

Electronic and steric effects in the S_NAr substitution reactions of substituted anilines with 2,4-dinitrophenyl 2,4,6-trinitrophenyl ether in acetonitrile

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ABSTRACT: Rate measurements are reported for the reactions of 12 ring-substituted anilines with 2,4-dinitrophenyl 2,4,6-trinitrophenyl ether (**1**) in acetonitrile. Formation of the products, the correspondingly substituted 2,4,6-trinitrodiphenylamines, occurs without the observation of intermediates in detectable amounts by both base-catalysed and uncatalysed pathways and Hammett ρ value were determined for these processes. The results show that although substituents at the 3- or 4-positions of the anilines have only small steric effects, alkyl substituents at the 2-position may result in considerable reductions in reactivity. These effects are more pronounced for the base-catalysed pathway and in 2,6-dimethylaniline the uncatalysed pathway takes all the reaction flux. In the case of the 2-fluoro substituent the electronic effect, strong inductive electron withdrawal, is dominant over steric effects. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: S_NAr substitution reactions; anilines; 2,4-dinitrophenyl 2,4,6-trinitrophenyl ether; electronic effects; steric effects

INTRODUCTION

Nucleophilic substitutions in the reactions of amines with activated aromatic substrates generally involve the S_NAr addition–elimination mechanism,^{1,2} as shown in Scheme 1. When the second step is rate limiting, general base catalysis may be observed.

The base-catalysed pathway may involve general acid catalysis, by the conjugate acid BH^+ , of leaving group departure, the SB–GA mechanism,³ or alternatively rate-limiting proton transfer from the zwitterionic intermediate to base followed by rapid loss of X^- , the RLPT mechanism.⁴ There is now good evidence that in acetonitrile^{5,6} and in dimethyl sulfoxide^{7,8} the displacement of phenoxide ions by amines involves the latter mechanism.

There have been several reports of substitutions involving aniline or substituted anilines.^{9–16} Most of these have involved displacement of halide ions where the k_1 step, nucleophilic attack by the amine, is rate limiting. For reactions involving aniline and anilines carrying ring substituents at the 3- or 4-positions, as for other primary amines,^{17,18} there is little evidence for a significant

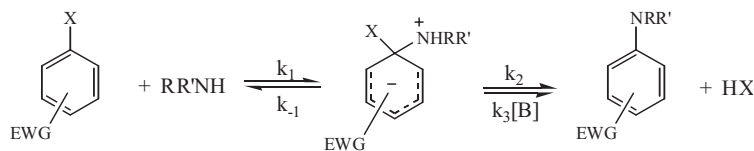
primary steric effect. Here electronic effects are dominant and Hammett ρ values are typically -3.5 to -4 in protic solvents.^{12,13,16,19} Nevertheless, for *N*-substituted anilines steric hindrance to nucleophilic attack may be severe so that the rates of substitution are considerably reduced relative to aniline.^{6,20}

We found recently²¹ that in the reaction of aniline with 2,4-dinitrophenyl 2,4,6-trinitrophenyl ether (**1**) in acetonitrile conversion of the zwitterionic intermediate to products was rate determining and involved both uncatalysed, k_2 , and base catalysed, $k_B[B]$, pathways. Here we report a kinetic study of the reactions of anilines containing both remote- and *ortho*-ring substituents, allowing the electronic and steric effects on the individual steps in Scheme 1 to be considered.

RESULTS AND DISCUSSION

The reactions of **1** with ring-substituted anilines, **2**, gave the expected substitution products, **4**, in $>95\%$ yield. Spectroscopic data are given in Table 1. Kinetic measurements were made in acetonitrile at 25 °C with amine concentrations in large excess of concentrations of **1**. Reactions proceeded without the observation of intermediates in detectable concentrations and first-order kinetics were observed. The results are interpreted by Scheme 2, where the zwitterion **3** may be treated as a

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Scheme 1. EWG = electron-withdrawing group

steady-state intermediate. Base catalysis is attributed to rate-limiting proton transfer from **3** to base followed by rapid expulsion of the phenoxide.^{5,6,21} Division of the first-order rate constants, k_{obs} , by the aniline concentration gave values of the second order rate constant, k_A , whose base dependence is given by Eqn (1). An alternative form of this equation is Eqn (2), where $K_1 = k_1/k_{-1}$ is the equilibrium constant for formation of the zwitterionic intermediate. Values are reported in Tables 2 and 3.

$$k_A = \frac{k_{\text{obs}}}{[\text{An}]} = \frac{k_1(k_2 + k_{\text{An}}[\text{An}])}{k_{-1} + k_2 + k_{\text{An}}[\text{An}]} \quad (1)$$

$$k_A = \frac{K_1 k_2 + K_1 k_{\text{An}}[\text{An}]}{1 + \frac{k_2}{k_{-1}} + \frac{k_{\text{An}}[\text{An}]}{k_{-1}}} \quad (2)$$

For anilines **2a–g** carrying substituents at the 3- or 4-positions, plots (not shown) of k_A versus aniline concentration had positive intercepts on the y-axis, representing the uncatalysed pathway and curved with decreasing slope as the aniline concentration increased. Values calculated using Eqn (2) with the parameters given in Table 4 gave good fits to the experimental data. The values of $K_1 k_2$ and of $K_1 k_{\text{An}}$ have low error limits although, because of the small curvature, values of k_{An}/k_{-1} are less precise. Similarly values of k_1 , calculated as $K_1 k_{\text{An}} k_{-1}/k_{\text{An}}$ have fairly high error limits.

For anilines **2h–l** carrying *ortho*-substituents there was no discernible curvature in plots of k_A versus aniline concentration. This indicates that here $k_{\text{An}}/k_{-1} < 1$ and also implies that $k_2/k_{-1} (\equiv k_{\text{An}}/k_{-1} \times k_2/k_{\text{An}}) < 1$. Hence values of $K_1 k_2$ and $K_1 k_{\text{An}}$ were obtainable from the intercepts and slopes, respectively, of the plots.

3- and 4-substituted anilines

The data in Table 4 show that for anilines carrying substituents at the 3- or 4-positions, values of both $K_1 k_2$ and $K_1 k_{\text{An}}$ decrease strongly with increasing electron withdrawal by the ring-substituents. Plots (not shown) versus Hammett σ values²² gave excellent straight lines with slopes, ρ , of -5.5 for $K_1 k_2$ and -5.4 for $K_1 k_{\text{An}}$.

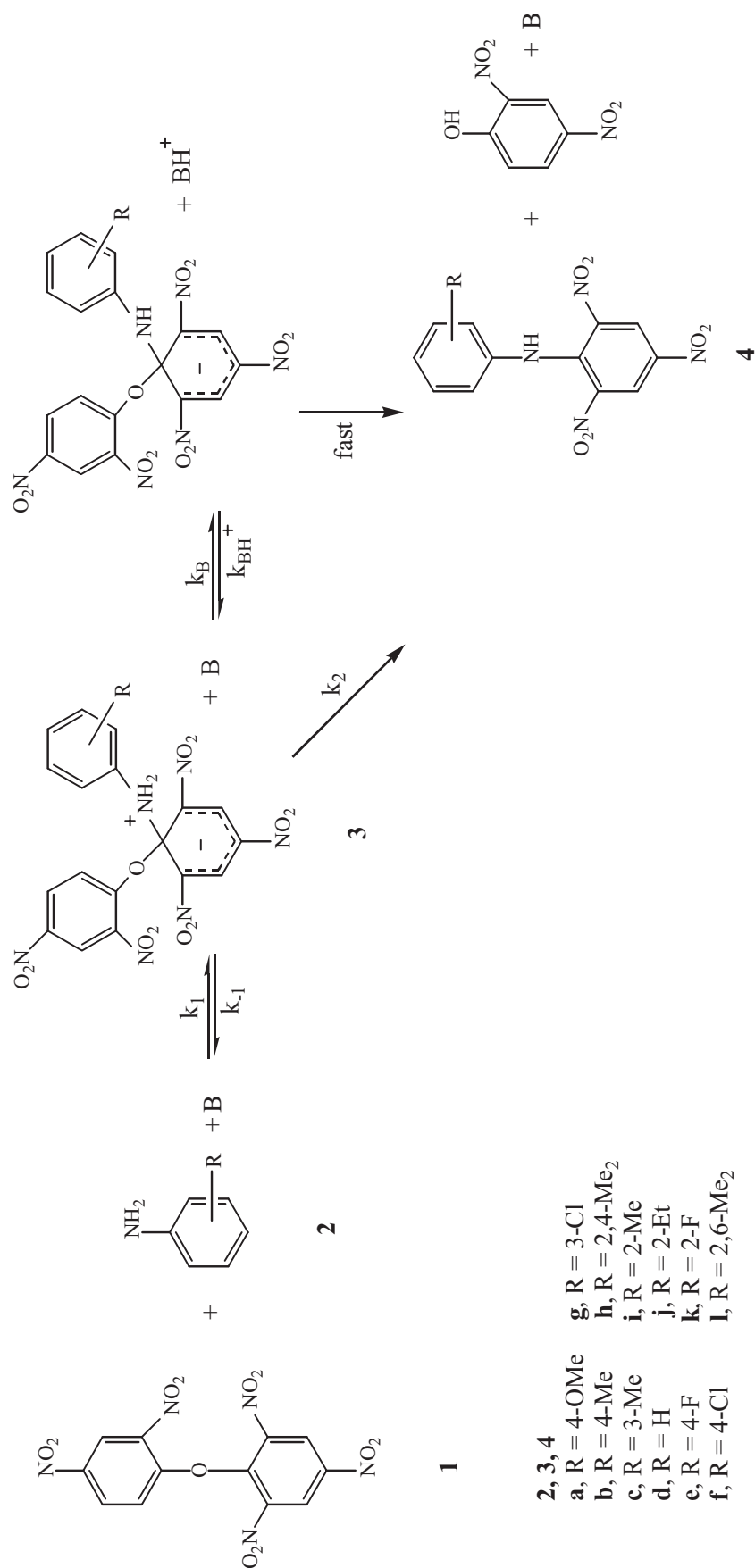
The rate constant k_{An} represents a proton transfer from the zwitterionic intermediate **3** to the corresponding aniline. It has been shown previously^{5,23,24} that such trinitro-activated zwitterions are considerably stronger acids than the parent anilinium ions. Hence k_{An} represents a thermodynamically favourable proton transfer between nitrogen atoms so that its value will depend on steric constraints rather than basicity considerations. For anilines **2a–g** carrying remote substituents the steric hindrance at the reaction centre for proton transfer should not change, so that values of k_{An} will be constant. This leads to a ρ value -5.4 for K_1 , consistent with the positive charge developed on nitrogen.

Table 1. Spectroscopic data for reaction products

Compound	¹ H NMR shifts (ppm) ^a			UV maximum ^b		
	NH	Picryl ring	Other aromatic	Alkyl	λ (nm)	$\text{Log}[\epsilon (\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1})]$
4a , R = 4-OMe	10.21	8.90	7.11, 6.87	3.73	370	1.6
4b , R = 4-Me	10.18	8.90	7.11, 7.04	2.26	355	1.5
4c , R = 3-Me	10.10	8.90	7.1	2.30	355	1.5
4d , R = H	9.96	8.96	7.33, 7.25, 7.15	—	365	1.4
4e , R = 4-F	10.21	8.93	7.2	—	360	1.5
4f , R = 4-Cl	10.19	8.94	7.36, 7.17	—	360	1.6
4g , R = 3-Cl	10.19	8.97	7.3	—	350	1.4
4h , R = 2,4-Me ₂	10.01	8.97	7.19, 7.0	2.33, 2.34	350	1.9
4i , R = 2-Me	9.95	8.90	7.28, 7.17 7.09, 7.03	2.30	350	1.6
4j , R = 2-Et	9.95	8.91	7.32, 7.22 7.10, 7.02	1.24 2.69	350	1.6
4k , R = 2-F	10.09	8.94	7.27, 7.13	—	350	1.6
4l , R = 2,6-Me ₂	10.10	8.87	7.12, 7.08	2.09	347	1.6

^aIn [2H₆]DMSO.

^bIn acetonitrile.



Scheme 2

Table 2. Kinetic results^a for the reaction of **1** with **2a–g** in acetonitrile at 25 °C

[Aniline] (mol dm ⁻³)	k_A (10 ⁻² dm ³ mol ⁻¹ s ⁻¹)					
	4-OMe	4-Me	3-Me	4-F	4-Cl	3-Cl
0.002				4.3 (4.3)		
0.004			17.1 (17.5)			
0.005	280 (280)	66 (65)				
0.008				4.8 (5.0)		
0.010	320 (320)	70 (71)	19.4 (19.4)	5.1 (5.2)	0.75 (0.70)	0.09 (0.10)
0.015						
0.020	380 (380)	80 (81)	22.0 (22.4)	6.1 (6.1)	0.86 (0.89)	0.13 (0.13)
0.030	430 (430)	90 (92)	25.3 (25.3)	7.5 (7.1)	1.03 (1.09)	
0.040	480 (480)	100 (98)	28.8 (28.1)		1.2 (1.3)	0.16 (0.17)
0.050	530 (530)	110 (112)			1.4 (1.5)	0.19 (0.19)
0.060			33.1 (33.3)		1.6 (1.6)	
0.070						0.20 (0.22)
0.080		138 (137)			2.0 (2.0)	0.25 (0.26)
0.10		153 (152)			2.4 (2.3)	0.31 (0.30)
0.14					2.9 (2.9)	
0.15						0.40 (0.40)
0.20						0.50 (0.49)

^aValues in parentheses were calculated using Eqn (2) with the values collected in Table 4.

Since values of K_1k_2 show an almost identical dependence on the substituents, ρ value of -5.4 , values of k_2 for intramolecular proton transfer within the zwitterions are essentially constant with these anilines. This is also apparent from the constancy, at $\sim 30 \text{ dm}^3 \text{ mol}^{-1}$, of the ratio k_{An}/k_2 in Table 4. Values of k_2 will, of course, be expected to show a strong dependence on the nucleofugality of the phenolic leaving group,^{2,21} which is constant in the present measurements.

A Hammett plot of values of k_1 , the rate constant for nucleophilic attack by the anilines, gives a ρ value of -4.2 . This indicates a strong dependence on the nature of the substituent and infers substantial development of

positive charge on nitrogen in the transition state. Correspondingly, there will be considerable development of negative charge on the other groups at the 1-position. Our previous measurements^{6,21} showed that the nature of the substituents in the phenolic leaving group had only a small effect on values of k_1 for nucleophilic attack by aniline. The data in Table 3 in Ref. 21 give a ρ value of ca $+0.5$. The conclusion drawn was that there was little charge development and hence an 'early' transition state. Nevertheless, consideration of the structure of the zwitterion **3** shows that the bulk of the negative charge will be delocalised into the trinitrophenyl ring so that substituents in the incipient leaving group have only a small influence on charge delocalisation. Hence our current results and those given previously accord better with a 'late' transition state for nucleophilic attack with considerable charge development.

Table 3. Kinetic results^a for the reaction of **1** with **2h–i** in acetonitrile at 25 °C

[Aniline] (mol dm ⁻³)	k_A (10 ⁻² dm ³ mol ⁻¹ s ⁻¹)				
	2,4-Me ₂	2-Me	2-Et	2-F	2,6-Me ₂
0.005	2.5				
0.010	2.6	0.48			
0.015	2.7	0.50			
0.020	2.8	0.53	0.20		
0.025		0.55			
0.030	2.9	0.56	0.21		
0.040			0.22	0.042	
0.050			0.24		
0.060		0.70	0.25	0.054	
0.080		0.79		0.071	
0.10		0.83		0.087	0.007
0.12				0.105	
0.15					0.006
0.20					0.006
0.30					0.006

^aLinear plots of k_A versus [aniline] yield the values given in Table 4.

2-Substituted anilines

Whereas the effects of remote substituents, at the 3- or 4-position, in the nucleophile are dominated by electronic effects, in 2-substituted anilines there is evidence for significant steric interactions. Thus the effect of a 2-methyl substituent is to reduce the value of K_1k_{An} by a factor of 55 in aniline and 80 in 4-methylaniline. The corresponding factor for 2-ethylaniline is 200. Our results do not allow the separation of steric effects on values of K_1 and k_{An} , although both terms are expected to be reduced by steric congestion at the reaction centre.

Comparison of the values of K_1k_2 for aniline and 2-methylaniline and for 4-methylaniline and 2,4-dimethylaniline yields ratios of 17 and 28, respectively. These ratios are 3–4 times smaller than those for the similar

Table 4. Summary of rate data for the reaction of **1** with ring-substituted anilines **2a-l** in acetonitrile at 25 °C

Substituent(s), R	K_1k_2 (dm ³ mol ⁻¹ s ⁻¹)	$K_1k_{An_2}$ (dm ⁶ mol ⁻² s ⁻¹)	k_{An}/k_{-1} (dm ³ mol ⁻¹)	k_1 (dm ³ mol ⁻¹ s ⁻¹)	k_{An}/k_2 (dm ³ mol ⁻¹)
a , 4-OMe	2.9 ± 0.3	90 ± 10	5 ± 1	18 ± 5	31
b , 4-Me	0.68 ± 0.05	16 ± 1	3.5 ± 1	4.5 ± 1.5	24
c , 3-Me	0.18 ± 0.05	4 ± 0.5	2.5 ± 1	1.6 ± 0.5	22
d , H ^a	0.08 ± 0.01	2.2 ± 0.2	2.7 ± 0.5	0.8 ± 0.3	28
e , 4-F	0.045 ± 0.01	1.25 ± 0.1	2.5 ± 0.5	0.5 ± 0.2	28
f , 4-Cl	(5 ± 1) × 10 ⁻³	0.23 ± 0.02	1.8 ± 0.5	0.12 ± 0.06	46
g , 3-Cl	(8 ± 1) × 10 ⁻⁴	0.026 ± 0.004	1 ± 0.5	0.026 ± 0.01	33
h , 2,4-Me ₂	0.024 ± 0.004	0.2 ± 0.05	<1		8
i , 2-Me	(4.5 ± 0.5) × 10 ⁻³	0.04 ± 0.005	<1		9
j , 2-Et	(1.8 ± 0.4) × 10 ⁻³	0.011 ± 0.003	<1		6
k , 2-F	(1 ± 0.2) × 10 ⁻⁴	(8 ± 1) × 10 ⁻³	<1		80
l , 2,6-Me ₂	(6 ± 1) × 10 ⁻⁵				

^aData from Ref. 21.

comparisons of K_1k_{An} values, indicating that steric effects on k_2 are less severe than on k_{An} . This effect is also seen in the reduction in value of k_{An}/k_2 in Table 4 from ~30 to ~8 for the *ortho*-alkyl-substituted anilines.

It might be argued that since k_2 involves an intramolecular proton transfer, steric effects should be small. Hence the major steric effect on K_1k_2 values is likely to be in the equilibrium formation of the zwitterionic intermediates yielding reduced values of K_1 . A reduction in the value of k_{An} represents hindrance of approach to the reaction centre carrying an *ortho*-substituted aniline by a second *ortho*-substituted aniline molecule. It is worth noting that in the reaction of 2,6-dimethylaniline (Table 4), this hindrance is so severe as to reduce the catalysed pathway below its observable limit. The value of K_1k_2 is reduced by a factor of 75 relative to its value for 2-methylaniline.

The effect of a 2-fluoro substituent is to reduce considerably the values of both K_1k_{An} and K_1k_2 relative to aniline. However, in contrast to the behaviour of the 2-alkyl derivatives, the ratio k_{An}/k_2 is somewhat higher than for aniline itself. Values of E_s , the Taft steric factor,²⁵ are H 1.24, F 0.78, Me 0.00 and Et -0.07, so that steric effects are likely to be less important for the 2-fluoro derivative. Here the results indicate the dominance of electronic effects. It is known²⁶ that owing to its strongly electron-withdrawing inductive effect, an *ortho*-fluorine substituent will have a strongly destabilising effect on the adjacent cationic nitrogen centre in the zwitterion **3k**. This is expected to result in a large reduction in the value of K_1 , which is likely to be the major effect with only relatively small steric effects on k_{An} or k_2 .

The product-forming steps involve loss of the phenolic leaving group and rotation of the aniline moiety towards the ring-plane of the trinitro-substituted ring. It is worth considering whether steric effects due to the presence of an *ortho*-substituent in the aniline might reduce values of rate constants for this process. Evidence that such effects are not severe comes from two sources. First, we report in

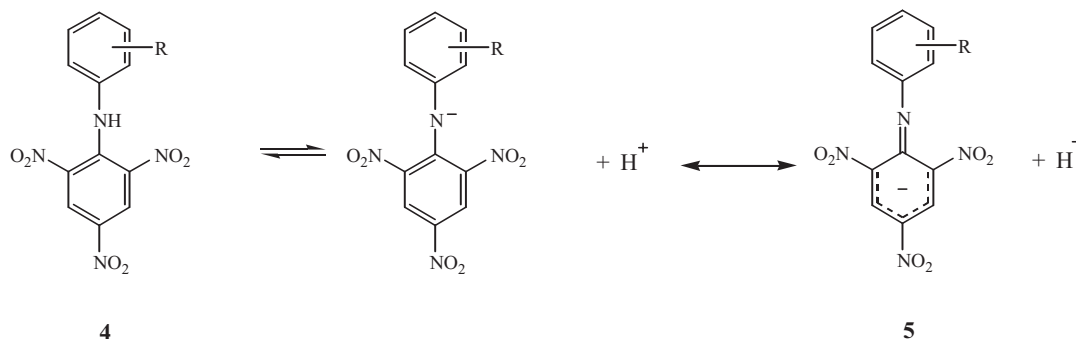
Table 5 the pK_a values, measured in acetonitrile, for some 2'-substituted-2,4,6-trinitrodiphenylamines which are the reaction products. These relate to the process shown in Scheme 3 and show that 2'-alkyl substituents have only small effects on the acidity of **4** whereas a 2'-fluoro-substituent increases the acidity by *about* one pK_a unit. The latter effect is consistent with the expected stabilisation of the anionic centre in **5** by the inductive electron withdrawal of the fluorine substituent. The small effect of the alkyl substituents argues against an increase in the steric interactions between the aromatic rings, which would be expected to make more difficult ionisation to give the delocalised anion **5**. The second piece of evidence comes from previously reported²¹ crystal structures of the related 2,6-disubstituted-phenoxy 2,4,6-trinitrophenyl ethers. Although relating to diphenyl ethers rather than diphenylamines, these show that steric interactions between the rings increase only slightly in the presence of the 2,6-substituents.

In conclusion, the results from this and our previous work²¹ show that all phenyl trinitrophenyl ethers are sterically strained structures. However, the steric hindrance to the steps involved in nucleophilic substitution by aniline and ring-substituted anilines is only significantly increased when either the entering or leaving groups contains two *ortho*-substituents or when both entering and leaving groups carry an *ortho*-substituent.

Table 5. pK_a values of **4i-k** in acetonitrile

Substituent	UV maximum ^a (nm)		K	pK_a
	4	5		
i , 2-Me	360, (4.15)	445, (4.37)	0.025	19.89
j , 2-Et	360, (4.15)	445, (4.37)	0.023	19.93
k , 2-F	353, (4.14)	436, (4.40)	0.19	19.02
d , H				19.97 ^b

^aValues of \log_e are given in parentheses.^bRef. 6.



Scheme 3

The main steric effects are thought to result in the reduction in values of K_1 for formation of the zwitterionic intermediates and in values of k_{An} for the base-catalysed pathway.

N-Substitution in the aniline does have, as shown previously,^{6,20} a dramatic steric effect on the substitution process.

EXPERIMENTAL

The diphenyl ether **1** was available from previous work.²¹ The substituted anilines **2** and DABCO were the purest available commercial samples, as was the acetonitrile solvent. ¹H NMR spectra of reaction products were recorded using a Bruker Avance 400 MHz instrument in DMSO-*d*₆ as the solvent. UV–visible spectral and kinetic measurements were made at 25 °C with a Perkin-Elmer Lambda 2 or a Shimadzu UV PC spectrophotometer. First-order rate constants were measured with concentrations of **2** in large excess of concentrations of **1**, $(0.5–1) \times 10^{-4}$ mol dm⁻³, and were evaluated using standard methods. Values are precise to $\pm 3\%$.

¹H NMR measurements have shown previously^{27,28} that reaction of 2,4,6-trinitrodiphenylamines with base results in proton loss. pK_a values of the *ortho*-substituted-2,4,6-trinitrodiphenylamines **4i–k** were measured^{6,27} using the changes in UV–visible absorbance associated with their deprotonation to give **5i–k**. In the presence of DABCO and/or DABCOH⁺, the equilibrium shown in Eqn (3) was established. Absorbance measurements at the λ_{max} value for **5** allowed the evaluation of values of the equilibrium constant K . Values of pK_a were determined using Eqn (4) with the known value²⁹ for $pK_a^{DABCOH^+}$ of 18.29. Results are given in Table 5.



$$pK_a = pK_a^{DABCOH^+} - \log K \quad (4)$$

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