveniently visualised by using a More O'Ferrall-Jencks diagram[22] (Figure 1).

With increasing basicity of the aniline the transition state moves back with respect to hydrogen-bonding but the degree
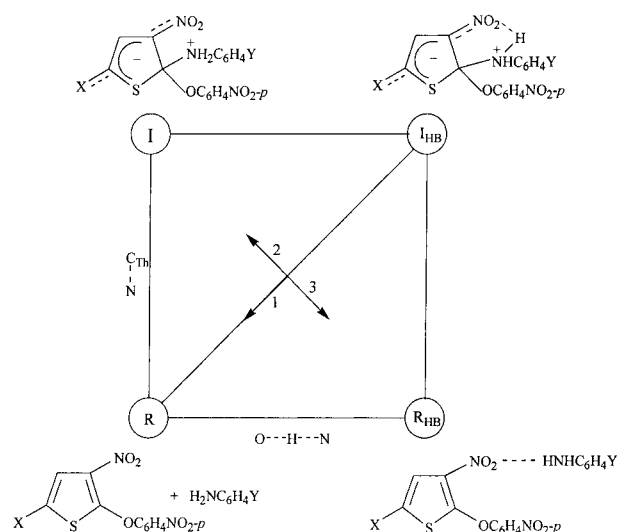

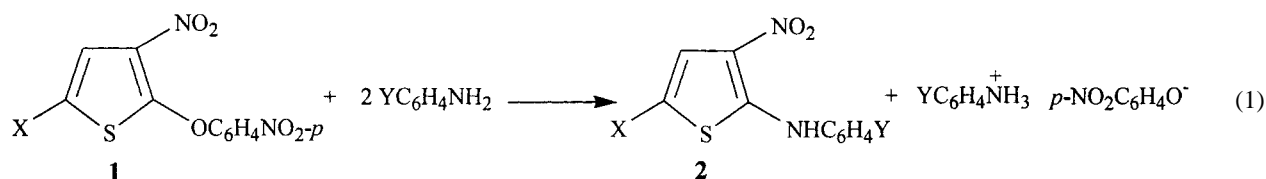**Fig. 1**   More O'Ferrall-Jencks structure-reactivity diagram

$$\mathbf{1} + 2\ YC_6H_4NH_2 \longrightarrow \mathbf{2} + YC_6H_4\overset{+}{N}H_3\ \ p\text{-}NO_2C_6H_4O^- \tag{1}$$

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Table 1 Logarithmic kinetic constants and activation parameters[a] for the reaction of 3-nitro-2-p-nitrophenoxy-5-X-thiophenes (**1**) with substituted anilines ($YC_6H_4NH_2$) in methanol at 20 °C

Y X/(pK_a)[b]	p-OMe (5.36)	p-Me (5.08)	H (4.60)	m-Cl (3.52)	p-Cl (3.98)
H	−3.624 48.0, −150	−4.022 48.9, −155	−4.476 50.7, −157	−5.498 54.6, −164	−4.993 51.5, −164
Br	−2.392 38.2, −160	−2.799 43.0, −152	−3.249 44.3, −156	−4.187 48.3, −160	−3.801 45.6, −162
$CONH_2$	−1.833 36.1, −156	−2.329 39.5, −155	−2.708 40.3, −159	−3.753 46.1, −159	−3.206 43.1; −159
CO_2Me	−1.474 33.9, −157	−1.859 35.6, −160	−2.274 38.3, −157	−3.329 42.4, −164	−2.849 40.3, −162
COMe	−0.996 32.2, −154	−1.407 32.8, −160	−1.802 36.2, −156	−2.848 38.5, −168	−2.381 36.1, −167
SO_2Me	−0.800 31.3, −150	−1.107 32.5, −155	−1.562 34.5, −157	−2.632 42.0, −152	−2.133 37.3, −158
CN	−0.710 31.5, −151	−1.112 31.9, 157	−1.549 35.8, −152	−2.568 40.9, −154	−2.071 36.2, −161
NO_2	−0.499 27.7, −140	−0.099 27.8,− 148	−0.353 30.6, −147	−1.396 32.1, −162	−0.879 31.6, −154

[a]For each couple X–Y the number on the first line represents log k calculated at 20 °C from activation parameters; the numbers on the second line are, respectively, $\Delta H^{\neq}$/kcal/mol at 20 °C, and $\Delta S^{\neq}$/cal/mol/K at 20 °C. The kinetic constants, k/l/mol/s, measured in the range 0–40 °C were reproducible to within ± 3 %; the maximun error of $\Delta H^{\neq}$ is ± 0.5/kcal/mol; the maximun error of $\Delta S^{\neq}$ is ± 2 cal/mol/K. [b]D. Spinelli, G. Consiglio, R. Noto and V. Frenna, *J. Org. Chem.*, 1976, **41**, 968.

Table 2 Substituent constants

	X	H	Br	$CONH_2$	CO_2Me	COMe	SO_2Me	CN	NO_2
1.	σ_p^{-} [a]	0.00	0.30	0.62	0.74	0.82	1.05	0.99	1.23
2.	σ_p^{-} [b]	0.00	0.41	0.59	0.72	0.88	0.95	0.97	1.37
3.	$\sigma_{anc.}^{-}$ [b]	0.00	0.37	0.53	0.65	0.79	0.86	0.87	1.23
4.	σ_T^{-} [c]	0.00	0.35	0.51	0.65	0.80	0.83	0.87	1.23

[a] Values from ref. 16. [b] See text. [c] Values from ref. 14.

of carbon–nitrogen bond formation is expected to be only slightly affected. This agrees with the invariance of the ρ(Y) value with changing Y.

On the other hand, β values near to unity point out that the substituents in the aniline moiety cause, with respect to X = H, a change in the position of the rate determining transition states along the reaction co-ordinate which is much the same for the two reactions, independently of the aromatic substrate.

In conclusion both ρ(Y) and β(X) values are nearly independent of the substituents, respectively, in the aniline and in the aromatic substrate, pointing out similar ranges of rate determining transition states.[23]

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