# Catalysis in aromatic nucleophilic substitution. Part 12.[1] Kinetics of the reactions of some 2-phenoxy- and 2-(*p*-nitrophenoxy)-3-nitro-5-X-thiophenes with benzylamine and *N*-benzylmethylamine in benzene

**Giovanni Consiglio,[a] Vincenzo Frenna,[b] Elisabetta Mezzina,[a]**
**Antonio Pizzolato[b] and Domenico Spinelli[a]**

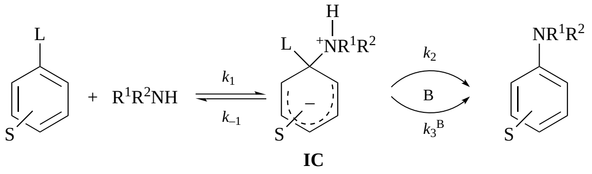
[a] *Dipartimento di Chimica Organica 'A. Mangini', Via S. Donato 15, Bologna, I-40127, Italy*
[b] *Dipartimento di Chimica Organica 'E. Paternò', Via Archirafi 20, Palermo, I-90123, Italy*

**The rate constants of the title reactions have been measured in benzene at 20 °C. The reactions with benzylamine are not base-catalysed. The second-order kinetic constant for the reactions with *N*-benzylmethylamine, with the exception of the unsubstituted compound (X = H), increases in a hyperbolical way with increasing nucleophile concentration. A non-linear regression treatment of kinetic data allows the calculation of $k_1$ and $k_3^B/k_{-1}$ for each catalysed system. $k_3^B/k_{-1}$ is not a monotonic function of the X substituent. This result has been rationalised on the grounds of a specific base–general acid (SB–GA) mechanism for the base catalysis.**

The most important evidence for the attachment–detachment mechanism of $S_NAr$ reactions comes from studies of base catalysis of reactions involving amine nucleophiles.[2–4]

The observation of base catalysis and the form of the catalysis law depend on the type of amine nucleophile, the nucleofugal group, the nature and the degree of activation of the aromatic substrate, the relative position of activating substituent(s) and reaction centre and the solvent.

The reaction pattern is that shown in Scheme 1, where the decomposition of the reaction intermediate can give the reaction products spontaneously or through base catalysis. The kinetic law which describes quantitatively this phenomenon is represented by eqn. (1), obtained by applying the steady-state approximation to the σ-adduct intermediate (**IC**) of Scheme 1.

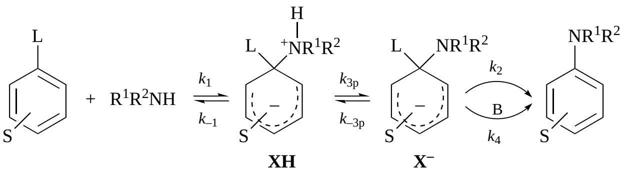


**Scheme 1**

$$k_A = (k_1k_2 + k_1k_3^B[B])/(k_{-1} + k_2 + k_3^B[B]) \qquad (1)$$

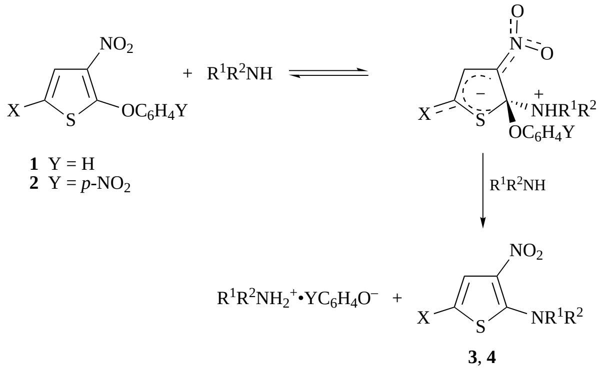
In eqn. (1) $k_A$ represents the apparent second-order kinetic constant, obtained by dividing the pseudo-first-order kinetic constant by amine concentration, and B is the base catalyst, which can be either the nucleophile itself or a base added from the outside to the reaction mixture, or the lyate ion of the solvent when the reaction is carried out in protic solvents.[2–4] Provided that $k_2 \ll k_{-1}$, eqn. (1) describes generally a dependence of $k_A$ on [B] which is linear at low concentrations but changes to a plateau as the base concentration is increased. In fact, at low [B] values $k_{-1} \gg (k_2 + k_3^B[B])$ and $k_A$ responds linearly to base concentration. If $k_{-1} \sim k_3^B[B]$ within the experimental range of base concentrations, $k_A$ depends curvilinearly (hyperbolically) on base concentration. By contrast, when $(k_2 + k_3^B[B]) \gg k_{-1}$, $k_A = k_1$ and the reaction is not base-catalysed. All three cases have been well documented by numerous kinetic studies.[2–4]

The catalysis mechanism implies necessarily the removal of the *ammonium* proton from the reaction intermediate and this can occur[5] substantially in two different ways (Scheme 2): (*a*) a *slow*, rate-limiting proton abstraction from the zwitterionic intermediate (**XH**) by the base to form the deprotonated intermediate ($X^-$), from which the leaving group breaks off *rapidly*, and (*b*) a *rapid* deprotonation equilibrium followed by a *slow* detachment of the leaving group which is general acid-catalysed by the conjugated acid of the amine [SB–GA (specific base–general acid) mechanism].



**Scheme 2**

In this paper we report a kinetic study of the reactions of some 2-phenoxy- (**1**) and 2-(*p*-nitrophenoxy)-3-nitro-5-X-thiophenes (**2**) with benzylamine (BZA) and with *N*-benzylmethylamine (BMA) in benzene at 20 °C. This study aims to provide information about the various aspects of base catalysis mechanism(s) in the $S_NAr$ reactions of nitro-activated thiophene derivatives with amines in various solvents.[6]



**1** Y = H
**2** Y = *p*-NO$_2$

**3** R$^1$ = H, R$^2$ = CH$_2$C$_6$H$_5$:BZA
**4** R$^1$ = Me, R$^2$ = CH$_2$C$_6$H$_5$:BMA

X = H, CONH$_2$, CO$_2$Me, COMe, SO$_2$Me, CN, NO$_2$

## Results and discussion

Compounds **1** and **2** gave the expected amino derivatives **3** and **4** on treatment with BZA or BMA in benzene, in high yields

**Table 1** Physical data for *N*-(3-nitro-5-X-2-thienyl)benzylamines **3**

| X | Crystallization solvent | Mp/°C | $\lambda_{max}$(benzene)/nm | Log $\varepsilon$ |
|---|---|---|---|---|
| H | Ligroin–benzene | 91–2 | 386 | 4.00 |
| $CONH_2$ | Methanol–dioxane | 199–200 | 385 | 3.99 |
| $CO_2Me$ | Methanol | 147–8 | 380 | 3.98 |
| COMe | Methanol | 133–4 | 383 | 4.02 |
| $SO_2Me$ | Methanol | 124–5 | 369 | 3.95 |
| CN | Methanol–dioxane | 193–4 | 376 | 3.94 |
| $NO_2$ | Methanol–dioxane | 117–8 | 400 | 4.17 |

**Table 2** Physical data for *N*-benzyl-*N*-(3-nitro-5-X-2-thienyl)methylamines **4**

| X | Crystallization solvent | Mp/°C | $\lambda_{max}$(benzene)/nm | Log $\varepsilon$ | $\sigma^{-}$ [b] |
|---|---|---|---|---|---|
| H | Methanol | 52–3 | 390 | 3.80 | 0.00 |
| $CONH_2$ | Methanol | 148–9 | 390 | 3.81 | 0.61 |
| $CO_2Me$ [a] | | | 384 | 3.78 | 0.70 |
| COMe | Methanol | 77–8 | 395 | 3.79 | 0.84 |
| $SO_2Me$ | Methanol | 108–9 | 386 | 3.82 | 0.85 |
| CN | Light petroleum–benzene | 89–90 | 382 | 3.78 | 0.89 |
| $NO_2$ | Ligroin–benzene | 75–6 | 398 | 4.19 | 1.23 |

[a] Liquid. [b] Values from ref. 10.

**Table 3** Apparent kinetic constants[a] for the reactions of 2-phenoxy-3-nitro-5-X-thiophenes **1** with benzylamine (BZA) in benzene at 20 °C

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| X = H | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.504 | 0.605 | 0.706 | 0.806 | 0.907 | 1.01 | |
| $k_A$/10$^{-5}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 2.23 | 2.41 | 2.74 | 2.94 | 3.24 | 3.52 | |
| X = $CONH_2$ | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.202 | 0.302 | 0.403 | 0.504 | 0.605 | | |
| $k_A$/10$^{-4}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 6.90 | 7.46 | 8.22 | 8.81 | 9.50 | | |
| X = $CO_2Me$ | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.0990 | 0.198 | 0.297 | 0.396 | 0.495 | 0.594 | |
| $k_A$/10$^{-3}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 1.09 | 1.30 | 1.53 | 1.75 | 1.97 | 2.21 | |
| X = COMe | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.0495 | 0.0990 | 0.148 | 0.198 | 0.297 | 0.396 | |
| $k_A$/10$^{-3}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 2.06 | 2.27 | 2.51 | 2.69 | 3.13 | 3.68 | |
| X = $SO_2Me$ | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.0510 | 0.102 | 0.153 | 0.204 | 0.307 | 0.409 | |
| $k_A$/10$^{-3}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 1.99 | 2.26 | 2.56 | 2.88 | 3.49 | 4.10 | |
| X = CN | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.0200 | 0.0500 | 0.100 | 0.150 | 0.200 | 0.300 | |
| $k_A$/10$^{-3}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 3.62 | 3.80 | 4.30 | 4.85 | 5.31 | 6.15 | |
| X = $NO_2$ | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.0050 | 0.0100 | 0.0150 | 0.0200 | 0.0400 | 0.100 | 0.150 |
| $k_A$/10$^{-3}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 3.69 | 3.71 | 3.80 | 3.88 | 4.09 | 4.70 | 5.53 |

[a] The rate constants are accurate to within ±3%.

(>95%) as shown by TLC and UV–VIS (200–450 nm) spectral analysis of the mixtures obtained after complete reaction. The relevant physical data are shown in Tables 1 and 2.

The apparent second-order kinetic constants, $k_A$, for the amino substitution reactions of **1** and **2**, at 20 °C, are given in Tables 3–6.

An examination of the kinetic data in Tables 3 and 4 shows that the $k_A$ increases linearly with increasing nucleophile concentration.

Many aromatic nucleophilic substitution reactions, especially those of activated chlorobenzenes in non-polar solvents, undergo small accelerations with increases in the amine nucleophile concentration,[7] as well as on addition of various other substances.[7a,8] The second-order kinetic constant obeys an equation such as (2) and typical $k_B/k_0$ ratios range from 0.5 to 5.

$$k_A = k_0 + k_B[B] \quad (2)$$

Although some authors have attributed these accelerations in rate to base catalysis, implicitly assuming that $k_{-1} \gg k_2$, this interpretation has been criticized by Bunnett and Garst.[9] According to the classification proposed by these authors, the inference that a genuine base catalysis is involved holds only for the reactions where $k_B/k_0 > 50$. When $k_B/k_0 < 5$ it is suggested that the acceleration observed is not caused by catalysis.

The addition of polar substances to an apolar solvent like benzene can affect the reaction rate either by changing the macro- and/or micro-relative permittivity of the medium, or by the specific solvation of the reactants and/or the relevant transition states. The nucleophile itself, being more polar than benzene, affects the medium polarity. Thus, the 'catalytic effects' observed at high amine concentrations have to be considered with some attention. Another complication with apolar solvents is represented by the association phenomena.

For the reactions studied in this work in the cases where $k_A$

**Table 4** Apparent kinetic constants[a] for the reactions of 2-(*p*-nitrophenoxy)-3-nitro-5-X-thiophenes **2** with benzylamine (BZA) in benzene at 20 °C

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| X = H | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.203 | 0.304 | 0.406 | 0.507 | 0.608 | 0.710 | |
| $k_A/10^{-4}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 0.719 | 0.871 | 1.03 | 1.18 | 1.32 | 1.50 | |
| X = CONH$_2$ | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.0513 | 0.103 | 0.154 | 0.203 | 0.308 | 0.406 | |
| $k_A/10^{-3}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 4.17 | 4.42 | 4.76 | 5.03 | 5.58 | 6.22 | |
| X = CO$_2$Me | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.0103 | 0.0205 | 0.0513 | 0.0769 | 0.103 | 0.205 | |
| $k_A/10^{-2}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 0.679 | 0.721 | 0.784 | 0.853 | 0.918 | 1.14 | |
| X = COMe | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.00510 | 0.0103 | 0.0154 | 0.0205 | 0.0513 | 0.103 | |
| $k_A/10^{-2}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 1.34 | 1.38 | 1.44 | 1.52 | 1.60 | 1.83 | |
| X = SO$_2$Me | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.00510 | 0.0103 | 0.0154 | 0.0205 | 0.0513 | 0.103 | |
| $k_A/10^{-2}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 1.41 | 1.46 | 1.54 | 1.56 | 1.74 | 2.16 | |
| X = CN | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.00520 | 0.0103 | 0.0207 | 0.0310 | 0.0517 | 0.103 | |
| $k_A/10^{-2}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 3.02 | 3.22 | 3.38 | 3.52 | 3.71 | 4.26 | |
| X = NO$_2$ | | | | | | | |
| [BZA]/mol dm$^{-3}$ | 0.0101 | 0.0151 | 0.0201 | 0.0402 | 0.0604 | 0.0805 | 0.101 |
| $k_A$/dm$^3$ mol$^{-1}$ s$^{-1}$ | 0.302 | 0.309 | 0.318 | 0.335 | 0.336 | 0.366 | 0.394 |

[a] As in Table 3.

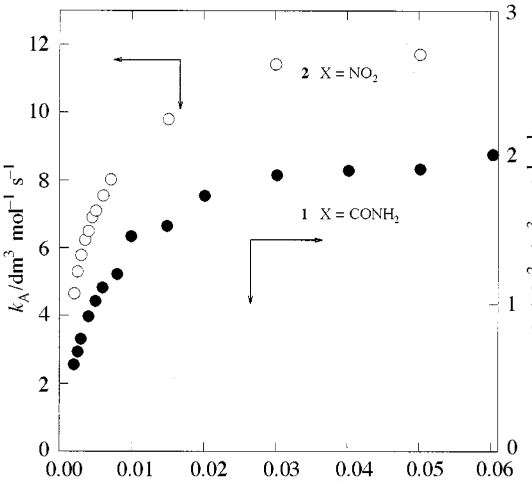


**Fig. 1** Plot of apparent second-order kinetic constants $k_A$ for the reactions of **1** (X = CONH$_2$) (●) and **2** (X = NO$_2$) (○) with BMA *versus* [BMA]

increases linearly with increasing nucleophile concentration, the data have been treated by the least-squares method according to eqn. (2) and the statistical results are reported in Table 7. The low values of $k_B/k_0$ ratios indicate that the increase in $k_A$ observed with increasing [B] is probably due to a polarity effect of the medium. So the $k_0$ values can be considered as equivalent to $k_1$ parameters.

An analysis of kinetic data reported in Tables 5 and 6 shows that except for the reactions pertaining to the unsubstituted compounds (X = H), $k_A$ varies in a curvilinear way as a function of [B] (see Fig. 1). Since the hyperbolic curves extrapolate to zero for [B] = 0, that is, cross the origin of axes, eqn. (1), which is descriptive of this situation, can be simplified to eqn. (3).

$$k_A = k_1k_3^B[B]/(k_{-1} + k_3^B[B]) \qquad (3)$$

A non-linear regression treatment of kinetic data, by the least-squares method, according to eqn. (3) has allowed us to calculate the values of $k_1$ and of the $k_3^B/k_{-1}$ ratio for each catalysed system: such values are reported in Table 8.

When the logarithms of the relative kinetic constants, log ($k_{1,X}/k_{1,H}$), for the reactions of 2-phenoxy- and of 2-(*p*-nitrophenoxy)-3-nitro-5-X-thiophenes with a given amine, in benzene, are plotted *versus* $\sigma^-$ constants of X substituents (Table 2)[10] excellent linear free energy correlations are obtained (Table 9). For the sake of comparison in Table 9 the corresponding data for 2-bromo-3-nitro-5-X-thiophenes are also reported.[10]

In an alternative data treatment, the log ($k_{1,X}/k_{1,H}$) values for the benzylamine reactions and a given leaving group have been plotted *versus* those for the corresponding *N*-benzylmethylamine reactions, or the log ($k_{1,X}/k_{1,H}$) values for a given leaving group have been plotted *versus* those for another leaving group, the amine being equal. In these 'cross-correlations' where the original concept of a relationship between free energies is implied, it is not necessary to know '*a priori*' the values of substituent constants.

The results of the cross-correlations are shown in Table 10. In each case the *a* value (the intercept of the straight line with the ordinate axis) is statistically indistinguishable from zero, as expected, and the *b* values coincide with the corresponding ratios between the susceptibility constants, $\rho$.

The excellent quality of the correlations obtained for each system give a clear indication that the substituent effects in a reaction series of thiophene substrates with a given amine are actually proportional to the corresponding effects for the reaction of the other amine.

An examination of the data in Table 9 shows for both amines the sequence $\rho_{Br} > \rho_{OC_6H_4Y}$. Although the reactivity–selectivity principle[11] should be used only to compare very similar systems, the variation in $\rho$(L) with a change in the head-atom of the leaving group seems to obey the principle: indeed, the compounds with a bromine leaving group display a greater $\rho$ value.

The compounds with L = OC$_6$H$_4$-*p*-NO$_2$ are more reactive than those with L = OC$_6$H$_5$ because in the former the C-2 carbon atom of the thiophene ring is more electrophilic and OC$_6$H$_4$-*p*-NO$_2$ is a better leaving group than OC$_6$H$_5$. On the other hand, both phenoxy groups, which are electron donors with respect to the thiophene ring, exert a levelling effect on the

**Table 5** Apparent kinetic constants[a] for the reactions of 2-phenoxy-3-nitro-5-X-thiophenes **1** with *N*-benzylmethylamine (BMA) in benzene at 20 °C

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| X = H | | | | | | | | | | | | | | |
| [BMA]/mol dm$^{-3}$ | 0.101 | 0.252 | 0.404 | 0.505 | 0.707 | 1.01 | | | | | | | | |
| $k_A$/10$^{-4}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 5.26 | 5.41 | 5.47 | 5.72 | 6.11 | 6.33 | | | | | | | | |
| X = CONH$_2$ | | | | | | | | | | | | | | |
| [BMA]/mol dm$^{-3}$ | 0.002 01 | 0.002 52 | 0.003 02 | 0.004 02 | 0.005 03 | 0.006 04 | 0.008 05 | 0.010 0 | 0.015 0 | 0.020 1 | 0.0302 | 0.0402 | 0.0502 | 0.0603 |
| $k_A$/10$^{-2}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 0.588 | 0.675 | 0.761 | 0.915 | 1.02 | 1.11 | 1.20 | 1.46 | 1.53 | 1.74 | 1.88 | 1.91 | 1.92 | 2.02 |
| X = CO$_2$Me | | | | | | | | | | | | | | |
| [BMA]/mol dm$^{-3}$ | 0.002 01 | 0.003 02 | 0.004 02 | 0.005 00 | 0.006 04 | 0.007 04 | 0.008 05 | 0.010 1 | 0.012 0 | 0.015 0 | 0.0356 | 0.0500 | 0.0958 | |
| $k_A$/10$^{-2}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 0.804 | 1.07 | 1.32 | 1.64 | 1.78 | 1.90 | 2.11 | 2.42 | 2.53 | 2.71 | 3.56 | 3.94 | 4.12 | |
| X = COMe | | | | | | | | | | | | | | |
| [BMA]/mol dm$^{-3}$ | 0.002 00 | 0.003 00 | 0.004 00 | 0.005 00 | 0.006 00 | 0.007 80 | 0.010 1 | 0.013 0 | 0.017 0 | 0.020 0 | 0.0375 | 0.0500 | | |
| $k_A$/10$^{-2}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 1.64 | 2.15 | 2.67 | 3.37 | 3.83 | 4.22 | 4.80 | 5.08 | 5.62 | 6.41 | 6.96 | 7.50 | | |
| X = CN | | | | | | | | | | | | | | |
| [BMA]/mol dm$^{-3}$ | 0.002 00 | 0.002 50 | 0.003 00 | 0.003 50 | 0.004 00 | 0.005 20 | 0.006 00 | 0.006 97 | 0.010 0 | 0.012 0 | 0.0200 | 0.0300 | | |
| $k_A$/10$^{-1}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | 0.441 | 0.525 | 0.560 | 0.647 | 0.703 | 0.832 | 0.863 | 0.984 | 1.10 | 1.18 | 1.36 | 1.51 | | |
| X = NO$_2$ | | | | | | | | | | | | | | |
| [BMA]/mol dm$^{-3}$ | 0.001 00 | 0.002 00 | 0.003 05 | 0.003 56 | 0.004 07 | 0.005 00 | 0.006 11 | 0.007 00 | 0.008 14 | 0.009 60 | 0.0120 | 0.0146 | 0.0182 | 0.0250 |
| $k_A$/dm$^3$ mol$^{-1}$ s$^{-1}$ | 0.363 | 0.595 | 0.738 | 0.774 | 0.791 | 0.859 | 0.902 | 0.931 | 1.00 | 1.05 | 1.12 | 1.16 | 1.20 | 1.29 |

[a] As in Table 3.

**Table 6** Apparent kinetic constants[a] for the reactions of 2-(*p*-nitrophenoxy)-3-nitro-5-X-thiophenes **2** with *N*-benzylmethylamine (BMA) in benzene at 20 °C

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| X = H | | | | | | | | | | | | | | |
| [BMA]/mol $dm^{-3}$ | 0.0400 | 0.0996 | 0.199 | 0.300 | 0.398 | 0.500 | | | | | | | | |
| $k_A/10^{-3}$ $dm^3$ $mol^{-1}$ $s^{-1}$ | 2.35 | 2.39 | 2.51 | 2.64 | 2.74 | 2.91 | | | | | | | | |
| X = $CONH_2$ | | | | | | | | | | | | | | |
| [BMA]/mol $dm^{-3}$ | 0.004 02 | 0.004 53 | 0.005 02 | 0.006 00 | 0.007 00 | 0.008 52 | 0.010 0 | 0.012 0 | 0.013 0 | 0.0152 | 0.0182 | 0.0201 | 0.0252 | 0.0302 |
| $k_A/10^{-1}$ $dm^3$ $mol^{-1}$ $s^{-1}$ | 0.594 | 0.626 | 0.686 | 0.744 | 0.830 | 0.904 | 0.966 | 1.05 | 1.08 | 1.12 | 1.19 | 1.22 | 1.24 | 1.30 |
| X = $CO_2Me$ | | | | | | | | | | | | | | |
| [BMA]/mol $dm^{-3}$ | 0.004 01 | 0.005 00 | 0.006 01 | 0.007 47 | 0.008 05 | 0.010 0 | 0.012 0 | 0.015 0 | 0.018 0 | 0.0200 | 0.0252 | 0.0300 | | |
| $k_A/10^{-1}$ $dm^3$ $mol^{-1}$ $s^{-1}$ | 0.910 | 1.08 | 1.20 | 1.44 | 1.49 | 1.70 | 1.88 | 2.10 | 2.25 | 2.36 | 2.50 | 2.75 | | |
| X = COMe | | | | | | | | | | | | | | |
| [BMA]/mol $dm^{-3}$ | 0.005 02 | 0.006 00 | 0.007 02 | 0.008 82 | 0.010 0 | 0.012 0 | 0.013 0 | 0.015 1 | 0.020 1 | 0.0302 | 0.0402 | 0.0604 | 0.0704 | 0.101 |
| $k_A/10^{-1}$ $dm^3$ $mol^{-1}$ $s^{-1}$ | 2.24 | 2.55 | 2.92 | 3.20 | 3.27 | 3.75 | 3.84 | 4.10 | 4.48 | 5.08 | 5.42 | 5.76 | 6.11 | 6.16 |
| X = CN | | | | | | | | | | | | | | |
| [BMA]/mol $dm^{-3}$ | 0.002 01 | 0.002 51 | 0.003 01 | 0.004 07 | 0.005 09 | 0.006 11 | 0.007 13 | 0.008 14 | 0.009 16 | 0.0102 | 0.0120 | 0.0153 | 0.0181 | 0.0204 |
| $k_A$/$dm^3$ $mol^{-1}$ $s^{-1}$ | 0.310 | 0.377 | 0.432 | 0.554 | 0.634 | 0.705 | 0.778 | 0.826 | 0.864 | 0.894 | 0.964 | 1.06 | 1.10 | 1.18 |
| X = $NO_2$ | | | | | | | | | | | | | | |
| [BMA]/mol $dm^{-3}$ | 0.002 10 | 0.002 54 | 0.003 05 | 0.003 56 | 0.004 07 | 0.004 58 | 0.005 09 | 0.006 11 | 0.007 13 | 0.0151 | 0.0301 | 0.0502 | | |
| $k_A$/$dm^3$ $mol^{-1}$ $s^{-1}$ | 4.64 | 5.28 | 5.77 | 6.22 | 6.48 | 6.89 | 7.08 | 7.54 | 8.01 | 9.78 | 11.4 | 11.7 | | |

[a] As in Table 3.

**Table 7** Linear regression analysis[a] of apparent second-order kinetic constants, $k_A$, for the reactions of 2-phenoxy- and 2-(*p*-nitrophenoxy)-3-nitro-5-X-thiophenes with benzylamine in benzene at 20 °C, according to eqn. (2)

| X | L | $k_0 \pm s_0$/dm$^3$ mol$^{-1}$ s$^{-1}$ | $k_B \pm s_B$/dm$^6$ mol$^{-2}$ s$^{-1}$ | $n$ | $r$ | $(k_B/k_0)$/dm$^3$ mol$^{-1}$ |
|---|---|---|---|---|---|---|
| H | $OC_6H_5$ | $(0.891 \pm 0.068) \times 10^{-5}$ | $(2.59 \pm 0.09) \times 10^{-5}$ | 6 | 0.998 | 2.9 |
| $CONH_2$ | $OC_6H_5$ | $(5.56 \pm 0.06) \times 10^{-4}$ | $(6.50 \pm 0.15) \times 10^{-4}$ | 5 | 0.999 | 1.2 |
| $CO_2Me$ | $OC_6H_5$ | $(0.859 \pm 0.007) \times 10^{-3}$ | $(2.26 \pm 0.02) \times 10^{-3}$ | 6 | 1.000 | 2.6 |
| COMe | $OC_6H_5$ | $(1.81 \pm 0.03) \times 10^{-3}$ | $(4.60 \pm 0.14) \times 10^{-3}$ | 6 | 0.998 | 2.5 |
| $SO_2Me$ | $OC_6H_5$ | $(1.67 \pm 0.01) \times 10^{-3}$ | $(5.94 \pm 0.05) \times 10^{-3}$ | 6 | 1.000 | 3.6 |
| CN | $OC_6H_5$ | $(3.40 \pm 0.04) \times 10^{-3}$ | $(9.30 \pm 0.25) \times 10^{-3}$ | 6 | 0.999 | 2.7 |
| $NO_2$ | $OC_6H_5$ | $(0.360 \pm 0.004) \times 10^{-1}$ | $(1.23 \pm 0.05) \times 10^{-1}$ | 7 | 0.995 | 3.4 |
| H | $OC_6H_4$-*p*-$NO_2$ | $(0.409 \pm 0.010) \times 10^{-4}$ | $(1.52 \pm 0.02) \times 10^{-4}$ | 6 | 1.000 | 3.7 |
| $CONH_2$ | $OC_6H_4$-*p*-$NO_2$ | $(3.86 \pm 0.03) \times 10^{-3}$ | $(5.75 \pm 0.11) \times 10^{-3}$ | 6 | 0.999 | 1.5 |
| $CO_2Me$ | $OC_6H_4$-*p*-$NO_2$ | $(0.667 \pm 0.006) \times 10^{-2}$ | $(2.34 \pm 0.06) \times 10^{-2}$ | 6 | 0.999 | 3.5 |
| COMe | $OC_6H_4$-*p*-$NO_2$ | $(1.36 \pm 0.02) \times 10^{-2}$ | $(4.69 \pm 0.50) \times 10^{-2}$ | 6 | 0.978 | 3.4 |
| $SO_2Me$ | $OC_6H_4$-*p*-$NO_2$ | $(1.39 \pm 0.02) \times 10^{-2}$ | $(7.37 \pm 0.32) \times 10^{-2}$ | 6 | 0.996 | 5.3 |
| CN | $OC_6H_4$-*p*-$NO_2$ | $(0.308 \pm 0.005) \times 10^{-1}$ | $(1.18 \pm 0.10) \times 10^{-1}$ | 6 | 0.986 | 3.8 |
| $NO_2$ | $OC_6H_4$-*p*-$NO_2$ | $(0.294 \pm 0.005)$ | $(0.916 \pm 0.088)$ | 7 | 0.978 | 3.1 |

[a] $s_0$ and $s_B$, standard deviations of $k_0$ and $k_B$, respectively; $n$, number of data points; $r$, correlation coefficient.

**Table 8** Linear regression analysis[a] of apparent second-order kinetic constants, $k_A$, for the reactions of 2-phenoxy- and 2-(*p*-nitrophenoxy)-3-nitro-5-X-thiophenes with benzylmethylamine in benzene at 20 °C, according to eqn. (2) and $k_A = ac[\mathrm{BMA}]/(1 + c[\mathrm{BMA}])$[b]

| X | L | $k_0 \pm s_0$/dm$^3$ mol$^{-1}$ s$^{-1}$ | $k_B \pm s_B$/dm$^6$ mol$^{-2}$ s$^{-1}$ | $n$ | $r$ | $(k_B/k_0)$/dm$^3$ mol$^{-1}$ |
|---|---|---|---|---|---|---|
| H | $OC_6H_5$ | $(5.09 \pm 0.01) \times 10^{-4}$ | $(1.27 \pm 0.07) \times 10^{-4}$ | 6 | 0.980 | 0.25 |
| H | $OC_6H_4$-*p*-$NO_2$ | $(2.28 \pm 0.01) \times 10^{-3}$ | $(1.21 \pm 0.07) \times 10^{-3}$ | 6 | 0.996 | 0.53 |

| X | L | $a$ | $c$ | $n$ |
|---|---|---|---|---|
| $CONH_2$ | $OC_6H_5$ | $2.19 \times 10^{-2}$ | 174 | 14 |
| $CO_2Me$ | $OC_6H_5$ | $4.57 \times 10^{-2}$ | 105 | 13 |
| COMe | $OC_6H_5$ | $8.68 \times 10^{-2}$ | 119 | 12 |
| CN | $OC_6H_5$ | 0.181 | 159 | 12 |
| $NO_2$ | $OC_6H_5$ | 1.39 | 336 | 14 |
| $CONH_2$ | $OC_6H_4$-*p*-$NO_2$ | 0.161 | 149 | 14 |
| $CO_2Me$ | $OC_6H_4$-*p*-$NO_2$ | $3.88 \times 10^{-2}$ | 77.4 | 12 |
| COMe | $OC_6H_4$-*p*-$NO_2$ | 0.680 | 99.5 | 14 |
| CN | $OC_6H_4$-*p*-$NO_2$ | 1.62 | 125 | 14 |
| $NO_2$ | $OC_6H_4$-*p*-$NO_2$ | 12.5 | 270 | 12 |

[a] $s_0$ and $s_B$, standard deviations of $k_0$ and $k_B$, respectively; $n$, number of data points; $r$, correlation coefficient. [b] $a = k_1$, $c = k_3^B/k_{-1}$.

**Table 9** Linear regression analysis of logarithmic relative kinetic constants $[\log(k_{1,X}/k_{1,H})]$ for the reactions of 2-L-3-nitro-5-X-thiophenes with amines in benzene at 20 °C, according to the equation $\log(k_{1,X}/k_{1,H}) = \rho\sigma^-$

| No. | Amine/L | $\rho \pm s_\rho$ | $i \pm s_i$ | $r$ | $n$ | CL > (%) |
|---|---|---|---|---|---|---|
| 1 | BZA/Br | $3.80 \pm 0.06$ | $0.01 \pm 0.05$ | 0.999 | 8 | 99.9 |
| 2 | BMA/Br | $3.65 \pm 0.06$ | $0.00 \pm 0.04$ | 0.999 | 8 | 99.9 |
| 3 | BZA/$OC_6H_5$ | $2.88 \pm 0.10$ | $-0.03 \pm 0.08$ | 0.997 | 7 | 99.9 |
| 4 | BMA/$OC_6H_5$ | $2.80 \pm 0.08$ | $-0.02 \pm 0.06$ | 0.998 | 6 | 99.9 |
| 5 | BZA/$OC_6H_4$-*p*-$NO_2$ | $3.11 \pm 0.10$ | $0.01 \pm 0.08$ | 0.998 | 7 | 99.9 |
| 6 | BMA/$OC_6H_4$-*p*-$NO_2$ | $3.06 \pm 0.10$ | $0.01 \pm 0.08$ | 0.998 | 6 | 99.9 |

[a] $\rho$, reaction constant; $i$, intercept of the regression line with the ordinate $\sigma^- = 0$; $s_\rho$ and $s_i$, standard deviations of $\rho$ and $i$, respectively; $r$, correlation coefficient; $n$, number of data points; CL, confidence level.

activation by the 5-X substituent and determine a $\rho$ value lower than that determined by bromine, which is a poorer electron donor and a more sterically hindered leaving group. Of course, the phenoxy group, being more electron donating than *p*-nitrophenoxy, displays a lower $\rho$ value.

A comparison between $\rho$(L) values for benzylamine reactions and those for *N*-benzylmethylamine reactions shows that the more reactive amine (BMA) gives rise to $\rho$ values lower than does the less reactive BZA, apparently again in accord with the reactivity–selectivity principle but the differences between the $\rho$ values, the leaving group being equal, are not statistically significant.

The greater reactivity of the secondary amine with respect to the primary amine reflects, although only qualitatively, the greater basicity of the first. Of course, the parallelism between proton affinity (basicity) and carbon affinity (nucleophilicity) can only exist to a certain extent. However, it is probable that in the two 'acid–base' reactions (amine protonation and aromatic nucleophilic substitutions) similar factors (electronic, steric and solvation factors) come into play, even though their 'combination' generally will give a different result for the two different bond formation processes. Of course, in the reaction of decomposition of the zwitterionic intermediate to give the reactants, the $k_{-1}$ reactivity order will be inverted, *i.e.* BZA > MBA. In other words, according to the Hammond postulate,[12] for a given substrate the transition state should be 'early' for the more reactive amine.

Considering the structure of the reaction intermediate, it is evident that because of the interaction by hydrogen bonding between the 'ammonium' nitrogen and 3-nitro group, the so

**Table 10** Cross-correlations carried out[a] (*a*) according to the equation: $\log(k_{1,X}/k_{1,H})_{A_1} = a + b \log(k_{1,X}/k_{1,H})_{A_2}$, and (*b*) according to the equation: $\log(k_{1,X}/k_{1,H})_{L_1} = a + b \log(k_{1,X}/k_{1,H})_{L_2}$

(*a*)

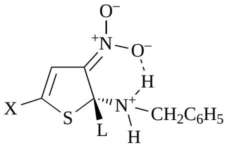
| L | $A_1$ | $A_2$ | $a \pm s_a$ | $b \pm s_b$ | *r* | *n* | CL > (%) | $\rho(A_1)/\rho(A_2)$ |
|---|---|---|---|---|---|---|---|---|
| $OC_6H_5$ | BZA | BMA | 0.01 ± 0.06 | 1.04 ± 0.03 | 0.999 | 6 | 99.9 | 1.04 |
| $OC_6H_4$-*p*-$NO_2$ | BZA | BMA | 0.00 ± 0.05 | 1.02 ± 0.02 | 0.999 | 6 | 99.9 | 1.02 |
| Br | BZA | BMA | 0.01 ± 0.06 | 1.04 ± 0.02 | 0.999 | 8 | 99.9 | 0.99 |

(*b*)

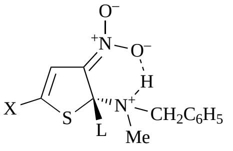
| Amine | $L_1$ | $L_2$ | $a \pm s_a$ | $b \pm s_b$ | *r* | *n* | CL (%) | $\rho(L_1)/\rho(L_2)$ |
|---|---|---|---|---|---|---|---|---|
| BZA | $OC_6H_5$ | $OC_6H_4$-*p*-$NO_2$ | −0.03 ± 0.04 | 0.93 ± 0.02 | 0.999 | 7 | 99.9 | 0.00 |
| BZA | $OC_6H_5$ | Br | −0.01 ± 0.07 | 0.75 ± 0.02 | 0.998 | 7 | 99.9 | 0.76 |
| BZA | $OC_6H_4$-*p*-$NO_2$ | Br | 0.03 ± 0.08 | 0.81 ± 0.03 | 0.998 | 7 | 99.9 | 0.99 |
| BMA | $OC_6H_5$ | $OC_6H_4$-*p*-$NO_2$ | −0.03 ± 0.04 | 0.91 ± 0.02 | 0.999 | 6 | 99.9 | 0.99 |
| BMA | $OC_6H_5$ | Br | −0.01 ± 0.08 | 0.76 ± 0.03 | 0.997 | 6 | 99.9 | 0.76 |
| BMA | $OC_6H_4$-*p*-$NO_2$ | Br | 0.03 ± 0.10 | 0.83 ± 0.03 | 0.997 | 6 | 99.9 | 0.84 |

[a] $s_a$ and $s_b$, standard deviations of *a* and *b*, respectively; *r*, correlation coefficient; *n*, number of data points; CL, confidence level.

called 'built-in solvation' effect,[13] namely the geometry of the groups bonded to the tetrahedral carbon atom, *i.e.* to the reaction centre, is fixed (**5** and **6**).



**5**
L = $OC_6H_5$,



**6**
L = $OC_6H_4$-*p*-$NO_2$

In the decomposition of the reaction intermediate into the reactants, both the aromatic carbon atom–nitrogen bond and hydrogen bonding are broken.

The more nucleophilic amine implies on one hand a stronger bond with the aromatic carbon atom and on the other hand a lower acidity of the 'ammonium' hydrogen and, consequently, less strong hydrogen bonding.

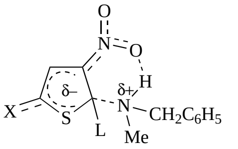
In the formation or the breaking of this bond the transition state would be 'later' with the more basic amine. It is evident that the effect depending on the nitrogen nucleophilicity, which according to the Hammond postulate would determine a given sequence in the position of the transition state along the reaction coordinate, is opposed to the 'anti-Hammond' hydrogen bonding effect, which would cause an inverted sequence, in the case where it was the only operating effect.

As a consequence, for each substrate, the nucleophile variation does not involve a significant variation in the transition state position. As a matter of fact the range of transition states corresponding to the various substituted thiophene substrates does not change its position along the reaction coordinate with a change in the amine nucleophile. This corresponds to a selectivity, as measured by $\rho$, practically independent of the amine used.

At variance with the benzylamine reactions of compounds with phenoxy leaving groups the reactions of these compounds with *N*-benzylmethylamine (except for the terms where X = H) are base-catalysed with a curvilinear catalysis law. The peculiar behaviour of these systems arises from the greater difficulty of the intermediate decomposition when the nucleophile is a secondary amine[2–4] and with a significantly basic and thus little nucleofugal leaving group.[2–4]

For the reactions which are genuinely base-catalysed it would be desirable to establish, if possible, the base catalysis mechanism by which the reaction intermediate decomposition occurs.

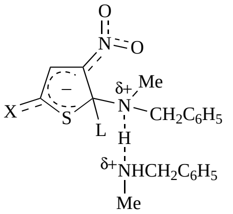
In the $k_{-1}$ step, *i.e.* in the decomposition of the reaction intermediate into the reactants, both the intramolecular hydrogen bonding between the ammonium proton and 3-nitro group and the bond between the nucleophilic nitrogen atom and the aromatic carbon atom are broken, as shown in **7**. The effect of an electron-withdrawing substituent present in the thiophene ring, with respect to hydrogen, is to favour the breaking of the first bond and to oppose that of the second one. It is evident that the more important effect is that on the carbon–nitrogen bond, because it is the extent to which this bond is formed or broken that controls predominantly the energy of the first transition state of the attachment–detachment mechanism. On these grounds, $\rho_{-1}$ should be negative.



**7**

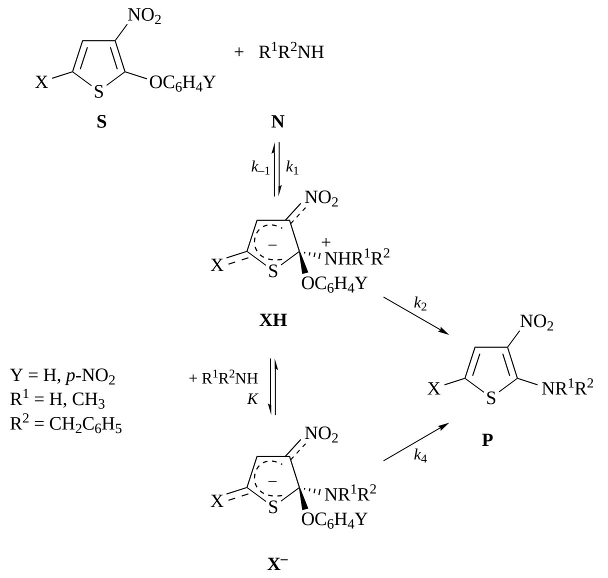
As far as the $k_3^B$ step is concerned it is convenient to take into consideration the possible catalysis mechanisms.

In the first mechanism the slow step involves the formation of the transition state **8**. With increasing electron-withdrawing power of the X substituent, the basicity of the oxygen atoms of the 3-nitro group decreases and the acidity of the hydrogen atom involved in the built-in solvation increases. Therefore, there is a balance between the effects brought about by the X substituent variation on the intramolecular hydrogen bond. In the base-catalysed step such a bond is broken by the intervention of a second molecule of amine, which behaving as a basic catalyst determines the slow elimination of the originally hydrogen-bonded proton. Since an electron-withdrawing X substituent increases the acidity of this proton, as a whole, in this catalysis mechanism $\rho_3^B > 0$ should be observed. Moreover, since the effect of the X substituent on the rate of proton elimination ($k_3^B$) is presumably lesser than that on the C–N bond breaking ($k_{-1}$) one should observe $|\rho_3^B| < |\rho_{-1}|$. As a matter of fact it should be $(\rho_3^B - \rho_{-1}) > 0$ with the implication that $k_3^B/k_{-1}$ should increase with electronic activation, *i.e.* with increasing electron-withdrawing power of the X substituent.



**8**

In the SB–GA mechanism (Scheme 3) there is a fast pre-

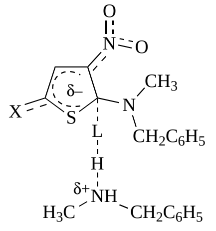


Scheme 3

equilibrium with a transition state similar to **8** where a proton transfer from (**XH**) to the amine occurs [reaction (4)].

$$\mathbf{XH} + C_6H_5CH_2(CH_3)NH \rightleftharpoons \mathbf{X}^- + C_6H_5CH_2(CH_3)NH_2^+ \quad (4)$$

For this first reaction of the SB–GA catalysis mechanism one should observe $\rho_K > 0$. The subsequent step, which involves the general acid catalysed detachment of the leaving group by the conjugated acid of the amine (transition state **9**), is disfavoured



**9**

by electron withdrawing X substituents and should give $\rho_4 < 0$.

An examination of data in Table 8 shows that $k_3^B/k_{-1}$ are not a monotonic function of the X substituent, *i.e.* they decrease on going from X = $CONH_2$ to X = $CO_2Me$ and increase on going from X = $CO_2Me$ to X = $NO_2$. This observation is in contrast with the base catalysis mechanism which involves the proton transfer to the base as the rate-determining step (see above).

Alternatively the trend of $k_3^B/k_{-1}$ observed can be easily accounted for in the framework of the SB–GA catalysis mechanism. In fact, it is evident that this trend arises from a balancing of electronic effects of the X substituent on the two parameters $k_3^B$ and $k_{-1}$. In the SB–GA mechanism the $k_3^B$ parameter corresponds to $Kk_4$. Since the decomposition reaction of $\mathbf{X}^-$ into the products, controlled by $k_4$, and the decomposition reaction of **XH** into the reactants, controlled by $k_{-1}$, are very similar processes, it is probable that $k_4$ and $k_{-1}$ parameters change in a homogeneous and regular way with changing X substituent. Moreover, since it should hold the condition $k_{-1} \gg Kk_4$ (otherwise no base catalysis would be observed) the relationship $|\rho_{-1}| < |\rho_K + \rho_4|$ has to be satisfied and, because of the much higher mobility of the amine leaving group as compared to phenoxy or *p*-nitrophenoxy leaving groups ($k_{-1} \gg Kk_4$), also the relationship $|\rho_{-1}| < |\rho_4|$.

As both $\rho_4$ and $\rho_{-1}$ are negative (see above), the difference $\rho_4 - \rho_{-1}$, should be negative, too. Therefore the observation of $k_3^B/k_{-1}$ ratios which decrease on going from X = $CONH_2$ to X = $CO_2Me$ implies that $\rho_K$ parameter should be less than $|\rho_4 - \rho_{-1}|$. On the other hand, the observation of $k_3^B/k_{-1}$ ratios which increase on going from X = $CONH_2$ to X = $CO_2Me$, to X = CN and to X = $NO_2$, would imply the condition $\rho_K > (\rho_4 - \rho_{-1})$. In conclusion, two different $\rho_K$ values corresponding, respectively, to the two substituent ranges would be required.

This dichotomy in the behaviour of the various substrates studied comes from the hypher-*ortho* relation.[14] In the compounds where the 5-X substituent has a relatively low conjugative effect, a preferential conjugative interaction occurs between the reaction centre and the 3-nitro group. This preferential interaction causes a levelling of electronic effects exerted by the X substituent on the equilibrium $\mathbf{XH} + B \rightleftharpoons \mathbf{X}^- + BH^+$ and a relatively low $\rho_K$ value. When the conjugation of the reaction centre with the 5-X substituent becomes important, it interferes successfully with the hyper-*ortho* relation and gives rise to a $\rho_K$ value so much greater than in the preceding case, as to change the sign of the algebraic sum $\rho_4 + \rho_3 - \rho_{-1}$. A positive sum produces $k_3^B/k_{-1}$ ratios which increase with increasing electron-withdrawing power of the 5-X substituent. This interpretation of the data obtained in the present work lends strong support to the hypothesis that the catalysis observed occurs *via* the SB–GA mechanism.

At variance with what happens with the substrates that have an electron-withdrawing substituent in the 5-position, the reactions of 2-phenoxy- and 2-(*p*-nitrophenoxy)-3-nitrothiophene with *N*-benzylmethylamine are not catalysed. As the 5-X substituent competes with the 3-nitro group in the conjugation with the thiophene ring and causes a reduction of the electronic density on the oxygen atoms of this group, with respect to 'unsubstituted' compounds, the intramolecular hydrogen bonding (the built-in solvation) in 5-substituted compounds is comparatively less. In these cases the $k_{-1}$ parameters are sufficiently higher to determine the condition $k_{-1} \gg (k_2 + k_3^B[B])$.

For each 'unsubstituted' compound (X = H) the lack of competition in the conjugation by the 5-substituent and the hyper-*ortho* relation cause a strong conjugative interaction between the reaction centre and the 3-nitro group and the greatest possible electron density on the oxygen atoms of this group. As a matter of fact the strongest possible hydrogen bonding of the series occurs and on the basis of the relationship $k_{-1} \ll (k_2 + k_3^B[B])$ the reactions involved are not catalysed.

## Experimental

### Materials

Compounds **1**,[15] **2**,[16] benzylamine,[17] *N*-benzylmethylamine[17] and benzene[18] were prepared and/or purified according to the methods reported. Amino derivatives **3** and **4** were prepared according to the general method of ref. 18. The relevant physical data are shown in Tables 1 and 2. All the new compounds gave correct analyses.

### Kinetic measurements

The kinetics were followed spectrophotometrically as previously described.[19] The concentrations used were $5 \times 10^{-4}$–$10^{-3}$ mol dm$^{-3}$ for substrates and those reported in Tables 3–6 for amines. The wavelength and log ε values for UV spectral measurements are shown in Tables 1 and 2.

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