Catalysis in Aromatic Nucleophilic Substitution. Part 9.[1] Kinetics of the Reactions of 2-Bromo-3,5-dinitrothiophene with Some *meta*- and *para*-Substituted Anilines in Benzene

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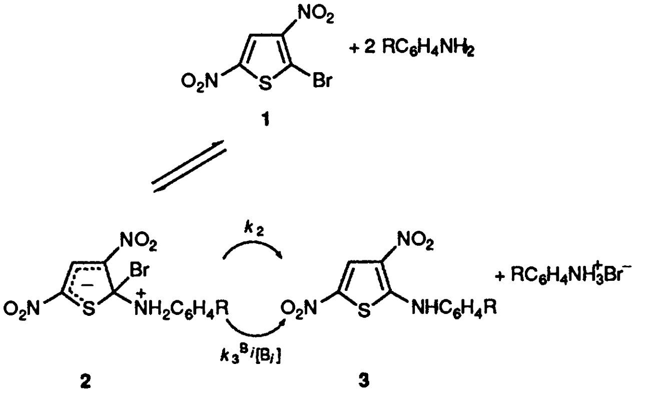
The rate constants of debromination of 2-bromo-3,5-dinitrothiophene by various *meta*- and *para*-substituted anilines have been measured in benzene at 25 °C. The reactions are mildly accelerated by increasing the amine concentration, showing 'low' k_B/k_0 ratios (4.6–11 dm^3 mol^{-1}). However, the reactions are inferred to be genuinely base-catalysed on the grounds of the excellent Hammett-type relationships followed by both log k_B and log k_0 parameters.

In contrast to the situation where the nucleophile is an anion, the S_NAr reactions involving primary and secondary amines as nucleophiles can be catalysed.[2] With reference to Scheme 1, this is expressed by eqn. (1), which is obtained by applying the



Scheme 1.

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

usual 'steady-state' approximation to the intermediate of the attachment-detachment mechanism.[3] In eqn. (1), k_A is the apparent second-order kinetic constant, obtained by dividing the pseudo-first-order rate constant by amine concentration.

According to eqn. (1), absence of base catalysis can mean that $(k_2 + k_3^{B_i}[B_i]) \gg k_{-1}$ or that $k_{-1} > k_2$ but $k_2 \gg k_3^{B_i}[B_i]$. Apart from the rare situation where, due to large steric effects, the $k_3^{B_i}$ coefficient could become very small, in general the insensitivity to base catalysis indicates that the overall reaction rate is controlled by the formation of the reaction intermediate, *i.e.*, $k_A = k_1$.

When $(k_2 + k_3^{B_i}[B_i]) \ll k_{-1}$ the reaction responds linearly to base catalysis and eqn. (1) is converted into eqn. (2).

$$k_A = k_1k_2/k_{-1} + k_1k_3^{B_i}[B_i]/k_{-1} \quad (2)$$

If k_2 is relatively small and $k_{-1} \cong k_3^{B_i}[B_i]$ within the experimental range of base concentrations, the dependence of k_A on $[B_i]$ varies in a curvilinear fashion.

Depending on the nature of the aromatic substrate, the amine, the nucleofugal group, the base and the solvent, different catalysis laws can be and are observed.[2]

Table 1. Spectroscopic data for *meta*- and *para*-substituted *N*-(3,5-dinitrothienyl)anilines **3**.

R	λ_{max}(benzene)/nm	log ε
p-OMe	400	4.23
p-Me	394	4.26
m-Me	392	4.27
H	392	4.27
p-Cl	390	4.30
p-Br	390	4.30
m-F	388	4.29
m-Cl	386	4.30
m-Br	386	4.30

Results and Discussion

2-Bromo-3,5-dinitrothiophene **1** gave the expected anilino derivatives **3** on treatment with anilines **2** in benzene, in high yields (>95%) as indicated by TLC and UV-VIS (200–450 nm) spectral analysis of the mixtures obtained after complete reaction. The relevant spectroscopic data are shown in Table 1.

The apparent second-order kinetic constants, k_A, for the anilino debromination reactions of **1** at 25 °C are given in Table 2.

Inspection of data shows that, for each substituted aniline, B_i, k_A increases with increasing amine concentration. Linear regression analysis of k_A values according to eqn. (3) gave the results reported in Table 3.

$$(k_A)_i = (k_0)_i + (k_B)_i[B_i] \quad (3)$$

With reference to Scheme 1 and eqn. (1); eqn. (3) would imply that $k_{-1} \gg (k_2 + k_3^{B_i}[B_i])$ with B_i = substituted aniline. In fact, under this condition, eqn. (1) becomes eqn. (4) and the k_B/k_0 values in Table 2 would represent $k_3^{B_i}/k_2$ ratios.

$$k_A = k_1k_2/k_{-1} + k_1k_3^{B_i}[B_i]/k_{-1} \quad (4)$$

It must be noted that many aromatic nucleophilic substitution reactions, especially those involving activated chlorobenzenes and amines in non polar solvents, are mildly accelerated by increasing the amine concentration[4] or by

Table 2. Apparent kinetic constants[a] for the reactions of 2-bromo-3,5-dinitrothiophene **1** with some *meta*- and *para*-substituted anilines **2** in benzene, at 25 °C.

[*p*-Anisidine]/mol dm^{-3}	0.0310	0.0620	0.0980	0.152	0.196	0.253	0.303	0.354	0.420
$k/10^{-3}$ dm^3 mol^{-1} s^{-1}	1.47	1.76	2.17	2.80	3.34	3.99	4.49	5.14	5.88
[*p*-Toluidine]/mol dm^{-3}	0.104	0.158	0.207	0.257	0.307	0.360	0.414	0.470	
$k/10^{-4}$ dm^3 mol^{-1} s^{-1}	3.85	4.68	5.56	6.42	7.39	8.42	9.37	10.3	
[*m*-Toluidine]/mol dm^{-3}	0.0550	0.106	0.155	0.200	0.258	0.309	0.412	0.525	
$k/10^{-4}$ dm^3 mol^{-1} s^{-1}	0.824	1.05	1.25	1.46	1.74	1.97	2.48	3.03	
[Aniline]/mol dm^{-3}	0.0550	0.105	0.158	0.210	0.255	0.315	0.368	0.430	0.547
$k/10^{-5}$ dm^3 mol^{-1} s^{-1}	5.16	6.23	7.59	8.90	9.96	11.3	12.8	14.3	17.3
[*p*-Chloroaniline]/mol dm^{-3}	0.104	0.166	0.208	0.255	0.297	0.374	0.416	0.495	
$k/10^{-6}$ dm^3 mol^{-1} s^{-1}	5.00	6.14	6.78	7.65	8.48	9.68	10.5	12.0	
[*p*-Bromoaniline]/mol dm^{-3}	0.102	0.153	0.204	0.255	0.306	0.357	0.408	0.510	
$k/10^{-6}$ dm^3 mol^{-1} s^{-1}	4.86	5.75	6.62	7.53	8.40	9.27	10.0	11.9	
[*m*-Fluoroaniline]/mol dm^{-3}	0.110	0.160	0.220	0.267	0.315	0.360	0.416	0.468	
$k/10^{-6}$ dm^3 mol^{-1} s^{-1}	1.22	1.40	1.63	1.84	2.01	2.18	2.38	2.61	
[*m*-Chloroaniline]/mol dm^{-3}	0.105	0.162	0.202	0.253	0.303	0.345	0.422	0.462	
$k/10^{-6}$ dm^3 mol^{-1} s^{-1}	1.08	1.28	1.42	1.58	1.78	1.91	2.15	2.32	
[*m*-Bromoaniline]/mol dm^{-3}	0.103	0.155	0.206	0.258	0.309	0.361	0.412	0.464	
$k/10^{-6}$ dm^{-3} mol^{-1} s^{-1}	0.797	0.923	1.04	1.17	1.29	1.43	1.55	1.69	

[a] The kinetic constants were reproducible to within ±3%.

Table 3. Linear regression analysis[a] of apparent second-order kinetic constants, k_A, for the reaction of 2-bromo-3,5-dinitrothiophene **1** with *meta*- and *para*-substituted anilines **2** in benzene, at 25 °C, according to the equation $k_A = k_0 + k_B[B]$.

R	$10^6(k_0 \pm s_0)$	$10^6(k_B \pm s_B)$	n	r	k_B/k_0	σ_{obs}^b
p-OMe	$1\,080 \pm 20$	$11\,400 \pm 100$	9	0.9998	11	−0.36
p-Me	189 ± 6	$1\,800 \pm 20$	8	0.9996	9.5	−0.18
m-Me	53.7 ± 1.5	471 ± 5	8	0.9997	8.8	−0.07
H	37.4 ± 0.5	245 ± 2	9	0.9998	6.6	0.00
p-Cl	3.14 ± 0.06	17.7 ± 0.2	8	0.9997	5.6	0.21
p-Br	3.13 ± 0.05	17.1 ± 0.2	8	0.9998	5.5	0.235
m-F	0.789 ± 0.012	3.87 ± 0.04	8	0.9997	4.9	0.337
m-Cl	0.723 ± 0.012	3.43 ± 0.04	8	0.9996	4.7	0.373
m-Br	0.537 ± 0.006	2.47 ± 0.02	8	0.9998	4.6	0.391

[a] s_0 and s_B are the standard deviations of the regression parameters k_0 and k_B, respectively; r is the correlation coefficient; n is the number of experimental points. The confidence levels for significance of regression are all better than 99.9%. [b] Ref. 7.

adding some suitable substance.[4a,5] The apparent second-order kinetic constants obey a law similar to eqn. (3) and typical k_B/k_0 ratios are 0.5–5. Although some authors have interpreted these accelerations as being due to base catalysis, with the implication that $k_{-1} \gg k_2$, this interpretation has been criticised by Bunnett and Garst.[6] According to them, the inference of genuine base catalysis is, in fact, justified only for reactions showing $k_B/k_0 > 50$: in the reactions where $k_B/k_0 < 5$ it is suggested that the observed acceleration is not due to catalysis.

Therefore the k_B/k_0 values in Table 3 have to be interpreted with great care.

If the observed acceleration, quantitatively accounted for by eqn. (3), is not determined by base catalysis but by some other factor of unclear origin, the k_0 parameter should correspond to k_1. According to this identification, the specific rate constant increases (decreases) on introduction of electron-repelling (electron-withdrawing) substituents into the nucleophile (Table 2) as expected on the grounds of the electronic effects of substituents on the nucleophilicity of the reactant amine.

However, k_B also increases or decreases in the same order and, more interestingly, log k_B values are linearly correlated with log k_0 values (slope 1.11 ± 0.01, intercept 1.38 ± 0.05, n 9, correlation coefficient 0.9997, CL > 99.9%).

Since we find it difficult to give an interpretation of this rigorously quantitative dependence of the phenomenon measured by k_B on the substituent effects by reference only to medium polarity effects, we conclude that in the reaction studied a genuine base catalysis is involved. The low values of $k_3^{B_i}/k_2$ ratios can be related to the low basicity of the anilines involved and thus to their low catalytic efficiency.

If log k_B or log k_0 values are plotted *versus* σ_{obs} substituent constants[7] (Table 3), one observes excellent linear correlations [eqns. (5) and (6); Fig. 1] with high susceptibility constants.

$$\log k_B = (-3.67 \pm 0.02) + (-4.93 \pm 0.07)\,\sigma_{obs} \quad (5)$$
$$n\,9,\ r\,0.999,\ \mathrm{CL} > 99.9\%$$

$$\log k_0 = (-4.53 \pm 0.02) + (-4.22 \pm 0.08)\,\sigma_{obs} \quad (6)$$
$$n\,9,\ r\,0.999,\ \mathrm{CL} > 99.9\%$$

Since $k_B = k_1k_3^{B_i}/k_{-1}$, $(k_0)_i = k_1k_2/k_{-1}$ and $\log k = \rho\sigma + i$, the slopes of the two straight lines in Fig. 1 correspond to $\rho_1 + \rho_3 - \rho_{-1}$ and $\rho_1 + \rho_2 - \rho_{-1}$, respectively. For the reactions of 2-bromo-3,5-dinitrothiophene with *meta*- and *para*-substituted anilines in methanol, where the rate-determining step is the formation of the intermediate and $k_A = k_1$, one can calculate[7] $\rho_1 = -3.00$, at 25 °C.

On the assumption that for the reactions in benzene $\rho_1 = -3.00$, one obtains $\rho_3 - \rho_{-1} = -1.9$, $\rho_2 - \rho_1 = -1.4$ and $\rho_3 - \rho_2 = -0.5$.

The decomposition of the reaction intermediate to reactants (k_{-1} step) involves the breaking of intramolecular hydrogen bonding between the anilinio proton and the 3-nitro group and the breaking of the bond between nitrogen and the thiophene aromatic carbon atom, as depicted in **4**.

The effect of an electron-withdrawing substituent in the

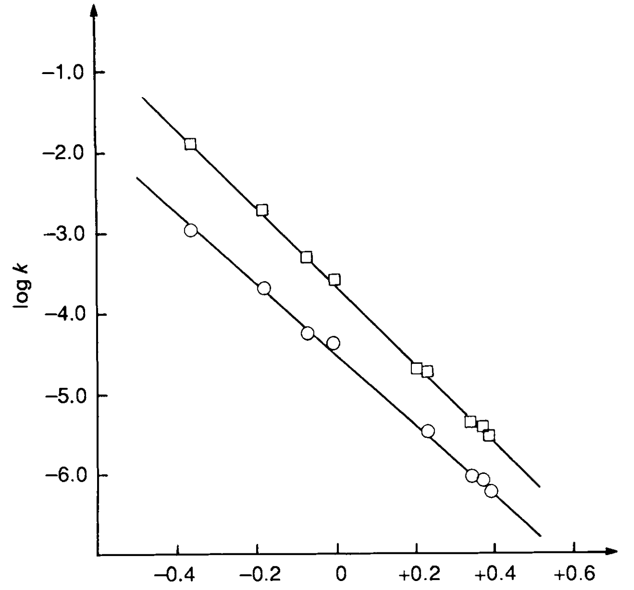
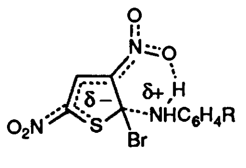


Fig. 1. Plot of log k_0 (○) or log k_B (□) for compound **1** *versus* σ_{obs}.



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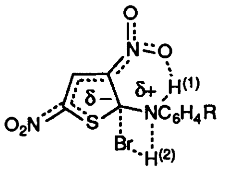

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aniline moiety, with respect to hydrogen in the unsubstituted parent aniline, is to oppose the breaking of the first bond and to favour breaking of the latter bond. The opposite effect occurs with electron-repelling substituents.

It is evident that the substituent effect on the carbon–nitrogen bond is of major importance since it is the extent of formation (or breaking) of this bond that predominantly controls the energy of the first transition state of the reaction mechanism; thus, it should be $\rho_{-1} > 0$.

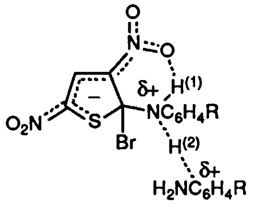
The mechanism of the k_2 step, *i.e.*, the spontaneous decomposition of the reaction intermediate into the reaction products, involves a transfer of an anilinio proton to the leaving group concerted with leaving group departure as shown in **5**.*

A substituent present in the aniline moiety controls the acidity of 2-H and, consequently, the intramolecular acid catalysis for the leaving group expulsion; as regards this factor it should be $\rho_2 > 0$.

However, the substituent effect controls, in a direct way, the breaking of the thiophene carbon–nitrogen bond (k_{-1} step) and only indirectly the breaking of the thiophene carbon–bromide bond (k_2 step). As a consequence it should be, and is observed, that $\rho_2 < \rho_{-1}$.

The substituent effect on $k_3^{B_i}$ is more difficult to predict because it is first necessary to settle the mechanism of this base-catalysed step. In fact, the removal of the acidic anilinio proton in the reaction intermediate could happen in different ways, *e.g.*, (*a*) rate-limiting proton abstraction by the base to form deprotonated intermediate, followed by rapid expulsion of leaving group; (*b*) rapid equilibrium deprotonation followed by rate-limiting general acid-catalysed detachment of the nucleofuge (SB-GA mechanism); or (*c*) concerted proton transfer and leaving group detachment with bifunctional catalysis by the amine.

On the hypothesis of a rate-determining proton transfer [mechanism (*a*)] the relevant transition state can be represented as **6**. On increasing the electron-withdrawing power of the substituent R the acidity of both 1-H and 2-H increases.



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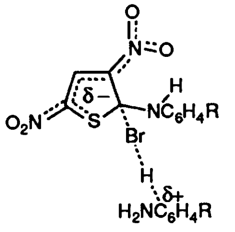

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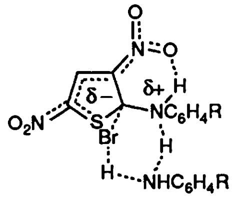

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The transfer of 2-H to the external aniline molecule reduces the acidity of 1-H and, consequently, the stabilization through hydrogen bonding. In fact, there is some compensation between the favourable substituent effect on the acidity of 2-H and the unfavourable effect on the intramolecular hydrogen bonding.

On the other hand, since the substituent variation controls in a direct way the basicity and thus the catalytic efficiency of the aniline molecule which acts as a base, it should be that $\rho^B < 0$. Moreover, ρ^B is likely to have a small absolute value.

In the SB-GA mechanism [mechanism (*b*)], the proton transfer is rapid and reversible and involves a transition state much the same as **6**. Indeed, the definition of specific base catalysis for the deprotonation equilibrium implies the condition $\rho = 0$.

An examination of the transition state for the general acid-catalysed leaving group expulsion **7** shows that increasing the electron-withdrawing power of R has the important effect of increasing the catalytic efficiency of the anilinium cation. Based on this effect it should be that $\rho > 0$. However, there is another molecule of substituted aniline incorporated in the transition state and here the effect of an electron-withdrawing R substituent is to oppose, to some extent, the breaking of the carbon–bromine bond. Thus, on the whole, the $k_3^{B_i}$ step should have $\rho^B > 0$ but probably ρ^B has a small absolute value.

The mechanism which involves bifunctional catalysis, with a transition state like **8** would represent a mechanism halfway between (*a*) and (*b*) (see above).

As a matter of fact, the above-mentioned differences between the susceptibility constants pertaining to the single steps of the reaction do not allow us to make a choice between the most feasible mechanisms for the base-catalysed step.

However, it is probable that, whereas in protic solvents (depending on the leaving group) general base catalysis could involve a rate-determining proton transfer, in aprotic solvents (like benzene) where the leaving group expulsion is not assisted by the solvent and there is a significant p*K* difference between

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* The transfer of 2-H to the leaving group reduces the acidity of the bonded 1-H and thus reduces the stabilisation through hydrogen bonding, but this is partially compensated by an increase in acidity due to the transformation from a *N*-alkyl to a *N*-aryl aniline.

leaving group and acid catalyst, the SB-GA mechanism is the most favoured.

Experimental

Synthesis and Purification of Compounds.—Benzene,[8] anilines **2**,[7] 2-bromo-3,5-dinitrothiophene **1**,[9] and *N*-(3,5-dinitro-2-thienyl)anilines **3**,[7] were prepared and/or purified as previously reported.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[10] The concentrations used were 2.4×10^{-4} mol dm^{-3} for **1** and those indicated in Table 2 for the anilines. The wavelength and log ε values for UV spectral measurements are reported in Table 1.

References

1 Part 8, C. Arnone, G. Consiglio, V. Frenna and D. Spinelli, *Collect. Czech. Chem. Commun.*, 1990, **5**, 223.

2 C. F. Bernasconi, in *MTP Int. Rev. Sci., Org. Chem. Ser. 1*, Butterworths, London, 1973, vol. 3, p. 33.

3 J. Miller, in *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam.

4 (*a*) S. D. Ross, *Prog. Phys. Org. Chem.*, 1963, **1**, 31; (*b*) T. O. Bamkole and J. Hirst, *J. Chem. Soc. B*, 1969, 1848; H. Suhr, *Ber. Bunsenges. Phys. Chem.*, 1963, **67**, 893; P. Beltrame, L. Bonomi, P. De Re and M. Simonetta, *Gazz. Chim. Ital.*, 1967, **97**, 470; N. K. Danilova and S. M. Shein, *Org. React.* (*USSR*), 1970, **7**, 476, 718; S. M. Shein and L. A. Suchkova, *Org. React.* (*USSR*), 1970, **7**, 748; V. N. Lisitsyn and V. A. Shul'chishin, *J. Org. Chem.* (*USSR*) (*Engl. Transl.*), 1970, **6**, 313; S. D. Ross in Bamford and Tipper, in *Comprehensive Chemical Kinetics*, American Elsevier, New York, vol. 13, p. 407.

5 C. F. Bernasconi, M. Kaufmann and H. Zollinger, *Helv. Chim. Acta*, 1966, **49**, 2563.

6 J. F. Bunnett and R. Garst, *J. Am. Chem. Soc.*, 1965, **87**, 3875.

7 D. Spinelli, G. Consiglio, R. Noto and V. Frenna, *J. Org. Chem.*, 1976, **41**, 968.

8 A. I. Vogel, in *Practical Organic Chemistry*, Longmans, London, 3rd edn., 1961, p. 73.

9 R. Motoyama, K. Sato and E. Imoto, *Nippon Kagaku Zasshi*, 1961, **82**, 1543.

10 D. Spinelli, G. Consiglio and R. Noto, *J. Heterocycl. Chem.*, **14**, 1325.

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