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Steric hindrance as a key factor on proton transfer in the σ-adduct forming reactions of *o*-substituted anilines with 1,3,5-trinitrobenzene in dimethylsulfoxide

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Abstract Kinetic and equilibrium studies are reported of the reactions of 1,3,5-trinitrobenzene (*TNB*) with a series of *o*-substituted anilines in dimethyl sulfoxide (*DMSO*) in the presence of 1,4-diazabicyclo[2.2.2.]octane (*DABCO*). The pK_a values in *DMSO* for the aniline derivatives were measured using the proton-transfer equilibrium with 2,4-dinitrophenol. Kinetic studies are compatible with a two-step process involving initial nucleophilic attack on *TNB* by amine to give a zwitterionic intermediate which may transfer an acidic proton to *DABCO* to yield the anionic product. The results indicate steric hindrance to proton transfer in reactions involving 2,6-disubstituted anilines.

Keywords Kinetic; *o*-Substituted anilines; σ-Adducts; 1,3,5-Trinitrobenzene; Steric hindrance.

Introduction

The reaction of 1,3,5-trinitrobenzene (**1**) with aliphatic amines in dimethyl sulfoxide (*DMSO*) results in the spontaneous formation of anionic σ-adducts [1, 2]. Kinetic studies are consistent with the two step process and show that the proton-transfer step may be rate-limiting [3–5]. The corresponding reaction with aniline does not occur since the initial formation of the zwitterion is thermodynamically unfavorable; the pK_a value for protonated aniline is 3.82 in *DMSO* [6]. However, *Buncel et al.* importantly showed that the presence of a strong base, such as the methoxide ion or *DABCO*, made the second step (proton transfer) sufficiently thermodynamically favorable as to allow observation of the anilide adduct [7–10]. Kinetic studies in the presence of *DABCO* showed that proton transfer was rate limiting [11–16]. *Buncel* and *Eggimann* [11] have previously examined the kinetics of the reaction of **1** with unsubstituted aniline in the presence of *DABCO*, but in the absence of added *DABCO*H^+. Under these conditions the reaction in Scheme 1 gives first order kinetics in the forward direction and second order kinetics in the reverse direction, making the evaluation of rate constants more difficult. More recently kinetic and equilibrium results have been reported for the reactions of 1,3,5-trinitrobenzene (*TNB*) with some substituted anilines in the presence of *DABCO* in *DMSO* [16].

In this paper kinetic and equilibrium results are reported for the reactions of **1** with a series of aniline derivatives (**2a**–**2f**) carrying substituents close to the reaction centre in the presence of *DABCO* in *DMSO*. Measurements were made in the presence of *DABCO* and its hydrochloride salt allowing a more complete evaluation of the competing processes compared with that achieved in earlier studies. The

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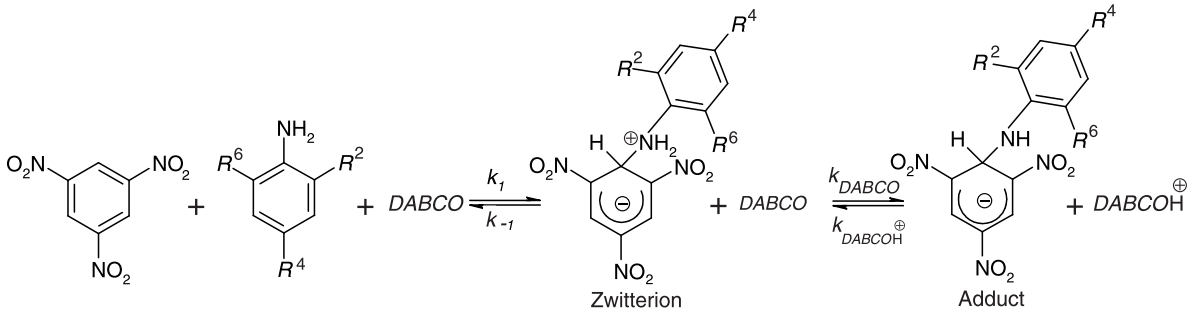


1 2 3 4

a, R^2,R^6= *Et*, R^4 = H
b, R^2,R^6= *Me*, R^4 = H
c, R^2,R^4= *Me*, R^6 = H
d, R^2 = F, R^4,R^6= H
e, R^2 = Cl, R^4,R^6=H
f, R^2 = CN, R^4,R^6 = H

Scheme 1

pK_a values for the substituted anilinium ions in *DMSO* were measured according to reported methods [16]. The results provide evidence that although there is little steric hindrance to nucleophilic attack to give the zwitterionic intermediates **3**, there is a pronounced reduction in rate constants for the proton-transfer step in 2,6-disubstituted anilines.

Results and discussion

The pK_a values for substituted anilinium ions in DMSO

The pK_a values for a number of amines in *DMSO* have been reported previously [6]. The value for aniline is 3.82, and for *DABCO* 9.06. However, the pK_a values for substituted anilines used in the present work in *DMSO* have not been reported previously.

In the present work a spectrophotometric method using 2,4-dinitrophenol (*DNP*) as an indicator was applied, as previously [6] reported, to measure values of the equilibrium constant, *K*, for the process shown in Eq. (1). The pK_a value of *DNP* is known [17] to be 5.12 ± 0.04 in *DMSO*, so values of $pK_a(AnH^+)$ for the substituted anilines were calculated using Eq. (2). Measurements of absorbance were made at 430 nm, which is the absorption maximum of the 2,4-dinitrophenolate anion in solutions containing excess concentrations of the aniline **2** and corresponding anilinium ions. In some cases it was necessary to make small corrections for the absorbance due to the substituted aniline. Wherever possible measurements were made with solutions containing a concentration of $0.01\,\mathrm{mol\,dm^{-3}}$ of the aniline hydrochloride. For less basic amines where concentrations of hydrochloride lower than $0.01\,\mathrm{mol\,dm^{-3}}$ were required, the ionic strength was maintained at $0.01\,\mathrm{mol\,dm^{-3}}$ with tetraethylammonium chloride. Representative data are shown in Table 1, and pK_a values are listed in Table 2.

Table 1 Absorbance data for 2,4-dinitrophenol, $1 \times 10^{-4}\,\mathrm{mol\,dm^{-3}}$, in *DMSO* containing **2b** and its hydrochloride at 25°C

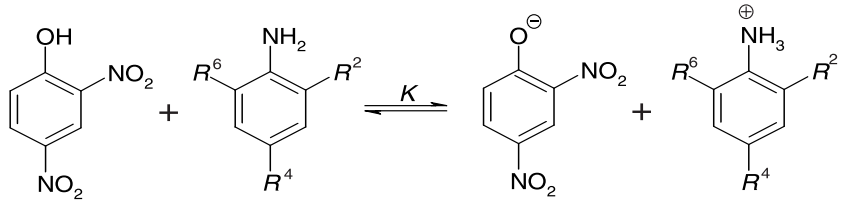
[**2b**]/ $\mathrm{mol\,dm^{-3}}$	[**2b** HCl]/ $\mathrm{mol\,dm^{-3}}$	*Abs* (430 nm)	*Abs**[a]	*K*[b]
0.00	0.01	0.006	0.006	–
0.05	0.01	0.082	0.081	0.0114
0.20	0.01	0.263	0.259	0.0111
0.30	0.01	0.354	0.347	0.0109
0.40	0.01	0.452	0.441	0.0113
0.30	0.00	1.41	1.40	–
0.60	0.00	1.43	1.40	–

[a] *Abs** values have been corrected for absorption by **2b**
[b] Calculated as $K = \frac{(Abs^* - 0.006)[\mathbf{2b}\cdot HCl]}{[1.40 - Abs^*][\mathbf{2b}]}$

Table 2 pK_a Values for substituted anilinium ions in *DMSO*

Anilines	*K*[a]	pK_a (*DMSO*)	pK_a (water)[b]
2a	0.010 ± 0.002	3.12 ± 0.07	–
2b	0.0113 ± 0.0002	3.17 ± 0.01	3.90
2c	0.172 ± 0.006	4.36 ± 0.01	4.90
2d	$(0.855 \pm 0.105) \times 10^{-3}$	2.05 ± 0.05	3.20
2e	$(1.93 \pm 0.02) \times 10^{-4}$	1.40 ± 0.05	2.60
2f	$(0.194 \pm 0.057) \times 10^{-4}$	0.41 ± 0.11	0.95

[a] Defined in Eq. (1)
[b] Ref. [18]



(1)

$$PK_a(AnH^+) = \log K + pK_a(DNP) \qquad (2)$$

The high acidity of the 2-cyanoanilinium ion in *DMSO* can be attributed to the electron-withdrawing effect of the CN group. It is interesting that the presence of two *o*-substituents in the anilinium ions formed from **2a** and **2b** greatly increases their acidity compared to **2c**. It is known [6] that *DMSO* is a good hydrogen-bond acceptor, particularly from charged species, so that these increases are likely to result from steric inhibition of solvation by *DMSO* of the anilinium ions.

Kinetic and equilibrium studies

Spectrophotometric measurements were made at the absorption maximum of the adducts formed, 440 nm, using the stopped-flow technique. The concentration of **1** was kept at 4×10^{-5} mol dm^{-3} and was very much lower than that of the other components, one of the substituted anilines **2a–2f** and *DABCO*. All measurements were made in the presence of *DABCO*H$^+$, 0.01 mol dm^{-3}. This kept the ionic strength of the solutions constant and inhibited any possible reaction between **1** and *DABCO*. Under these conditions, accurate first-order kinetics were observed and the variation in value of the rate constant with aniline and *DABCO* concentrations was examined. Specimen data are shown in Table 3.

Table 3 Kinetic results for the reaction of **1** with **2b** in *DMSO*[a] at 25°C

[**2b**]/mol dm^{-3}	[*DABCO*]/mol dm^{-3}	k_{obs}/s^{-1}	k^b_{calc}/s^{-1}
0.10	0.10	0.034	0.038
0.10	0.20	0.044	0.046
0.10	0.30	0.052	0.054
0.05	0.10	0.037	0.034
0.15	0.10	0.046	0.042
0.20	0.10	0.048	0.046

[a] All solutions contain *DABCO*H$^+$, 0.01 mol dm^{-3}. Measurements were made at 440 nm using the stopped-flow method
[b] Calculated from Eq. (4) with $K_1 k_{DABCO} = 0.8$ dm^6 mol^{-2} s^{-1} and $k_{DABCOH^+} = 3.0$ dm^3 mol^{-1} s^{-1}

The treatment of the zwitterions **3** in Scheme 1 as steady state intermediates leads to Eq. (3), where [*An*] represents the concentration of the subsitituted aniline and [*B*] represents the concentration of the base.

$$k_{obs} = \frac{k_1[An]k_B[B] + k_{-1}k_{BH^+}[BH^+]}{k_{-1} + k_B[B]} \qquad (3)$$

Results are compatible only with the condition $k_{-1} \gg k_B[B]$, corresponding to rate limiting proton transfer. Eq. (3) then simplifies to Eq. (4), where $K_1 = k_1/k_{-1}$.

$$K_{obs} = K_1 k_B[An][B] + k_{BH}{}^+[BH^+] \qquad (4)$$

Buncel and *Eggimann* [11] have previously examined the kinetics of the reaction of **1** with unsubstituted aniline in the presence of *DABCO*, but in the absence of added *DABCO*H$^+$. Under these conditions the reaction in Scheme 1 gives first order kinetics in the forward direction and second order kinetics in the reverse direction, making the evaluation of rate constants more difficult. They showed, importantly, that the proton-transfer step was rate limiting. It was also shown [13] that stabilisation of *DABCO*H$^+$ by association with chloride ions may result in increases in the overall equilibrium constant for adduct formation. Hence in the present work all rate measurements were made with a low and constant concentration of chloride ions.

Buncel and *Eggimann* [11] assumed that only *DABCO* would be effective as a base in the proton-transfer stage of the reaction. However, it has been shown [15] in a related system that even though aniline is a much weaker base it might also contribute to the proton transfer equilibrium. Thus, it is known that the trinitrocyclohexadienate group in **3**, even though negatively charged, is electron-withdrawing [3, 4, 9, 19]. Hence **3** will be more acidic than the corresponding anilinium ion, so the proton-transfer step **3** $\rightleftharpoons$ **4** will be thermodynamically favored even when the reaction involves aniline as *B* and the corresponding anilinium ion as *B*H$^+$.

Table 4 Summary of results for the reactions of **1** with **2a**–**2f** and *DABCO* in *DMSO* at 25°C

Aniline	K_1k_{DABCO}/ $dm^6\,mol^{-2}\,s^{-1}$	$k_{DABCOH}{}^+$/ $dm^3\,mol^{-1}\,s^{-1}$	K_1K_{DABCO}[a]/ $dm^3\,mol^{-1}$
2a 2,6-*Et*	0.3	2.20	0.14
2b 2,6-*Me*	0.8	3.00	0.26
2c 2,4-*Me*	35	258	0.14
2d 2-F	1.8	8.00	0.22
2e 2-Cl	0.6	2.61	0.23
2f 2-CN	0.4	2.70	0.15

[a] Calculated as $K_1k_{DABCO}/k_{DABCOH}{}^+$

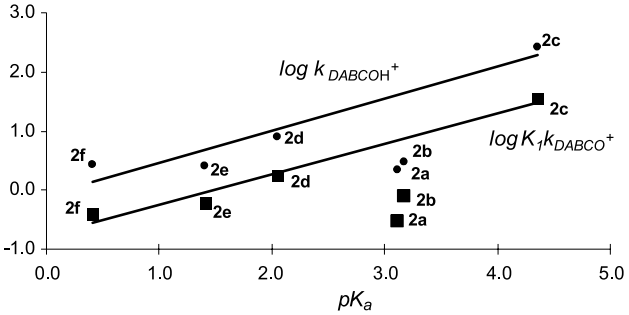


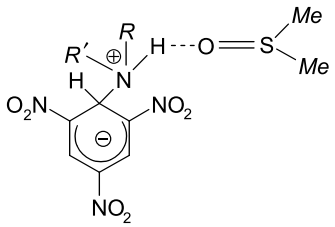
Fig. 1 Plots of log $k_{DABCOH}{}^+$ and $\log K_1k_{DABCO}$ for the reaction of **1** with anilines *versus* the pK_a values of the corresponding anilinium ions. The slopes are 0.54 and 0.51

Variations in the values of k_{obs} with the concentrations of both of aniline and *DABCO* were used to calculate the values of the parameters K_1k_{DABCO}, $k_{DABCOH}{}^+$. The data are summarized in Table 4. K_1K_{DABCO} ($= K_1k_{DABCO}/k_{DABCOH}{}^+$) which show little variation with the nature of the substituent since changes in K_1k_{DABCO} are compensated by similar changes in $k_{DABCOH}{}^+$.

The present work is concerned with anilines **2a**–**2f** carrying substituents close to the reaction centre. Figure 1 shows logarithmic plots of the values of log $k_{DABCOH}{}^+$ and $\log K_1k_{DABCO}$ *versus* the *pKa* values of the corresponding anilinium ions. This shows that for anilines **2a** and **2b** which have two groups at *o*-positions values are considerably below the lines defined by the other substituents. These deviations are likely to result from steric effects. These might involve either steric hindrance to nucleophilic attack, which would affect values of K_1, or steric hindrance to proton transfer, which would affect values of $k_{DABCOH}{}^+$ and also k_{DABCO}. The observation that both values of K_1k_{DABCO} and values of $k_{DABCOH}{}^+$ are lowered in **2a** and **2b** indicates that the major steric effect is to the proton transfer step from the zwitterionic intermediate **3** to *DABCO*.

Rate constants for proton transfer

In previous work *Buncel* and *Eggimann* [11] proposed a value for k_{DABCO} of $1 \times 10^9\,dm^3\,mol^{-1}\,s^{-1}$, which is close to the diffusion limit. However, it is now known [4, 20] that in *DMSO* values for such proton transfers may be slowed down by hydrogen-bonding to the solvent as shown for **5**.



It is necessary to break the hydrogen bond before the proton transfer. Steric congestion at the reaction centre may also reduce proton transfer rates [3, 4, 21, 22]. Thus, previous studies have indicated steric hindrance to proton transfer when reaction involves a bulky secondary amine, such as piperidine, acting as both nucleophile and proton-acceptor base [3, 4, 23]. Proton transfer rates may also be reduced by the pressure of a ring-substituent bulkier than hydrogen at the reaction center [21, 22].

Here, for **2c**–**2f** where steric effects to proton transfer seem to be small it is reasonable, as previously, [16] to assume a value for k_{DABCO} of $1 \times 10^8\,dm^3\,mol^{-1}$, which is reduced below the diffusion limit only by hydrogen-bonding to the solvent. However, for **2a** and **2b** where steric effects are in evidence the value of k_{DABCO} will be further reduced. A reduction of *ca.* twenty five was estimated from the vertical difference between the points for **2a** and **2b** and the straight lines in Fig 1. This would lead to a value of k_{DABCO} for **2a** and **2b** of $4 \times 10^6\,dm^3\,mol^{-1}$. On this basis it is possible to calculate values for K_{DABCO} using Eq. (5).

$$K_{DABCO} = \frac{k_{DABCO}}{k_{DABCOH}{}^+} \tag{5}$$

The results in Table 5 show that values of K_{DABCO} increase in value as the ring-substituents *R* are made more electron-withdrawing. These increases reflect increasing acidity of the zwitterionic intermediates **3**. Interestingly, values of K_{DABCO} for **2a** and **2b** are

Table 5 Derived values for the reaction of **1** in *DMSO*

Aniline	K_a^a (AnH^+)/ mol dm^{-3}	K_{DABCO}	K_1/ dm^3 mol^{-1}
2a 2,6-*Et*	7.58×10^{-4}	1.8×10^6	8.0×10^{-8}
2b 2,6-*Me*	6.76×10^{-4}	1.3×10^6	2.0×10^{-7}
2c 2,4-*Me*	4.36×10^{-5}	3.87×10^5	3.5×10^{-7}
2d 2-F	8.91×10^{-3}	1.25×10^7	1.8×10^{-8}
2e 2-Cl	0.04	3.83×10^7	6.0×10^{-9}
2f 2-CN	0.39	3.70×10^7	4.0×10^{-9}

[a] Values from Table 2

around a factor of ten larger than that for **2c** and this may indicate the higher acidities of **3a** and **3b** than of **3c**. Steric inhibition of solvation caused by the two *o*-subsitituents is the likely cause.

The results in Table 5 show that increasing electron withdrawal in the ring-subsitituents, *R*, in the aniline nucleophiles results in decreased values of K_1. This is reasonably attributed to an electronic effect. The steric effects on K_1 as previously mentioned, appear to be relatively small. However, the significantly lower value for 2,6-diethylaniline (**2a**) than for 2,6-dimethylaniline (**2b**) may be evidence for some unfavorable steric interactions in the zwitterion **3a**.

In the present work involving *o*-substituted anilines there was no evidence that the anilines can compete with *DABCO* in the proton-transfer process. Even though the equilibrium $\mathbf{3} \rightleftharpoons \mathbf{4}$ should be in favor of **4** with anilines as the proton-accepting bases, it is likely that the increased steric-hindrance when 2-substituted anilines act both as nucleophile and base kinetically disfavors this process.

Experimental

1,3,5-Trinitrobenzene and 2,4-dinitrophenol, anilines, *DABCO*, and *DMSO* were the purest available commercial samples from Aldrich. Amine salts were prepared in solution by the accurate neutralisation of amines with concentrated hydrochloric acid. UV-Vis spectra and kinetic measurements were made with an Applied Photophysics SX-17MV stopped-flow instrument, or with Shimadzu UV-2101 PC or Sp6-550 UV/vis Pye unicam spectrophotometers. All measurements were made at 25°C. First-order rate constants, precise to ±3%, were evaluated using standard methods.

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