# The Reaction of 2-Phenoxy-3,5-dinitropyridine with Substituted Anilines in the Presence of 1,4-Diazabicyclo[2.2.2]octane in Dimethyl Sulfoxide: Kinetic and Equilibrium Studies

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ABSTRACT: The reactions of 2-phenoxy-3,5-dinitropyridine (1) with a series of substituted anilines (**4a–d**) in dimethyl sulfoxide (DMSO) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) yield the 2-anilino derivatives without the accumulation of intermediates. The kinetics is compatible with a two-step reaction involving initial nucleophilic attack followed by either base-catalyzed or uncatalyzed conversion to the product. The base-catalyzed pathway is likely to involve rate-limiting proton transfer from the zwitterionic intermediate to base. The results are compared with those for reactions of 1,3,5-trinitrobenzene (**2**) and phenyl 2,4,6-trinitrophenyl ether (**3**, **R** = **Ph**) with anilines. © 2008 Wiley Periodicals, Inc. Int J Chem Kinet 41: 198–203, 2009

### INTRODUCTION

Kinetic studies of nucleophilic substitution reactions of aromatic substrates have been the subject of several excellent reviews and books [1–4] and are still an area of active research [5–9]. The presence of electronwithdrawing ring substituents such as the nitro group strongly accelerates substitution, and ring nitrogen atoms have also been found to exert a powerful activating effect [7]. However, ring nitrogen *ortho* to the substitution position has generally been found to be less effective than a corresponding nitro group [8-12].

Substitutions involving amine nucleophiles are of particular interest, since studies have shown that these may be general base catalyzed, indicating

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that the rate-limiting step involves proton transfer. In previous work, the reactions of 1,3,5-trinitrobenzene (2), which contains no good leaving group, with anilines in DMSO in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), have been shown to yield anionic  $\sigma$ -adducts. Kinetic and equilibrium studies are compatible with a two-step processes involving initial nucleophilic attack by amine at an unsubstituted ring position followed by proton transfer from the zwitterionic intermediate to base [13].

In agreement with the classic work of Orvik and Bunnett [14], the results for ethyl 2,4,6-trinitrophenyl ether (**3**) indicated that substitution involves the specific base-general acid catalysis mechanism, SB-GA, in which leaving group expulsion is the overall ratelimiting step. However, the phenoxy group is a considerably better leaving group than the ethoxy group, and the observation of base catalysis in reactions of the phenyl aryl ethers was best explained in terms of rate-limiting proton transfer from a zwitterionic intermediate to base [15,16].

In this paper, kinetic and equilibrium results are reported for the reactions of 2-phenoxy-3,5-dinitropyridine (1) with a series of substituted anilines (4a–d) in DMSO in the presence of DABCO (Scheme 1). This allows the effects of a ring nitrogen in 1 to be compared with those of a nitro group in 3,  $\mathbf{R} = \mathbf{Ph}$ .

The p $K_a$  values for the substituted anilinium ions in DMSO were available from previous work [13] using the proton-transfer equilibrium with 2,4-dinitrophenol.



Scheme 1 The reactions of 1 with a series of substituted anilines (4a–d) in DMSO in the presence of DABCO.

#### **EXPERIMENTAL**

2-Phenoxy-3,5-dinitropyridine (2) was prepared by reaction of 2-chloro-3,5-dinitropyridine with 1 equiv of base in the presence of 1.3 equiv of phenol in aqueous ethanol, mp 158°C (lit. [17], 159°C). Anilines, DABCO, and DMSO were the purest available commercial samples. Amine salts were prepared in a solution by the accurate neutralization of amines with concentrated hydrochloric acid.

<sup>1</sup>HNMR spectrum was recorded in [<sup>2</sup>H<sub>6</sub>]-DMSO using a Bruker Avance-400 MHz instrument. Mass spectrum was recorded on a Waters Micromass LCT spectrometer. UV–visible spectra and kinetic measurements were made with Shimadzu UV-2101 PC or Perkin Elmer Lambda 2 spectrophotometers. All measurements were made at 25°C. First-order rate constants, precise to  $\pm 3\%$ , were evaluated using standard methods.

#### **RESULTS AND DISCUSSION**

#### Spectroscopy for 2-Anilino-3,5-dinitropyridine

The reaction of **1** (0.2 g,  $1.3 \times 10^{-3}$  mol) with aniline (1 mL, 0.01 mol) in the presence of DABCO (0.1 g,  $1 \times 10^{-3}$  mol) dissolved in ethanol gave 2-anilino-3,5-dinitropyridine (7). The <sup>1</sup>HNMR spectrum recorded in [<sup>2</sup>H<sub>6</sub>]-DMSO showed bands due to H<sub>a</sub> and H<sub>b</sub> at  $\delta$  9.23 and 9.05 ppm, respectively, J = 2.6 Hz. The singlet at  $\delta$  10.56 ppm is attributed to H<sub>c</sub>, while bands due to phenyl protons are observed at  $\delta$  7.60, 7.44, and 7.28 ppm with J<sub>de</sub> and J<sub>ef</sub> = 8 Hz.

The mass spectrum (ES<sup>+</sup>) for 7 showed a line at 261 corresponding to  $C_{11}H_9N_4O_4$  (M + H<sup>+</sup>).

## pK<sub>a</sub> for 2-Anilino-3,5-dinitropyridine in DMSO

The p $K_a$  value for the 2-anilino-3,5-dinitropyridine in DMSO was measured using the equilibria with DABCO p $K_a$  [18] = 9.06 and piperidine p $K_a$  = 10.85. The reaction involved is shown in Scheme 2.

$$pK_{a} = pK_{a}(BH^{+}) - \log_{10} K$$
 (1)

Measurements of absorbance were made at 450 nm, which is the absorption maximum for the anionic form of **7** in solutions containing excess concentrations of DABCO or piperidine and the corresponding DABCO or piperidine hydrochloride ions. The values obtained for *K* were  $8.8 \times 10^{-3}$  for reaction with DABCO and





0.548 for reaction with piperidine. The p $K_a$  value was calculated using Eq. (1) to be  $11.12 \pm 0.05$ . Data are shown in Tables I and II.

From previous work, the  $pK_a$  value for 2,4,6-trinitrodiphenylamine<sup>[13]</sup> was 8.20. The lower acidity of **7** compared with 2,4,6-trinitrodiphenylamine may be attributed to the less effective mesomeric role that the ring nitrogen plays in stabilization of the anion compared with that of the nitro group.

#### **Kinetic and Equilibrium Studies**

Kinetic measurements of the reactions with substituted anilines (**4a–d**) were generally made in the presence of DABCO and DABCO hydrochloride (0.01 mol dm<sup>-3</sup>). The absorption maxima of the adducts formed is ca. 380 nm. The concentration of **1** was kept at  $5 \times 10^{-5}$  mol dm<sup>-3</sup> and was very much lower than that of the other components, one of the substituted anilines (**4a–d**) and DABCO. Under these conditions, accurate first-order kinetics was observed, and the variation in value of the rate constant with aniline and DABCO concentrations was examined. Measurement was also made in the absence of DABCO, and plots of the

**Table I**Absorbance Data for 2-Anilino-3,5-dinitropyridine ( $5 \times 10^{-5} \text{ mol dm}^{-3}$ ) in DMSOContaining Various Concentrations of DABCO at  $25^{\circ}$ C

[DABCO] (mol dm <sup>-3</sup> )	[DABCO HCl] (mol dm <sup>-3</sup> )	Absorbance (Abs)	$10^{-3}$ $K^{a,b}$
0	0.01	0.123	_
0.1	0.01	0.212	9.5
0.4	0.01	0.387	8.7
0.6	0.01	0.463	8.2
0.4	0	1.06	_
0.6	0	1.11	_

<sup>*a*</sup> Measurements of absorbance were made at 450 nm.

<sup>b</sup> Calculated as [Abs - 0.123] [DABCOH<sup>+</sup>]/[1.15 - Abs] [DABCO].

[Piperidine] (mol dm <sup>-3</sup> )	[Piperidine HCl] (mol dm <sup>-3</sup> )	Absorbance (Abs)	$K^{a,b}$
0	0.01	0.137	_
0.005	0.01	0.327	0.535
0.008	0.01	0.402	0.522
0.010	0.01	0.456	0.549
0.015	0.01	0.523	0.501
0.020	0.01	0.614	0.564
0.100	0	1.037	_

**Table II** Absorbance Data for 2-Anilino-3,5-dinitropyridine ( $5 \times 10^{-5}$  mol dm<sup>-3</sup>) in DMSO Containing Various Concentrations of Piperidine at 25°C

<sup>*a*</sup> Measurements of absorbance were made at 450 nm.

 $^b$  Calculated as [Abs - 0.137] [PiperideneH<sup>+</sup>]/[1.037 - Abs] [Piperidene].

second-order rate constant,  $k_{obs}$ /[aniline], versus aniline concentration were linear with positive intercepts.

These results are interpreted in terms of the process shown in Scheme 1. It is known [15,19] that phenoxide is a considerably better leaving group than ethoxide, by a factor of ca.  $10^6$ . The failure to observe **6**, the intermediate on the substitution pathway, may by attributed to its rapid decomposition by loss of phenoxide. The assumption that **5** may be treated as a steady-state intermediate leads to the rate expression of Eq. (2), where  $k_{An}$  and  $k_{DABCO}$  represent  $k_B$  for the respective bases.

$$K_{\text{obs}} = \frac{k_1[\text{An}](k_2 + k_{\text{An}}[\text{An}] + k_{\text{DABCO}}[\text{DABCO}])}{k_{-1} + k_2 + k_{\text{An}}[\text{An}] + k_{\text{DABCO}}[\text{DABCO}]}$$
(2)

The results, which provide evidence for base catalysis, indicate that the condition  $k_{-1} \gg k_2 + k_{An}$  [An]  $+ k_{DABCO}$ [DABCO] applies so that Eq. (2) reduces to Eq. (3).

$$k_{\text{obs}} = K_1[\text{An}] (k_2 + k_{\text{An}}[\text{An}] + k_{\text{DABCO}}[\text{DABCO}])$$
(3)

Kinetic measurements at 380 nm showed a single first-order process. Values of the rate constant,  $k_{obs}/[4a]$  for reaction with 4-methoxyaniline (4a), are given in Table IIIa.

Data are interpreted in a manner similar to that given for **3**, **R** = **Ph** so that Scheme 1 is applicable and Eq. (3) will apply. Values calculated with  $K_1k_{\text{DABCO}} = 0.12 \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$ ,  $K_1k_{\text{An}} = 0.035 \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$ , and  $K_1k_2 = 6 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  give good agreement with values of  $k_{\text{obs}}$ . Corresponding data for reaction with aniline (**4c**) are in Table IIIb.

It is known that reaction at unsubstituted ring positions to give anionic adducts may precede the attack at the 2-positon [15,19]. In the present work, measurements were made in the presence of DABCO

Гable IIIa	Kinetic Results for the Reaction of 1 with
4-Methoxyaı	iline ( <b>4a</b> ) in DMSO at 25°C

[4a] $mol^{-1} dm^{-3}$	$[DABCO]^a$ mol <sup>-1</sup> dm <sup>-3</sup>	$k_{\rm obs}  [4a] \ {\rm mol}^{-1}  {\rm dm}^3  {\rm s}^{-1}$	$k_{\text{calc}}^{b}$ [4a]
0.05	_	0.0020	0.0023
0.075	_	0.0034	0.0032
0.10	_	0.0044	0.0041
0.20	_	0.0078	0.0076
0.30	_	0.0110	0.0110
0.06	0.10	0.0147	0.0147
0.10	0.10	0.017	0.0160
0.15	0.10	0.020	0.0180
0.10	0.03	0.007	0.0080
0.10	0.06	0.013	0.0110
0.10	0.15	0.022	0.0220

 $^a$  Solutions containing DABCO also contain DABCO hydrochloride, 0.01 mol dm $^{-3}.$  Measurements were made at 380 nm.

<sup>b</sup> Calculated from Eq. (3) with  $K_1 k_{DABCO} 0.12 \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$ ,  $K_1 k_{An} 0.035 \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$ , and  $K_1 k_2 6 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ .

hydrochloride, which inhibits their formation so that such adducts were not formed. Previous work [10,20] at lower base concentrations and in different solvents did not find evidence for base catalysis. However, the present work shows that in DMSO such catalysis occurs and values calculated for  $K_1k_{An}$  and  $K_1k_{DABCO}$ for reactions of **1** are found. Base catalysis indicates that proton transfer from zwitterion to base is rate limiting.

The presence of a phenoxy group is not expected to drastically affect the value of  $K_1$  for formation of zwitterions [21]. The  $k_2$  step is likely to involve intramolecular proton transfer from nitrogen to oxygen coupled with carbon–oxygen cleavage. Leaving group expulsion is part of the rate-limiting step here.

Table IIIb Kinetic Results for the Reaction of 1 with Aniline (4c) in DMSO at 25°C

$\frac{[4c]}{mol^{-1} dm^{-3}}$	$[DABCO]^a$ mol <sup>-1</sup> dm <sup>-3</sup>	$k_{\rm obs}$ [4c] mol <sup>-1</sup> dm <sup>3</sup> s <sup>-1</sup>	$k_{\text{calc}}^{b}$ [4c]
0.10	_	$1.5 \times 10^{-4}$	$1.5 \times 10^{-4}$
0.20	_	$1.9 \times 10^{-4}$	$1.9 \times 10^{-4}$
0.30	_	$2.2 \times 10^{-4}$	$2.3 \times 10^{-4}$
0.40	_	$2.6 \times 10^{-4}$	$2.7 \times 10^{-4}$
0.10	0.05	$1.5 \times 10^{-3}$	$1.5 \times 10^{-3}$
0.10	0.10	$2.8 \times 10^{-3}$	$3.0 \times 10^{-3}$
0.10	0.15	$4.2 \times 10^{-3}$	$4.3 \times 10^{-3}$
0.10	0.20	$6.0 \times 10^{-3}$	$5.8 \times 10^{-3}$

<sup>*a*</sup> Solutions containing DABCO also contain DABCO hydrochloride, 0.01 mol dm<sup>-3</sup>. Measurements were made at 380 nm.

<sup>b</sup> Calculated from Eq. (3) with  $K_1 k_{\text{DABCO}} 0.028 \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$ ,  $K_1 k_{\text{An}} 4 \times 10^{-4} \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$ , and  $K_1 k_2 1.1 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ .

Values obtained for  $K_1k_{DABCO}$ ,  $K_1k_2$ , and  $K_1k_{An}$ are summarized in Table IV together with  $pK_a$  values, measured in DMSO, for the conjugate acids of the anilines. The highest value for 4-OMe indicates that the higher basicity of 4-OMe is reflected in higher values of  $K_1k_2$ ,  $K_1k_{An}$ , and  $K_1k_{DABCO}$ . Values of  $K_1k_{DABCO}$ ,  $K_1k_2$ , and  $K_1k_{An}$  decrease strongly as the substituent R is made more electron withdrawing.

The proton-transfer process,  $k_{DABCO}$ , will be a strongly favored process thermodynamically. This is because proton transfer is to a strong base (DABCO). Values would, in absence of steric effects, be close to the diffusion limit. The reaction center in **5** is quite hindered, hence values will be lower than the diffusion limit. However, since the steric effects will be the same for **4a–4d**, values of  $k_{DABCO}$  will be the same for each aniline. Hence, changes in  $K_1k_{DABCO}$  in **4a–4d** reflect changes in values of  $K_1$ , the equilibrium constant for formation of zwitterions, rather than changes in  $k_{DABCO}$ .

A linear plot, not shown, of values of log  $K_1k_{\text{DABCO}}$  versus Hammett  $\sigma$  values gives a slope,  $\rho$ , of -2.0. Since values of  $k_{\text{DABCO}}$  are expected to be independent of the nature of the remote substituent, this  $\rho$  value reflects the substituent effect on values of  $K_1$ . The negative value obtained is consistent with the increase in positive charge on nitrogen associated with the formation of **5**.

Values of  $K_1k_2$  show similar changes with the nature of the substituent to values of  $K_1k_{Dabco}$ . Both fall by a factor of 10 going from **4a** to **4d**. The implication is that values of  $k_2$  vary very little with the nature of the substituent R.

Values of  $K_1k_{An}$  decrease much more dramatically going from **4a** to **4d** (factor of 350). This indicates that the  $k_{An}$  process is far more favorable with 4-methoxyaniline than with 4-chloroaniline. A possible explanation is that the proton-transfer equilibrium is not strongly thermodynamically favored (Scheme 3). Hence as the basicity of the aniline decreases, the rate constant for the process is reduced.



It should be noted that since proton transfer is rate determining in all these reactions, it is not possible to obtain values for the rate constants  $k_{1-1}$ .

The results for reaction of 1 are compared in Table IV with results for the comparable reactions of 3,  $\mathbf{R} = \mathbf{Ph}$  with aniline (4c). They show that both values of  $K_1 k_{\text{DABCO}}$  and  $K_1 k_{\text{An}}$  are considerably higher for **3** than for 1. Both electronic and steric factors will be important in determining the relative reactivities. Proton transfer from the zwitterions to DABCO will be strongly favored thermodynamically so that steric effects will be dominant in determining values of  $k_{\text{DABCO}}$ . Replacing the ortho-nitro group in 3 with ring nitrogen in 1 will make the reaction center more accessible to the approaching base so that  $k_{\text{DABCO}}$  should be higher for reaction with 1 than with 3. The fact that the product  $K_1 k_{\text{DABCO}}$  has a higher value for the reaction of **3** (ratio **3**: **1** is 57) indicates that the value of  $K_1$  must be considerably higher for 3 than for 1. Two factors responsible for this will be the greater electron-withdrawing influence of the ortho-NO<sub>2</sub> group in 3 than the ring nitrogen in 1, and also the greater relief of steric strain present in the parent molecule 3 as the 1-substituent is rotated from the ring plane on formation of the zwitterion [3,4].

The ratio of the values of  $K_1k_{An}$  for **3**:1 is 680 and is higher than the corresponding ratio of values of  $K_1k_{DABCO}$ . This is likely to result from a reduction in the value of  $k_{An}$  in the reaction of **1**, since the proton-transfer process involved (see Scheme 3) is less thermodynamically favorable than in the corresponding reaction involving **3**.

The results in Table IV show that the value of  $K_1k_{\text{DABCO}}$  for reaction of **2** is higher than for the reaction of **3** or **1**. The predominant factor here, as discussed previously [16], will be the higher value of  $k_{\text{DABCO}}$ 

**Table IV** Summary of Results for the Reactions of Anilines (4a–d) with 2-Phenoxy-3,5-dinitropyridine (1) and Related Compounds in DMSO at 25°C

Parent	Aniline	$K_1 k_{\text{DABCO}} (\text{dm}^6 \text{mol}^{-2} \text{s}^{-1})$	$K_1 k_{\rm An}  ({\rm dm}^6  {\rm mol}^{-2}  {\rm s}^{-1})$	$K_1 k_2 (\mathrm{dm}^3 \mathrm{mol}^{-1} \mathrm{s}^{-1})$	pK <sub>a</sub>
1	<b>4a</b> 4-OMe	0.12	0.035	$6 \times 10^{-4}$	5.08
1	<b>4b</b> 4-Me	0.052	$7.1 \times 10^{-3}$	$2.5 \times 10^{-4}$	4.48
1	<b>4c</b> H	0.028	$4 \times 10^{-4}$	$1.1 \times 10^{-4}$	3.82
1	<b>4d</b> 4-Cl	0.012	$1 \times 10^{-4}$	$6 \times 10^{-5}$	2.86
3, $\mathbf{R} = \mathbf{P}\mathbf{h}^a$	<b>4c</b> H	1.6	0.27	0.050	3.82
$2^{b}$	<b>4c</b> H	28	0.14	-	3.82

<sup>a</sup> Results from [16].

<sup>b</sup> Results from [13].

associated with the lower steric hindrance to proton transfer when reaction occurs at an unsubstituted ring position.

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