

Leaving group effects on the mechanism of aromatic nucleophilic substitution (S_NAr) reactions of some phenyl 2,4,6-trinitrophenyl ethers with aniline in acetonitrile

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ABSTRACT: Kinetic studies are reported for the reactions with aniline in acetonitrile of a series of X-phenyl 2,4,6-trinitrophenyl ethers [X = H, 2-, 3-, 4-CH₃, 2,4-, 2,6-(CH₃)₂, 2-, 3-, 4-NO₂, 2,4-, 2,6-(NO₂)₂]. X-ray crystal structures for X = H, 2,6-(CH₃)₂ and 2,6-(NO₂)₂ are reported and provide evidence for steric crowding around the 1-position of these molecules. Nevertheless, the kinetic data show that increasing substitution does not sterically inhibit nucleophilic attack by aniline and an 'early' transition state is likely. In general, the reactions are base catalysed; interpreted as rate-limiting deprotonation of the zwitterionic intermediates. Only with the dinitro derivatives is an uncatalysed reaction involving intramolecular proton transfer observed and when X = 2,6-(NO₂)₂ this pathway takes all the reaction flux. Copyright © 2003 John Wiley & Sons, Ltd.

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KEYWORDS: leaving group effects; S_NAr reactions; phenyl 2,4,6-trinitrophenyl ethers; aniline; crystal structures

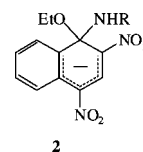
INTRODUCTION

Many aromatic substitutions involving primary and secondary amines as nucleophiles are subject to general base catalysis,^{1,2} and there is current interest in these reactions.^{3–7} The overall mechanism is given in Scheme 1, where EWG denotes a generalized substituent. Equation (1) is the steady-state expression for the observed second-order rate constant, k_A , expressed in terms of the component steps in Scheme 1.

$$k_A = \frac{k_1(k_2 + k_B[B])}{k_{-1} + k_2 + k_B[B]} \quad (1)$$

In Scheme 1, B with a catalytic constant k_B could be a nucleophilic amine itself or an added base. The zwitterionic intermediate **1** can proceed to products either spontaneously (k_2) or through base catalysis ($k_B[B]$). The base-catalysed pathway may involve rate-limiting proton transfer from the zwitterionic intermediate to base or general acid catalysis (by BH^+) of leaving group expulsion from an anionic intermediate in equilibrium with the zwitterion. The latter pathway, the SB–GA mechanism, has been shown to be generally applicable to reactions involving displacement of alkoxide groups

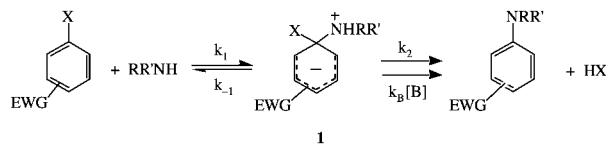
by amines in dimethyl sulfoxide (DMSO). This follows the study of Orvik and Bunnett⁸ of the reactions of 1-ethoxy-2,4-dinitrophenyl ether with amines in DMSO. They were able to observe in separate steps the formation of intermediates of structure **2** and their acid catalysed conversion into product. Related intermediates have been observed during the reactions of several other ring-activated alkyl aryl ethers and there is no doubt that in these reactions the SB–GA mechanism applies.^{9–11}



However, studies with phenyl 2,4,6-trinitrophenyl ethers, involving the displacement of phenoxide groups, have provided good evidence that in both DMSO^{12,13} and acetonitrile¹⁴ the observation of base catalysis is attributable to rate-limiting proton transfer from the zwitterionic intermediates to base.

We have recently studied¹⁵ the reactions of some 3'- and 4'-substituted phenyl 2,4,6-trinitrophenyl ethers with aniline and with *N*-methylaniline in acetonitrile and DMSO. In the former solvent the main reaction flux was found to occur through the base-catalysed pathway ($k_B[B]$ in Scheme 1), whereas in DMSO both catalysed and uncatalysed (k_2) pathways were important. In order to assess the electronic and steric effects of ring

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EWG = electron withdrawing group

Scheme 1

substituents on the relative importance of these pathways, we made kinetic measurements on the reaction with aniline in acetonitrile of a series of mono- and dimethyl-substituted phenyl 2,4,6-trinitrophenyl ethers, **3**, and the corresponding mono- and dinitro-substituted derivatives, **4**. The results show that there is a dramatic change in behaviour from the 2,6-dimethyl derivative, **3f**, where the substitution is wholly base catalysed, to the 2,6-dinitro derivative, **4f**, where only the uncatalysed substitution is observed. The x-ray crystallographic structures of phenyl 2,4,6-trinitrophenyl ether, **3a**, and also the 2,6-disubstituted derivatives **3f** and **4f**, are reported and provide evidence for the increasing steric congestion at the reaction centre with increasing substitution.

RESULTS AND DISCUSSION

The results are discussed in terms of Scheme 2. Kinetic measurements were made spectrophotometrically using the absorbance at 365 nm of the product 2,4,6-trinitrophenylamine, **7**. With concentrations of aniline, 0.01–0.5 mol dm⁻³, in large excess of the concentration of the diphenyl ethers, 10⁻⁴ mol dm⁻³, first-order kinetics were observed, and rate constants, *k*_{obs}, were evaluated by standard methods. For some reactions, 1,4-diazabicyclo[2,2,2]octane (DABCO) was added in large excess of the substrate concentration. The UV–visible spectra and, in more concentrated solutions, the ¹H NMR spectra at the completion of reaction corresponded exactly to those of authentic samples of the substitution products in

the reaction medium. Division by the concentration of aniline of values of *k*_{obs} gave second-order rate constants *k*_A. The results are given in Tables 1 and 2. There was no evidence either from the spectra or the kinetics for the accumulation of intermediates **5** or **6** on the reaction pathway.

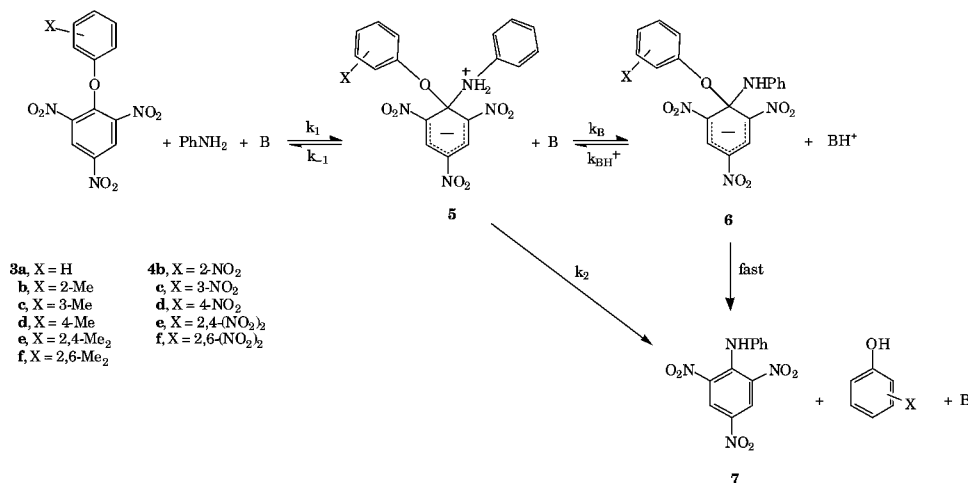
The methyl series, **3a–f**

Plots, not shown, of second-order rate constants, *k*_A, versus aniline concentration pass through the origin, indicating that the uncatalysed pathway (*k*₂ in Scheme 2) is unimportant, and curve with decreasing slope as the aniline concentration is increased. Hence Eqn (1) reduces to Eqn (2), where *k*_{An} represents catalysis by aniline, and this in turn may be written as Eqn (3).

$$k_A = \frac{k_{\text{obs}}}{[\text{An}]} = \frac{k_1 k_{\text{An}} [\text{An}]}{k_{-1} + k_{\text{An}} [\text{An}]} \quad (2)$$

$$k_A = \frac{K_1 k_{\text{An}}}{1 + \frac{k_{\text{An}} [\text{An}]}{k_{-1}}} \quad (3)$$

The values in Table 1 were used to obtain the values of *K*₁*k*_{An} and *k*_{An}/*k*₋₁ given in Table 3. Combination of these values yielded *k*₁ = *K*₁*k*_{An}*k*₋₁/*k*_{An}. Values of *K*₁*k*_{An} could be obtained with good precision but, because of the small degree of curvature in the plots of *k*_A vs [aniline], the values of *k*_{An}/*k*₋₁ are subject to more error, hence leading to higher errors associated in the *k*₁ values. In the case of the dimethyl derivatives **3e** and **3f**, the plots were essentially linear so that only maximum values could be assigned to *k*_{An}/*k*₋₁. Hence the values quoted here for *k*₁ are minimum values, and for the 2,6-dimethyl derivative it is possible that *k*₁ has a value which is no lower than that for its isomer.



Scheme 2

Table 1. Kinetic results for the reactions of **3a–f** with aniline in acetonitrile at 25 °C

[Aniline]/(mol dm ⁻³)	$k_A/(10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1})$					
	4-H	2-CH ₃	3-CH ₃	4-CH ₃	2,4-CH ₃	2,6-CH ₃
0.01	0.47	0.14	0.33	0.47	0.14	
0.02	0.93	0.25	0.63	0.95	0.23	
0.03	1.38	0.36	0.91	1.42	0.33	
0.04	1.71	0.48	1.21	1.90	0.44	0.0047
0.05	2.22	0.58	1.49	2.25	0.53	
0.06		0.70	1.77	2.85	0.64	0.0081
0.07		0.81	2.04	3.23	0.73	0.0093
0.08		0.94	2.33	3.49	0.86	0.010
0.1						0.012
0.15						0.018
0.2						0.022
0.3						0.034
0.4						0.046
0.5						0.056

Table 2. Kinetic results for the reactions of **4b–f** with aniline in acetonitrile at 25 °C

[Aniline]/(mol dm ⁻³)	$k_A/(10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1})$				
	2-NO ₂	3-NO ₂	4-NO ₂	2,4-NO ₂ ^a	2,6-NO ₂
0.01	0.92	1.10	0.93	9.0 (9.0)	150
0.02	1.79	2.12	1.98	10.6 (10.7)	150
0.03	2.55	3.14	2.78	12.1 (12.3)	150
0.04	3.35	4.06	3.62	13.6 (13.9)	150
0.05	4.06	5.00	4.26	15.0 (15.3)	150
0.06	4.57	6.10	5.02	17.2 (16.8)	
0.07	5.60		5.68		
0.08			6.24	19.3 (19.4)	

^a Values in parentheses were calculated using Eqn (5) with the values given in Table 3.

Table 3. Summary of the rate data for the reactions of **3** and **4**, X-phenyl-2,4,6-trinitrophenyl ethers, with aniline in acetonitrile

Reactant	X	$K_1 k_{An_2}$ (dm ⁶ mol ⁻² s ⁻¹)	k_{An}/k_{-1} (dm ³ mol ⁻¹)	k_1 (dm ³ mol ⁻¹ s ⁻¹)	$K_1 k_{DABCO}$ (dm ⁶ mol ⁻² s ⁻¹)	k_{An}/k_{DABCO}	$K_1 k_2$ (dm ³ mol ⁻¹ s ⁻¹)
3f	2,6-(CH ₃) ₂	0.0011 ± 0.0001	<0.2	>0.0055	—	—	—
3e	2,4-(CH ₃) ₂	0.10 ± 0.005	<1	>0.1	—	—	—
3b	2-CH ₃	0.15 ± 0.01	1 ± 0.5	0.13 ± 0.05	—	—	—
3c	3-CH ₃	0.34 ± 0.02	2.6 ± 1	0.13 ± 0.05	—	—	—
3d	4-(CH ₃)	0.48 ± 0.02	1 ± 0.5	0.48 ± 0.20	1.5 ± 0.3	0.32 ± 0.10	—
3a	4-H	0.48 ± 0.02	2 ± 1	0.24 ± 0.10	1.6 ± 0.2	0.30 ± 0.05	—
4b	2-NO ₂	0.95 ± 0.03	3 ± 1	0.32 ± 0.10	—	—	—
4c	3-NO ₂	1.13 ± 0.05	3 ± 1	0.38 ± 0.10	3.2 ± 0.4	0.35 ± 0.10	—
4d	4-NO ₂	1.03 ± 0.03	4 ± 1	0.26 ± 0.08	3.4 ± 0.3	0.30 ± 0.05	—
4e	2,4-(NO ₂) ₂	2.2 ± 0.20	2.7 ± 0.5	0.8 ± 0.3	4 ± 0.5	0.50 ± 0.1	0.08 ± 0.01
4f	2,6-(NO ₂) ₂	—	—	1.5 ± 0.2	—	—	Large

Rate constants measured in the presence of DABCO are given in Table S2 as Supplementary Information available at the epoc website at <http://www.wiley.com/epoc>, and allowed the calculation of values of $K_1 k_{DABCO}$.

The nitro series, **4b–f**

For the mononitro derivatives, **4b–d**, the behaviour was qualitatively similar to that for the methyl derivatives; va-

lues of k_2 were negligibly small and the data in Table 2 conform to Eqn (3) with the values summarized in Table 3. However, the plot of k_A versus aniline concentration for **4e**, the 2,4-dinitro derivative, had a distinct intercept indicating the contribution of the uncatalysed pathway. Hence Eqn. (4) applies, which may be written as Eqn (5):

$$k_A = \frac{k_1(k_2 + k_{An}[An])}{k_{-1} + k_2 + k_{An}[An]} \quad (4)$$

$$k_A = \frac{K_1 k_2 + K_1 k_{An} [An]}{1 + \frac{k_2}{k_{-1}} + \frac{k_{An} [An]}{k_{-1}}} \quad (5)$$

The values in Table 2 correspond to Eqn (5) with the values $K_1 k_{An} = 2.2 \text{ dm}^3 \text{ mol}^{-2} \text{ s}^{-1}$ and $k_{An}/k_{-1} = 2.75 \text{ dm}^3 \text{ mol}^{-1}$, leading to a value for k_1 of $0.8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, and with $K_1 k_2 = 0.08 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and $k_2/k_{-1} = 0.1$. Calculated values for k_{An} are given in Table 2. DABCO catalysis was observed.

For **4f**, the 2,6-dinitro derivative, the values of k_A were independent of aniline concentration, indicating that either the condition $k_2 + k_{An} [An] \gg k_{-1}$ applies so that $k_A = k_1$, and/or that the condition $k_2 \gg k_{An} [An]$ applies so that $k_A = k_1 k_2 / (k_{-1} + k_2)$. Hence the minimum value that can be assigned to k_1 is $1.5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.

Before discussing these results, it is useful to consider the x-ray crystal structures which have been determined for **3a**, **3f** and **4f**.

X-ray crystal structures

Selected bond lengths and angles for **3a**, **3f** and **4f** are given in Table 4 and perspectives of **3f** and **4f** are shown in Fig. 1. In all of the three structures there is evidence of steric crowding around the C(1) position. The shortened O(1)—C(1) bond lengths indicate p- π conjugation with the strongly electron-withdrawing trinitro-substituted ring. There is also evidence of some conjugation with the dinitro-substituted ring of **4f**. The C(1)—O(1)—C(7) bond angle is close to 120° except for **4f**, where it opens to 130° . The steric interaction of the two rings is accommodated partly by rotation, by around 45° , of the *o*-nitro groups in the trinitro-substituted ring. There are also small deviations of O(1) from the ring plane. How-

ever, major steric interactions between the *ortho* substituents in the two rings are avoided by twisting of the planes of the two aromatic rings by an angle which increases from 66° in **3a** to 76° in **4f**.

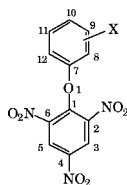
Although it is not, of course, possible to obtain x-ray structures, it is expected that steric crowding around C(1) will be reduced in the zwitterionic intermediates **5**, as the hybridization changes from sp^2 to sp^3 .

Comparisons

In general, the values of $K_1 k_{An}$, in Table 3, increase regularly as the X substituents become more electron-withdrawing. Exceptions are **3f**, the 2,6-dimethyl-substituted derivative, where the value is ~ 100 times smaller than for **3e**, its 2,4-disubstituted isomer, and **4f**, the 2,6-dinitro-substituted compound, where base catalysis is not observed. Similarly, values of k_1 increase slightly, by a factor of ~ 6 , from **3e** to **4e**. Significantly, the minimum possible value for k_1 for **4f** is higher than for **4e**, its 2,4-disubstituted isomer. Also, the value of k_1 , in Table 3, for **3f** is a minimum so that the value may be no lower than for **3e**. These results show that there can be little steric hindrance to attack by aniline at the 1-position of the parent molecules, even in the presence of di-*ortho* substitution. In fact, the crystal structure in Fig. 1(c) indicates that a relatively unhindered trajectory exists for approach of the aniline molecule. Similarly, Nudelman and co-workers^{16,17} have noted the absence of a primary steric effect in their work on the reactions of amines with 4- and 6-substituted-2-nitroanisoles. The small increases in k_1 observed in the present work are consistent with increasing electron withdrawal by the X substituents at the reaction centre and, as argued previously,¹⁵ with an 'early' transition state for nucleophilic attack.

Base catalysis will involve rate-limiting proton transfer from the zwitterions, **5**, to amine.^{14,15} In previous work, it has been shown^{14,15,18,19} that in reactions involving trinitro-activated compounds, this proton-transfer process is thermodynamically favoured. In the present systems, values of k_{An}/k_{DABCO} are 0.4 ± 0.1 , showing that despite the differences in basicity (Coetzee and Padmanabhan²⁰ give pK_a values of DABCO- H^+ 18.29 and aniline- H^+ 10.56), the abilities of aniline and DABCO to catalyse the reaction are similar. Hence steric effects are dominant in determining the values of the rate constant k_{An} ; for the range of compounds **3e** to **4e**, the results in Table 3 provide no evidence for increases in steric hindrance to proton transfer with increasing substitution. Thus, the increases in $K_1 k_{An}$ are reasonably attributed to increases in K_1 as the electron withdrawal at the 1-position increases. Similarly, increases in k_{An}/k_{-1} will reflect decreases in k_{-1} . The low value observed for $K_1 k_{An}$ for **3f** and the absence of base catalysis in **4f** may then be attributed to decreases in k_{An} . Thus 2,6-disubstitution

Table 4. Selected bond lengths and angles



	3a	3f	4f
O(1)—C(1) (Å)	1.350	1.343	1.359
O(1)—C(7) (Å)	1.406	1.423	1.373
C(1)—O(1)—C(7) (°)	120.3	119.4	130.4
2-Nitro (twist) (°)	45	53	45
6-Nitro (twist) (°)	46	58	36
4-Nitro (twist) (°)	14	10	2
Deviation of O(1) from trinitro ring plane (°)	7	6	12
Angle between aromatic rings (°)	66	74	76

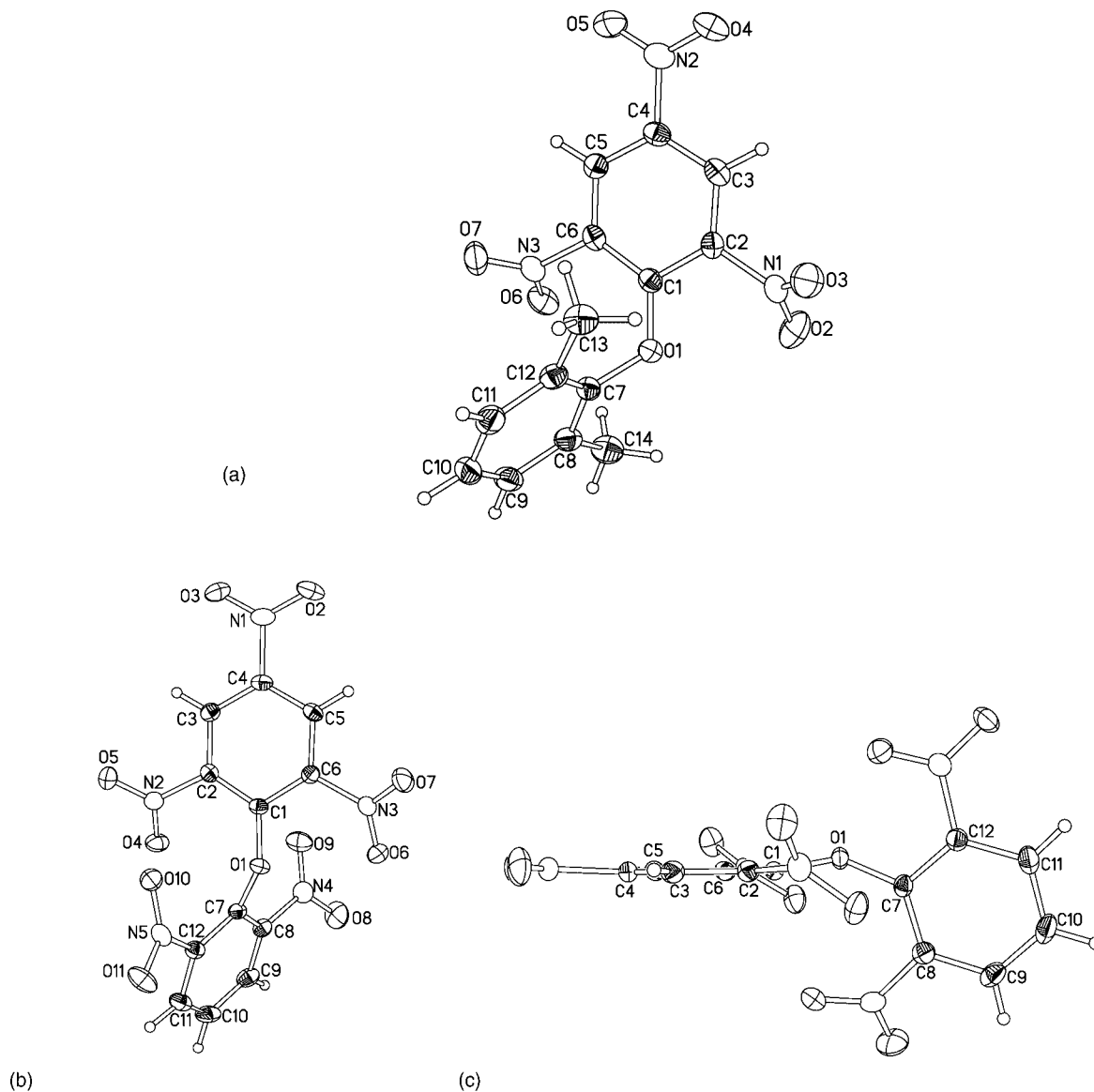


Figure 1. X-ray structures: (a) **3f** and (b) and (c) two perspectives of **4f**

inhibits the approach of aniline to the zwitterions **5** so that intermolecular proton transfer is inhibited.

The importance of the uncatalysed decomposition, the k_2 pathway, is expected to depend markedly on the acidity of the phenolic leaving group.² In water²¹ the pK_a values are **3f** 10.6, **3a** 10.0, **4e** 4.1 and **4f** 3.7, and in acetonitrile these differences are expected to be magnified.²² Our results indicate that it is only with **4e** and **4f** derived from the most acidic phenols, i.e. the least basic phenoxides, that the uncatalysed reaction can compete with the base-catalysed pathway. With **4f**, the 2,6-dinitro derivative, the steric hindrance to intermolecular proton transfer to base is sufficient to make the base-catalysed pathway insignificant relative to the k_2 pathway. Since the latter involves intramolecular proton transfer, steric effects are unlikely to be important. It is worth noting that also

with benzene as solvent the reaction of **4f** with aniline is uncatalysed.²³

CONCLUSION

Our results provide an interesting example of how substituents in the leaving phenoxy group may give rise to a change in the nature of the rate-determining step in the substitution pathway. Steric effects appear to be unimportant in determining the value of k_1 , the rate constant for nucleophilic attack. However, they can, in the 2,6-disubstituted compounds, slow rate constants for intermolecular proton transfer to a catalysing base. Values of k_2 for the uncatalysed process are expected to vary depending on the acidity of the leaving group. The

result is a change from the 2,6-dimethyl compound where substitution is wholly base catalysed to the 2,6-dinitro compound where the uncatalysed reaction is observed.

EXPERIMENTAL

Diphenyl ethers **3** and **4** were prepared by the reaction of picryl chloride with 1 equiv. of base in the presence of an excess of the appropriate phenol in aqueous ethanol. Recrystallization was from ethanol. 2,4,6-Trinitrodiphenylamine, **7**, was prepared by reaction of picryl chloride with excess aniline in ethanol. All substrates had m.p.s in satisfactory agreement with published values^{15,23,24} and ¹H NMR spectra consistent with the expected structures. DABCO and acetonitrile were the purest available commercial samples and aniline was redistilled before use.

¹H NMR spectra were measured with a Varian Mercury 200 MHz or Varian Unity 300 MHz instrument. UV-visible spectra 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 aniline concentration in large excess of substrate concentration, $(0.5-1) \times 10^{-4}$ mol dm⁻³, and were evaluated using standard methods. Values are precise to $\pm 3\%$.

X-ray crystallography. The x-ray diffraction experiments were carried out on SMART three-circle diffractometers with a 6K (for **3f** and **4f**) and 1K (for **3a**) CCD area detector, using graphite monochromated Mo K α radiation. A hemisphere of reciprocal space was covered by a combination of four and five sets of ω scans for the 6K and 1K CCD area detector, respectively, each set at different φ and 2θ angles. Crystals were cooled using a Cryostream (Oxford Cryosystems) open-flow N₂ gas cryostat. Absorption corrections were performed by a semi-empirical method based on Laue equivalents and multiple scans of reflections. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of all data, using SHELXTL²⁵ software. Hydrogen atoms were located in all three structures and refined freely with isotropic displacement parameters. Crystal data and the details of data collections,

structure solutions and refinements are summarised in Table S1, which is available as Supplementary Material at the epoc website on Wiley Interscience.

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