Aromatic Nucleophilic Substitution Reactions of Some 2-L-3-Nitro-5-X-thiophenes with Piperidine and Aniline in Methanol. Substituent Constants for the Thiophene System

Giovanni Consiglio,[a] Vincenzo Frenna,[b] Caterina Arnone,[a] Elisabetta Mezzina[a] and Domenico Spinelli[a]

[a] *Dipartimento di Chimica Organica 'A. Mangini', Università di Bologna, Via S. Donato 15, 40127 Bologna, Italy*

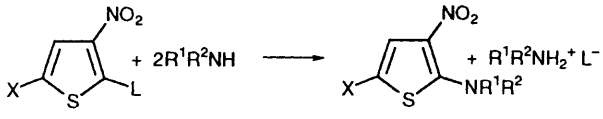
[b] *Dipartimento di Chimica Organica, Università di Palermo, Via Archirafi 20, 90123 Palermo, Italy*

The rate constants for the reactions of some 2-L-3-nitro-5-X-thiophenes **1**–**4** with aniline and of compounds (**4**) with piperidine in methanol have been measured at various temperatures. By using the data obtained in this work as well as previously available data sets, a series of optimized 'thiophene' σ_T values has been calculated. The susceptibility constants ρ(L) of the various sets have been analysed in the framework of the reactivity–selectivity principle.

The Hammett equation, orginally proposed to evaluate quantitatively the substituent effects in the reactions of *meta*- and *para*-substituted benzene derivatives,[1] has also been successfully applied to the reactions of six- and five-membered heterocyclic compounds.[2]

The validity and the application of such linear free energy relationships as the Hammett equation and its modified forms have been extended to the study of aromatic nucleophilic substitutions.[3]

We have studied the application of the Hammett equation to piperidino-substitutions of some 2-L-3-nitro-5-X-thiophenes (**1**–**3**, **5** and **6**).[4] Since the effect of a substituent conjugated



1–6 **7, 8**

R^1R^2NH = aniline or piperidine

1 L = Cl	**a** X = H
2 L = Br	**b** X = Br
3 L = $OC_6H_4NO_2$-*p*	**c** X = $CONH_2$
4 L = OC_6H_5	**d** X = CO_2Me
5 L = I	**e** X = Ac
6 L = $SO_2C_6H_5$	**f** X = SO_2Me
7 R^1R^2N = NHC_6H_5	**g** X = CN
8 R^1R^2N = $N(CH_2)_5$	**h** X = NO_2

Scheme 1

directly with the reaction centre cannot be adequately described by a 'normal' Hammett substituent constant,[5] the S_NAr reactivities were correlated by means of 'thiophene' σ-substituent constants[4] suitable for this kind of aromatic substitution.

We now report on a study of the reactions of some 2-L-3-nitro-5-X-thiophenes with aniline in methanol at 293.15 K. This reaction offers the possibility of verifying whether or not the 'thiophene' σ-values are generally applicable, and of gaining information about the influence of the nature of the nucleophilic amine on the Hammett susceptibility constant ρ.

For the sake of comparison we have also measured the kinetic constants of the reactions of 2-phenoxy-3-nitro-5-X-thiophenes **4** with piperidine in methanol.

Results and Discussion

Reaction Products.—Compounds **1**–**4** gave the expected amino derivatives **7**, **8** on treatment with aniline or piperidine in methanol, in high yields (> 95%) as indicated by TLC and UV–VIS (200–450 nm) spectral analysis of the mixtures obtained after complete reaction.

Kinetic Data.—Rate constants and activation parameters for anilino-substitutions of 2-L-3-nitro-5-X-thiophenes **1**–**4** and for piperidino-substitution of compounds **4** are shown in Table 1. All the reactions were first order in both substrate and nucleophile. An increase in reactivity was observed upon introduction of electron-withdrawing groups into the parent aromatic substrate (X = H). According to the generally accepted attachment–detachment mechanism (bimolecular, with significant involvement of the solvent in the transition state), all the reactions are controlled mainly by the activation enthalpy and show nearly constant and large, negative activation entropy values.

Linear Free Energy Correlations.—The kinetic data for the anilino-substitution reactions of compounds **1**–**4** have been correlated using a monolinear relationship of the Hammett type with the σ_p^- constants defined from acidity constants of anilinium ions[5a] (Table 2, entry 1). The same treatment has been applied to the piperidino-substitution reaction of compounds **4**. The ρ(L) values at 293.15 K (data for **1f**–**4f** have been excluded)† are reported with other statistical data in Table 3, columns 4–6.

To optimize the statistical results and obtain a homogeneous set of 'thiophene' σ constants, we have applied Brown's method (extended selectivity treatment).[7] Thus, $\log(k/k_H)$ values for the reactions of 2-L-3-nitro-5-X-thiophenes with aniline or piperidine have been plotted, for a given 5-X substituent, against the corresponding ρ(L) values. The slopes of the various straight lines so obtained represent a series of optimized 'thiophene' σ_X values (Table 2, entry 2). This scale of σ constants can be 'anchored' to the σ constant for NO_2 as the substituent, as derived from the acidity constant of *p*-nitroanilinium ion[5a] (σ_{NO_2} 1.23; Table 2, entry 1), by multiplying each value σ_X by the ratio 1.23:1.29. The anchored thiophene σ constants, σ_T, are reported in Table 2, entry 3, where the differences, $\Delta\sigma$, between σ_T constants and the reference σ values of the first entry are also shown.

† Owing to the intrinsic inadequacy of the benzene σ_p^- value for X = SO_2Me, the correlations were improved significantly on exclusion of the data pertaining to this substituent.

Table 1 Logarithmic constants and activation parameters[a] for the reactions of 2-L-3-nitro-X-thiophenes **1**–**4** with aniline and of 2-phenoxy-3-nitro-5-X-thiophenes **4** with piperidine, in methanol at 293.15 K

	L				
X	Cl[b]	Br[b,c]	$OC_6H_4NO_2$-*p*[b]	OC_6H_5[b]	OC_6H_5[d]
H	−5.953 57.4, −163	−6.415 65.2, −145	−4.476 50.7, −157	−5.266 53.4, −163	−2.890 57.3, −105
Br		−4.909 52.6, −159	−3.249 44.3, −156		
$CONH_2$	−4.155 48.2, −160	−4.298 49.2, −159	−2.708 40.3, −159	−3.758 46.8, −157	−1.637 42.7, −130
CO_2Me	−3.588 43.6, −165	−3.755 47.5, −156	−2.275 38.3, −157	−3.393 41.5, −168	−1.132 41.4, −126
Ac	−2.957 41.6, −159	−3.135 45.0, −151	−1.802 36.2, −156	−2.837 43.6, −150	−0.842 50.2, −88
SO_2Me	−2.757 41.2, −157	−2.940 43.8, −151	−1.562 34.5, −157	−2.579 43.1, −147	−0.805 47.3, −100
CN	−2.687 41.1, −156	−2.901 43.7, −151	−1.549 35.8, −152	−2.559 41.0, −155	−0.587 44.8, −105
NO_2	−1.164 35.2, −147	−1.380 38.4, −140	−0.353 30.6, −147	−1.359 31.6, −163	0.263 44.4, −88

[a] For each couple X–L the number on the first line represents log *k* calculated at 293.15 K from activation parameters; the numbers on the second line are, respectively, $\Delta H^{\ddagger}$/kJ mol^{-1} at 293.15 K and $\Delta S^{\ddagger}$/J mol^{-1} K^{-1} at 293.15 K. The kinetic constants, k/dm^3 mol^{-1} s^{-1}, measured in the range 273.15–313.15 K were reproducible to within ±3%: the maximum error of $\Delta H^{\ddagger}$ is ±2 kJ mol^{-1}; the maximum error of $\Delta S^{\ddagger}$ is ±8 J mol^{-1} K^{-1}. [b] Anilino-substitutions. [c] See ref. 6. [d] Piperidino-substitutions.

Table 2 Substituent constants

	X							
	H	Br	$CONH_2$	CO_2Me	Ac	SO_2Me	CN	NO_2
σ_p^-[a]	0.00	0.30	0.62	0.74	0.82	1.05	0.99	1.23
σ_X[b]	0.00	0.37	0.54	0.68	0.84	0.87	0.91	1.29
σ_T[b]	0.00	0.35	0.51	0.65	0.80	0.83	0.87	1.23
$\Delta\sigma$[b]	0.00	0.05	−0.11	−0.09	−0.02	−0.22	−0.12	

[a] Values from ref. 5(*a*). [b] See the text.

Table 3 Susceptibility constants and other statistical data[a] for the reactions of 2-L-3-nitro-5-X-thiophenes with aniline or piperidine in methanol at 293.15 K

	Amine	L	ρ(L) ± s_ρ	r	n	ρ(L) ± s_ρ	r	n
1	Aniline	Cl	3.78 ± 0.34	0.984	6	3.90 ± 0.09	0.999	7
2	Piperidine[b]	Cl	3.47 ± 0.20	0.994	6	3.53 ± 0.09	0.998	7
3	Aniline[c]	Br	3.81 ± 0.29	0.986	7	4.07 ± 0.04	1.000	8
4	Piperidine[b]	Br	3.27 ± 0.19	0.992	7	3.44 ± 0.07	0.999	7
5	Aniline	$OC_6H_4NO_2$-*p*	3.14 ± 0.21	0.989	7	3.35 ± 0.05	0.999	8
6	Piperidine[b]	$OC_6H_4NO_2$-*p*	2.68 ± 0.11	0.997	6	2.73 ± 0.08	0.998	7
7	Aniline	OC_6H_5	3.09 ± 0.27	0.985	6	3.19 ± 0.10	0.998	7
8	Piperidine	OC_6H_5	2.53 ± 0.16	0.992	6	2.58 ± 0.06	0.998	7
9	Piperidine[b]	I	3.30 ± 0.25	0.989	6	3.36 ± 0.09	0.998	7
10	Piperidine[b]	$SO_2C_6H_5$	3.97 ± 0.18	0.995	7	4.18 ± 0.09	0.998	8

[a] ρ(L), reaction constants; s_ρ, standard deviation of ρ(L); r, correlation coefficient; n, number of data points. [b] See ref. 4. [c] See ref. 6.

The 5-Br substituent seems to be a more electron attracting substituent than would have been expected on the grounds of the acidity of *p*-bromoanilinium ion.[5a] This behaviour can be accounted for by considering that this substituent has to exert its effect on a reaction where the reaction centre requires the delocalization of a negative charge. The remaining substituents, with the only exception of the 5-acetyl group, display σ_T constants significantly lower than the corresponding reference σ values (Table 2, entry 1).

Even though the anchoring of σ_T scale to σ_{NO_2} has been enforced, it is evident that acetyl and nitro groups are able to transmit their electron-withdrawing effect to the reaction centre more efficiently than are the other 5-X substituents. This result is consistent with previous discussions[8] concerning the

behaviour of such groups as $CONH_2$, CO_2Me, CN, *etc.*, which would interact with the aromatic and heteroaromatic rings mainly by π-electron polarization, at variance with Ac and NO_2 groups, which, in contrast, would genuinely conjugate with the aromatic ring.

Using the σ_T values we have obtained new ρ(L) constants (Table 3, columns 7–9). Cross-correlation of log k/k_H for a leaving group with the same ratio for another leaving group was considered to be a significant statistical test (data not shown). In every case the values of b (the intercept of the straight line with the ordinate log $k/k_H = 0$) was, as expected, near zero whereas the a values practically coincided with the relevant ratios between the ρ(L) values.

All the regression parameters calculated indicate that, the amine being equal, the leaving-group variation can influence significantly the susceptibility constant ρ(L).

There is a minor variation within each pair of halogen and phenoxy leaving groups and a major variation between the two classes of leaving group. Although the reactivity–selectivity principle[9] should only be used to compare very similar systems, the change in ρ(L) with changing the head-atom of the leaving group seems to obey this principle in that halogen leaving groups, which give slower amino-substitution reactions than phenoxy leaving groups, display higher ρ(L) values than do the latter (Table 3; compare entries 1–4 with entries 5–8).

p-Nitrophenoxy derivatives are the most reactive compounds because the C(2) carbon atom of the thiophene moiety is more electrophilic than it is in phenoxy compounds and the *p*-nitrophenoxy group is a better nucleofuge than the phenoxy group. On the other hand, both phenoxy leaving groups, which are electron donors, increase the electron density in the starting compound, thus exerting a levelling effect on the activation of the variable 5-X substituent and causing lower ρ values with respect to halogen leaving groups. Of course, the more electron-donating phenoxy shows a lower ρ value than does the *p*-nitrophenoxy group.

A different combination of the electronic effects renders the halogens less conjugating than oxygen leaving groups and, accordingly, the halogen derivatives display higher ρ values.

A comparison between the ρ(L) values for the anilino-substitution reactions with the ρ(L) values for the piperidino-substitution reactions of the same substrates (Table 3) shows that the more reactive piperidine gives rise to lower ρ values than does aniline, once again in accord with the reactivity–selectivity principle.

The general applicability of such relationships as the Hammett-type equations to thiophene compounds shows that, within each series of substrates, the transition state structure is a regular function of the substrate structure as determined by the variable 5-X substituent. This implies that by changing this substituent the relevant transition state moves along the reaction coordinate getting closer to the intermediate σ complex as the reactivity decreases. In this case we can speak of an 'internal' consistency of our data with the Hammond postulate.

On the other hand, any variation of the ρ value with changing leaving group and/or amine nucleophile puts the comparison on an 'external' basis. We have already pointed out[4] that the absolute ρ value is an index of the sensitivity of the reaction studied to the changes of position of the rate-determining transition state (rdts) on the reaction coordinate as a function of change of the substituent present. The sensitivity is higher if the rdts is late than if it is early because of the different 'average' extent of charge development in the two types of situation.

Experimental

Synthesis and Purification of Compounds.—Compounds **1**–**3**,[4] **7**,[6] **8**,[4] **4a**,[10] **4e**,[10] **4h**,[10] aniline,[5b] piperidine[11] and methanol,[12] were prepared and/or purified as previously reported. Compounds **4c**, **d**, **f**, **g** were prepared as below and gave correct analyses.

Ethers **4c**, **d**, **f**, **g**.—Potassium phenoxide (0.01 mol) was added to a solution of the corresponding 2-bromo-3-nitro-5-X-thiophene (**2**, 0.01 mol) in ethanol and the mixture was kept at room temperature (30 min) or refluxed for 5 min–3 h depending on the nature of the 5-substituent. The mixture was evaporated under reduced pressure. The residue was washed with water and crystallized. The physical data (crystallization solvent in parentheses) are as follows: **4c**, m.p. 225–226 °C (methanol–dioxane); **4d**, m.p. 106–107 °C (methanol); **4e**, m.p. 158–159 °C (methanol); **4f**, m.p. 149–150 °C (methanol–dioxane).

Kinetics Measurements.—The kinetics were followed spectrophotometrically as previously described[13] at the wavelengths previously reported.[4,6] The concentrations used were 5×10^{-5} to 10^{-3} mol dm^{-3} for substrates and 10^{-3} to 1 and 5×10^{-4} to 2×10^{-2} mol dm^{-3} for aniline and piperidine, respectively.

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