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Medium Effect on the Reaction of *N*-Butyl-2,4,6-trinitroaniline with NaOH[‡]

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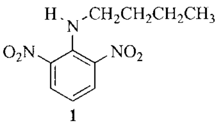
The kinetics of the reaction of *N*-butyl-2,4,6-trinitroaniline (**3**) with NaOH have been studied in 10 and 60 % 1,4-dioxane/H_2O at 25 °C. In both cases, several processes were observed. In 10 % 1,4-dioxane/H_2O the only product formed was 2,4,6-trinitrophenol (**4**), whereas in 60 % 1,4-dioxane/H_2O a mixture of **4** and 5,7-dinitro-2-propyl-1*H*-benzimidazole 3-oxide (**5**) was observed in ratios that depend on the HO^- concentration. A mechanism involving the formation of σ complexes through the addition of one or two HO^- anions to unsubstituted ring positions is proposed for 2,4,6-trinitrophenol formation. The presence of these complexes was confirmed by NMR studies in 60 % [D_8]1,4-dioxane/D_2O. The mechanism suggested for the formation of the *N*-oxide includes the cyclization of an *N*-alkylidene-2-nitrosoaniline-type intermediate as the rate-determining step. The decrease in solvent polarity produces a decrease in the observed rate constant for the formation of **4** of about one order of magnitude making the cyclization reaction a competitive pathway. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2007)

Introduction

In previous work we have demonstrated that in aqueous solutions cyclic amines like pyrrolidine, piperidine and morpholine can act as leaving groups in aromatic nucleophilic substitution reactions.[1,2] Imidazole also acts as a leaving group when 2,4,6-trinitrobenzene derivatives react with hydroxide ions[3] or butylamine[4] and when 2,4-dinitrobenzene derivatives react with piperidine or butylamine.[5]

N-Alkyl derivatives of 2-nitroaniline behave in a different way in the presence of base. For instance, *N*-butyl-2,6-dinitroaniline (**1**) reacts with NaOH in 10% 1,4-dioxane/H_2O at 25 °C to give the substitution product, 2,6-dinitrophenol and a cyclization product, 7-nitro-2-propyl-1*H*-benzimidazole 3-oxide (**2**) in ratios that depend on the base concentration.[6] On the other hand, in 60% 1,4-dioxane/H_2O either at 25 °C[6] or at reflux[7] **1** gives only the *N*-oxide **2**.



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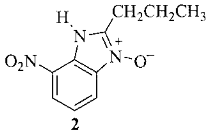
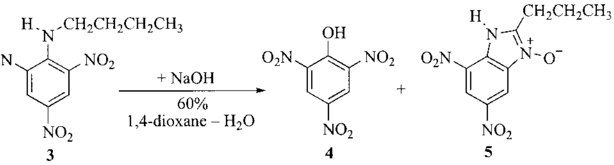


2

In 60% 1,4-dioxane/H_2O at reflux, substitution of the amino group and *N*-oxide formation were also observed in the reactions of *N*-butyl- and *N*-propyl-2,6-dinitro-4-(trifluoromethyl)aniline, whereas the *N*-oxide was the only product observed in the reactions of *N*-butyl-2,4-dinitro-6-(trifluoromethyl)aniline and *N*-propyl-2,6-dinitroaniline.[8] Under the same reaction conditions, *N*-butyl-2,4,6-trinitroaniline (**3**) gives only 2,4,6-trinitrophenol (**4**) with 0.2 M NaOH, whereas 46% of 5,7-dinitro-2-propyl-1*H*-benzimidazole 3-oxide (**5**) along with **4** is obtained with 0.01 M NaOH [Equation (1)].[7]



(1)

In order to get a better understanding of the mechanism of these reactions as well as the factors responsible for the formation of the different products, we undertook a kinetic investigation of the reaction of **3** with NaOH under different reaction conditions. The results presented here confirm the previously proposed mechanisms for *N*-oxide formation[6,9] and substitution of the amino group in 1-amino-2,4,6-trinitrobenzene derivatives.[2] In addition, they have allowed us to conclude that the product distribution depends on the polarity of the reaction media as a consequence of a decrease in the rate of the substitution reaction with decreasing polarity.

Results and Discussion

Kinetic Studies in 10 % 1,4-Dioxane/H_2O

The spectrum of **3** in 10% 1,4-dioxane/H_2O shows two absorption bands at 420 and 350 nm (Figure 1, see part A).

[‡] Amines as Leaving Groups in Nucleophilic Aromatic Substitution Reactions, 6. Part 5: Ref.[6]

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Spectra with maxima at 490, 400 and 250 nm result instantly on addition of 0.5 M NaOH at 25 °C. The spectra of the species formed in this process recorded with a conventional spectrophotometer at 6 °C are shown in parts B–D of Figure 1. Addition of acid after the formation of any of these species gives the starting materials; at longer times these species are transformed quantitatively into the picrate ion with a good isosbestic point at 380 nm. The spectral changes observed indicate that at least two intermediates are formed which are probably σ complexes because their spectra are similar to those of other σ complexes.[10–13]

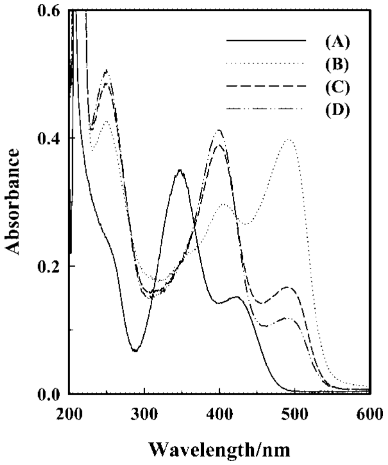


Figure 1. Absorbance of **3** (2.5×10^{-5} M) in 10% 1,4-dioxane/H_2O at 6 °C (A) and in the presence of 0.5 M NaOH at different reaction times: (B) *t* = 0.25 min; (C) *t* = 1 min; (D) *t* = 8 min.

Three kinetic processes were observed at 25 °C; the slowest process leads to the quantitative formation of the picrate ion. The fastest processes were followed in a stopped-flow spectrophotometer by recording the change in absorbance at 489 nm and two relaxation times were measured. The absorbance versus time plot (not shown) shows an increase followed by a decrease in absorbance that can be fitted to a double-exponential expression [Equation (2)]. The first relaxation time (τ_1) was calculated from Equation (2) with data recorded up to 6 s. The results are shown in Table 1 and Figure 2. From these data the second relaxation time can also be calculated, but better results are obtained when the change in absorbance is recorded over a longer time period with the process having gone closer to completion. The results shown in Table 1 and Figure 3 for τ_2 were obtained by fitting the data obtained during 200 s to Equation (2).

$$Abs = a_1 e^{t/\tau_1} + a_2 e^{t/\tau_2} + Abs_\infty \tag{2}$$

The non-linear plot of $1/\tau_1$ versus [NaOH] was fitted by Equation (3), whereas that of $1/\tau_2$ versus [NaOH] was fitted using Equation (4).

$$\frac{1}{\tau_1} = \frac{a[HO^-]}{1+c[HO^-]} + \frac{b}{1+d[HO^-]} \tag{3}$$

$$\frac{1}{\tau_2} = \frac{a[HO^-]^2}{1+b[HO^-]+c[HO^-]^2} + d \tag{4}$$

The rate of formation of the picrate ion was measured by following the increase in absorbance at 359 nm, the λ_{max} of this ion, and by varying the NaOH concentration from 0.01 to 1 M (Table 2). There is a non-linear dependence of the observed rate constants with HO^- concentration, as can be seen in Figure 4; data were fitted using Equation (5).

Table 1. Observed reciprocal relaxation times $1/\tau_1$ and $1/\tau_2$ in the hydrolysis of *N*-butyl-2,4,6-trinitroaniline (**3**) in 10% 1,4-dioxane/H_2O at 25 °C.[a]

[NaOH]/M	τ_1^{-1}/s^{-1}	τ_2^{-1}/s^{-1}
0.040	0.37 ± 0.01	0.0204 ± 0.0005
0.050	0.38 ± 0.01	0.0262 ± 0.0005
0.060	0.39 ± 0.01	0.0260 ± 0.0002
0.070	0.42 ± 0.02	0.0270 ± 0.0002
0.080	0.44 ± 0.02	0.0316 ± 0.0005
0.090	0.45 ± 0.02	0.030 ± 0.001
0.150	0.52 ± 0.02	0.039 ± 0.001
0.176	0.51 ± 0.05	0.032 ± 0.002
0.220	0.57 ± 0.01	0.051 ± 0.008
0.253	0.55 ± 0.04	0.061 ± 0.007
0.276	0.60 ± 0.04	0.0462 ± 0.0006
0.299	0.55 ± 0.05	0.0491 ± 0.0004
0.322	0.59 ± 0.06	0.0509 ± 0.0004
0.352	0.61 ± 0.02	0.0514 ± 0.0007
0.375	0.59 ± 0.06	0.058 ± 0.001
0.400	0.64 ± 0.03	0.0542 ± 0.0005
0.498	0.66 ± 0.05	0.065 ± 0.002
0.600	0.68 ± 0.04	0.0644 ± 0.0008
0.700	0.76 ± 0.04	0.069 ± 0.001
0.800	0.77 ± 0.05	0.0754 ± 0.0009

[a] Ionic strength *I* = 1 M (NaCl); $[\mathbf{3}]_0 = 2.51\times10^{-5}$ M. The errors shown are standard deviations from 15 determinations.

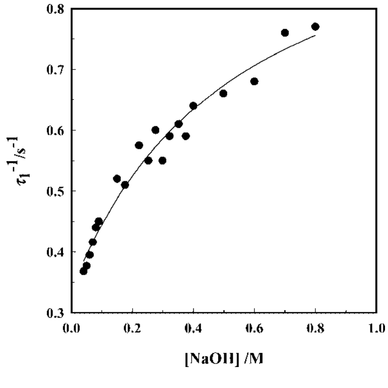


Figure 2. Plot of τ_1^{-1} versus [NaOH] for the reaction of **3** with NaOH in 10% 1,4-dioxane/H_2O at 25 °C. $[\mathbf{3}]_0 = 2.51\times10^{-5}$ M. The line was drawn using Equation (3) and the values of the rate and equilibrium constants reported in Table 3.

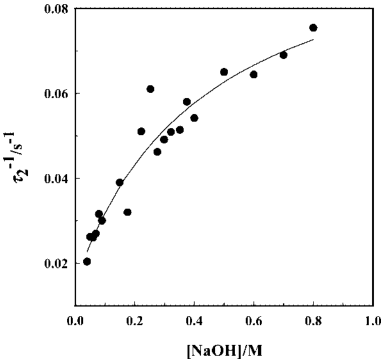


Figure 3. Plot of τ_2^{-1} versus [NaOH] for the reaction of **3** with NaOH in 10% 1,4-dioxane/H_2O at 25 °C. $[\mathbf{3}]_0 = 2.51 \times 10^{-5}$ M. The line was drawn using Equation (4) and the values of the rate and equilibrium constants reported in Table 3.

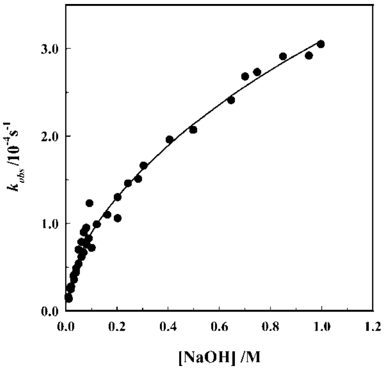


Figure 4. Plot of k_{obs} versus [NaOH] for the formation of picrate ion from **3** and NaOH at 25 °C in 10% 1,4-dioxane/H_2O. $[\mathbf{3}]_0 = (5.11–7.97) \times 10^{-5}$ M. The line was drawn using Equation (5) and the values of rate and equilibrium constants reported in Table 3.

$$k_{obs} = \frac{a[\mathrm{HO}^-] + b[\mathrm{HO}^-]^2}{1 + c[\mathrm{HO}^-] + d[\mathrm{HO}^-]^2} \qquad (5)$$

Table 2. Observed rate constants for the formation of the picrate ion in the hydrolysis of *N*-butyl-2,4,6-trinitroaniline (**3**) in 10% 1,4-dioxane/H_2O at 25 °C.[a]

[NaOH]/M	$k_{obs}/10^{-4}$ s^{-1}	[NaOH]/M	$k_{obs}/10^{-4}$ s^{-1}
0.010	0.160	0.090	0.830
0.012	0.140	0.101	0.721
0.020	0.250	0.121	0.990
0.020	0.280	0.162	1.100
0.030	0.401	0.202	1.300
0.032	0.360	0.243	1.460
0.040	0.440	0.283	1.510
0.041	0.490	0.304	1.660
0.050	0.700	0.405	1.960
0.050	0.540	0.498	2.070
0.061	0.790	0.646	2.410
0.061	0.607	0.701	2.680
0.069	0.667	0.748	2.730
0.070	0.900	0.849	2.910
0.080	0.950	0.950	2.920
0.081	0.760	0.997	3.050

[a] Ionic strength $I = 1$ M (NaCl); $[\mathbf{3}]_0 = (5.11–7.97) \times 10^{-5}$ M.

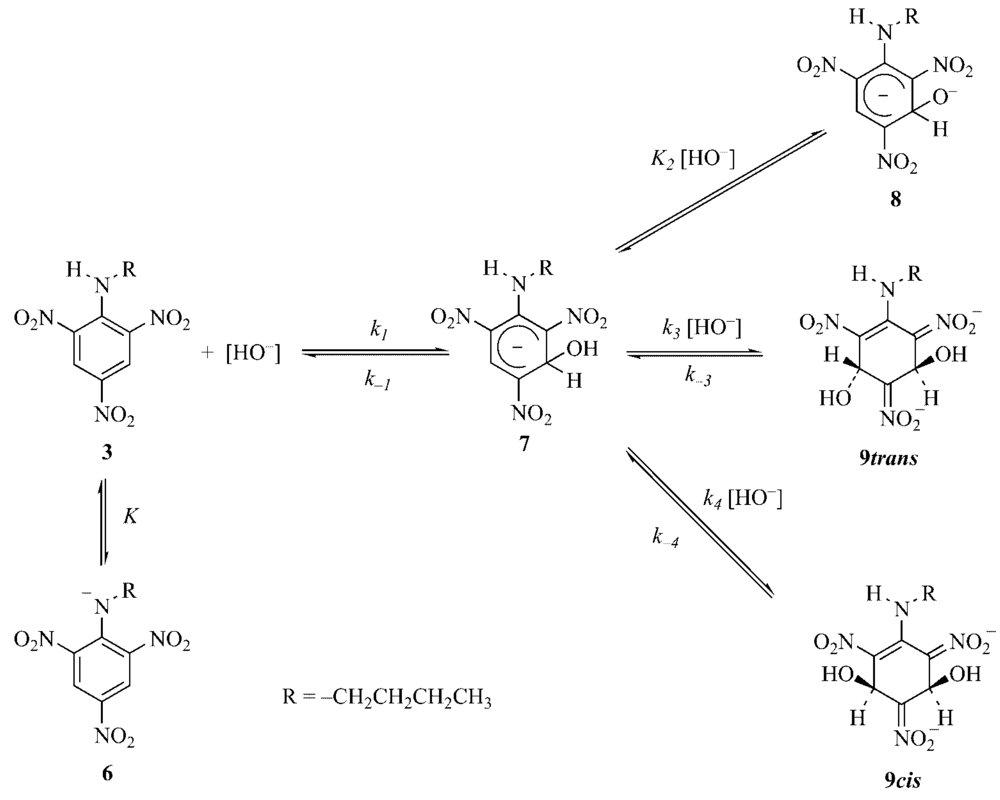
On the basis of the kinetic and spectroscopic data presented here and in previous reports on related systems,[2] we suggest the mechanism shown in Scheme 1 for the fastest processes occurring in the hydrolysis of **3**. In this mechanism, substrate **3** is deprotonated to give the anion **6** and HO^- can add to C3 of the aromatic ring to form σ complex **7**. Complex **7** is rapidly deprotonated to afford σ complex **8** and another HO^- can also add to **7** to give the isomeric complexes ***9trans*** and ***9cis***. Ionization of **3** has previously been observed in its reaction with butylamine in DMSO.[11,12] In addition, in the reaction of **1** with NaOH, KOH or $(CH_3)_4NOH$ in DMSO/H_2O, ionization of the substrate and the formation of σ complexes through the addition of HO^- to the substrate and its anion have also been observed.[14] The ionization of σ complexes of type **7** to give **8** has been reported in several cases.[2b,13,15,16] The formation of isomeric *cis*/*trans* σ complexes was observed in the reaction of 1,3,5-trinitrobenzene with sulfite anions[17] and in the hydrolysis reactions of 2,4,6-trinitro-1-piperidinobenzene (**10**) and 2,4,6-trinitro-1-pyrrolidinobenzene (**11**).[2b]

For the mechanism depicted in Scheme 1, five relaxation times are expected.[18] The first two must be related to the ionization of the substrate and complex **7**; these processes are expected to be very fast because proton transfer between electronegative atoms such as nitrogen or oxygen are known to be limited by diffusion control.[19] On the other hand, in the reaction of **3** with butylamine in DMSO, deprotonation of the substrate to give **6** is faster than the addition of the nucleophile to C3 of the aromatic ring and the equilibrium constant for deprotonation is 3.2 M^{-1}.[11,12] In addition, deprotonation of σ complexes of similar substrates by HO^- in water has been shown to be a fast process, not measurable in the timescale of the stopped-flow technique.[20] Thus, the proton-transfer processes in the mechanism of Scheme 1 are not expected to be measurable by our techniques.

The monoanionc σ complex **7** in Scheme 1 is probably formed faster than the dianionic complexes. Literature data indicate that the rate constants for the formation of σ complexes resulting from the addition of HO^- to the 3 position of **10** and **11** are 3.48 and 5.05 $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, respectively, whereas those for the formation of 1:2 σ complexes are 0.6 and 1.0 $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, respectively.[2b]

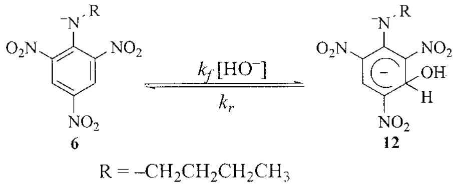
The first process measured in the hydrolysis of **3** is attributed to the formation of **7** in equilibrium with **8**, with **6** formed in a fast pre-equilibrium. The expression for the first relaxation time for the mechanism in Scheme 1 is given by Equation (6) and was derived by standard procedures[18] assuming that $k_{-1} >> k_3[\mathrm{HO}^-] + k_{-3} \approx k_4[\mathrm{HO}^-] + k_{-4}$. Note that Equation (6) has the same mathematical form as Equation (3).

$$\frac{1}{\tau_1} = \frac{k_1[\mathrm{HO}^-]}{1 + K[\mathrm{HO}^-]} + \frac{k_{-1}}{1 + K_2[\mathrm{HO}^-]} \qquad (6)$$



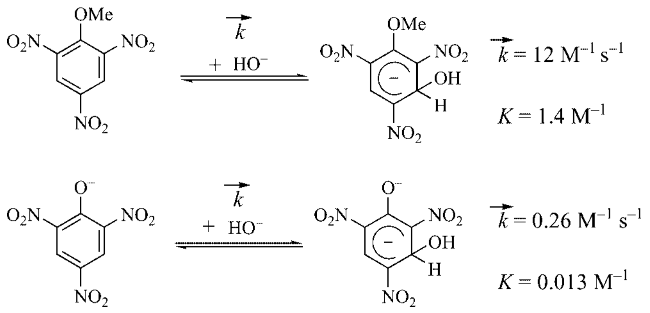
Scheme 1.

The experimentally determined second relaxation time is related to the formation of the complexes **9*trans*** and **9*cis*** with other species in equilibrium. The possibility of the formation of complex **12** must be considered [Equation (7)], but this was discarded based on the following facts. The rate constant for the addition of HO^- to C3 of 2,4,6-trinitroanisole in water at 25 °C is $12\ \text{M}^{-1}\,\text{s}^{-1}$, whereas that for addition to the picrate anion is $0.26\ \text{M}^{-1}\,\text{s}^{-1}$ (Scheme 2).[15] The mean value of the rate constants for the addition of one HO^- ion to unsubstituted ring positions of 1-amino-2,4,6-trinitrobenzene in 10% 1,4-dioxane/H_2O is $4\ \text{M}^{-1}\,\text{s}^{-1}$, whereas the rate constants for the addition of a second HO^- ion have a mean value of $0.8\ \text{M}^{-1}\,\text{s}^{-1}$ (Scheme 3).[2b] These results indicate that the addition of an HO^- ion to an anionic compound is slower than the addition of a second HO^- to a σ complex. Besides, by comparing the equilibrium constants for the formation of these two dianionic complexes, that is, 0.013 and $4.7\ \text{M}^{-1}$, respectively, we can conclude that the formation of the double complex **9** is kinetically and thermodynamically favoured over the formation of complex **12**.

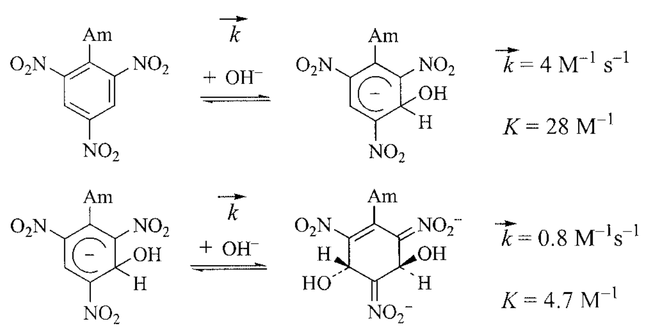


(7)

R = –CH2CH2CH2CH3



Scheme 2.



10 Am = piperidine
11 Am = pyrrolidine
13 Am = morpholine

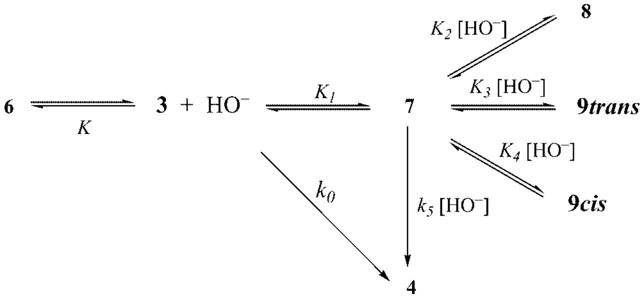
Scheme 3.

Thus, we propose that the second relaxation time measured in the hydrolysis of **3** corresponds to the formation of the 1:2 σ complexes **9** in Scheme 1. The expression for the second relaxation time is given by Equation (8) which has the same mathematical form as Equation (4).

$$\frac{1}{\tau_2} = \frac{k_d K_1 \left[\mathrm{HO^-}\right]^2}{1+\left(K+K_1\right)\left[\mathrm{HO^-}\right]+K_1K_2\left[\mathrm{HO^-}\right]^2} + k_{-d} \qquad (8)$$

In Equation (8), k_d and k_{-d} represent the rate constants for the formation and decomposition of both the *cis* and *trans* isomers or of one of them since by our experimental techniques we could not distinguish between them. *cis–trans* isomerism of the σ complexes has been detected previously in the hydrolysis of **10** and **11**, but could not be detected in the hydrolysis of 1-morpholino-2,4,6-trinitrobenzene **13**.[2b] As discussed by Bernasconi and Wang,[21] this isomerism process may not be kinetically observed when one or more of the following situations hold: a) the UV/Vis spectra of the *cis* and *trans* isomers are very similar; b) the formation of one of them is thermodynamically and kinetically favoured over the other; c) both isomers have the same stability and form and decompose at equal rates.

A good fit of the experimentally determined values of $1/\tau_1$ to Equation (6) was obtained when K_2 was varied from 1 to 4 M^{-1}.[22] These values are in agreement with those obtained with other 1-amino-2,4,6-trinitrobenzenes[2b] and *O*-ethyl *S*-(2,4,6-trinitrophenyl) thio- and dithiocarbonates in the same solvent[16] and that of *N*,*N*-dipropyl-2,6-dinitro-4-(trifluoromethyl)aniline in DMSO/H_2O.[23] It is known that the value of the deprotonation equilibrium constant for σ complexes does not change much with the substituent at C1.[13]



Scheme 4.

The best fit of the experimentally determined values of $1/\tau_2$ to Equation (8) was obtained by using $K_1 = 8\ \mathrm{M}^{-1}$ and $K + K_1 = 10.6\ \mathrm{M}^{-1}$, calculated by using the first relaxation time and with $K_2 = 4\ \mathrm{M}^{-1}$. The values thus obtained for the rate and equilibrium constants for the mechanism shown in Scheme 1 are summarized in Table 3.

For the slow process leading to the formation of the picrate ion, we propose the mechanism shown in Scheme 4 in which displacement of the leaving group takes place from the substrate and from the σ complex **7**. Nucleophilic displacement of the leaving group by hydroxide within 3-nucleophile σ complexes was previously proposed and it was suggested that this facilitates the displacement of the leaving group.[1,2,15]

The rate law for the mechanism shown in Scheme 4 is given by Equation (9) which has the same mathematical form as Equation (5).

$$k_{obs} = \frac{k_0\left[\mathrm{HO^-}\right]+k_5K_1\left[\mathrm{HO^-}\right]^2}{1+\left(K+K_1\right)\left[\mathrm{HO^-}\right]+K_1\left(K_2+K_3+K_4\right)\left[\mathrm{HO^-}\right]^2} \qquad (9)$$

The experimental data for k_{obs} fit to Equation (9) using the values of the other calculated equilibrium constants shown in Table 3, giving $k_0 = 1.6\times10^{-3}\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$ and $k_5 = 3.3\times10^{-4}\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$. However, no reasonable value for (K_2 + K_3 + K_4) was obtained, probably due to the small contribution of this parameter in the concentration range studied. Therefore, we could not determine $K_3 + K_4$. The relative contributions of the two competing pathways in the hydrolysis reaction measured by the ratio k_0/K_1k_5 is 0.60 indicating that, for this substrate, both pathways contribute similarly to the reaction rate. It was observed for the hydrolysis of **1**[6] and other 1-amino-2,4-dinitro-[1] and 2,4,6-trinitrobenzenes[2] that the formation of a σ complex of type **7** is the main reaction pathway. This difference can be explained by analysing the equilibrium and rate constants calculated for the related compounds **10**, **11** and **13** included in Table 3. It can be seen that K_1 for **3** is at least twice as small as that for the other compounds mainly because of a greater value of k_{-1}. Besides, the addition of the nucleophile to C1 both in the substrate (k_0) and in the 1:1 intermediate (k_5) is

Table 3. Calculated rate and equilibrium constants for the hydrolysis of *N*-butyl-2,4,6-trinitroaniline (**3**), 2,4,6-trinitro-1-piperidinobenzene (**10**), 2,4,6-trinitro-1-pyrrolidinobenzene (**11**) and 1-morpholino-2,4,6-trinitrobenzene (**13**) in 10% 1,4-dioxane/H_2O at 25 °C.

	3	**10**[a]	**11**[a]	**13**[a]
$k_1/\mathrm{M}^{-1}\,\mathrm{s}^{-1}$	2.6 ± 0.2	3.48 ± 0.05	3.2 ± 0.1	5.05 ± 0.03
k_{-1}/s^{-1}	0.34 ± 0.02	0.08 ± 0.02	0.06 ± 0.02	0.28 ± 0.06
K_1/M^{-1}	8 ± 1	45 ± 19	53 ± 19	18 ± 4
K_2/M^{-1}	4	0.9 ± 0.4	1	1.0 ± 0.3
K/M^{-1}	2.6 ± 0.4			
$k_d/\mathrm{M}^{-1}\,\mathrm{s}^{-1}$	0.30 ± 0.08	0.6 ± 0.2[b]		1.0 ± 0.3[b]
k_{-d}/s^{-1}	0.021 ± 0.003	0.023 ± 0.007[c]	0.04 ± 0.01[c]	
$k_0/10^{-3}\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$	1.60 ± 0.08	3.1 ± 0.5	15 ± 2	10.6 ± 0.9
$k_5/10^{-4}\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$	3.3 ± 0.4	10 ± 3	13 ± 5	90 ± 20

[a] Data taken from ref.[3b] [b] Corresponds to k_3 in Scheme 1. [c] Corresponds to k_{-4} in Scheme 1.

slower for compound **3** than for the others. In the hydrolysis of **1** only K_1k_5 could be calculated indicating that k_0 is negligible.[6] These differences in rates may be attributed to stronger stabilization of the substrate by resonance of the nitrogen electron pair into the ring which is favoured compared with **10**, **11** and **13** for steric reasons.

Aromatic amines with electron-withdrawing substituents are quite resistant to elimination of the amino group. This behaviour is considered to be a consequence of the interaction of the nitrogen lone-pair electrons with the π system which stabilizes the ground state of the substrate. If the nitrogen atom of the amino group is rotated out of the aromatic plane, this interaction decreases and the amine can be displaced.[1,2,24] We have previously reported that, based on structural calculations and spectroscopic investigations, rotation and bending of the amino group occurs in compound **3**.[8] Thus, we conclude that rotation and bending of the amino group, which destabilizes the ground state of **3**, favours the substitution reaction, whereas the formation of a σ complex by addition of HO^- to C3 of the aromatic ring provides another route to substitution of the amino group with similar energetic requirements.

Kinetic Studies in 60% 1,4-Dioxane/H_2O

The spectrum of **3** in 60% 1,4-dioxane/H_2O in neutral media shows two absorption bands at 345 and 415 nm (Figure 5, A). At 25 °C, the addition of 0.19 M NaOH rapidly leads to the formation of an orange species with a maximum at 435 nm which slowly changes to yellow (Figure 5, B,C). At 6 °C, the addition of NaOH produces a species with a maximum at 440 nm and a shoulder at 500 nm which slowly gives the products (Figure 6).

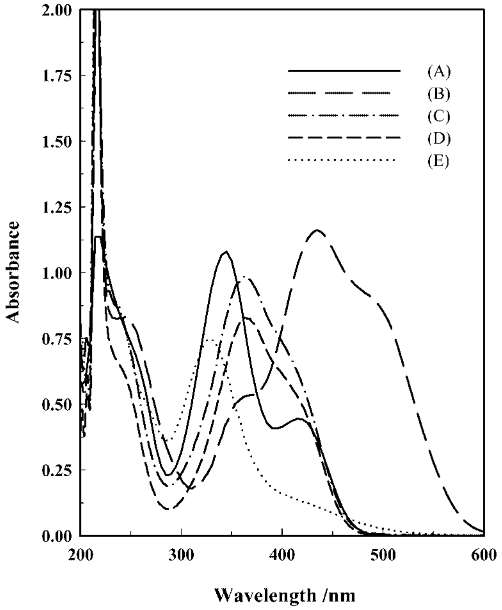


Figure 5. Spectra at 25 °C in 60% 1,4-dioxane/H_2O of **3** (7×10^{-5} M) (A) and in the presence of 0.19 M NaOH at different reaction times: (B) t = 1.6 min; (C) t = 77 h. Spectra of (D) **4** (5×10^{-5} M) and (E) 5 (5×10^{-5} M).

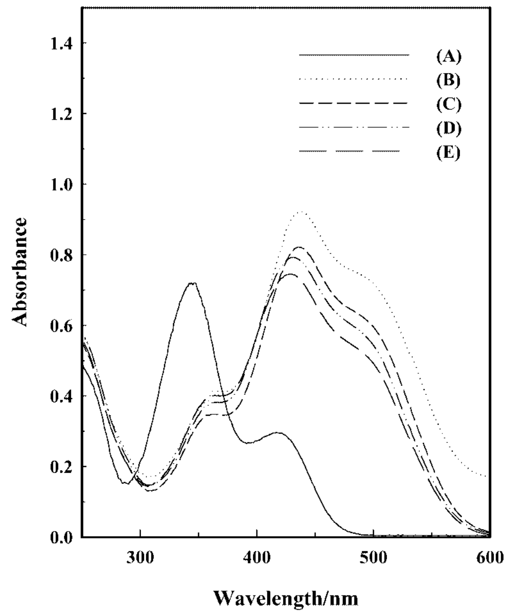


Figure 6. Spectra at 6 °C in 60% 1,4-dioxane/H_2O of **3** (5×10^{-5} M) (A) and in the presence of 0.20 M NaOH at different reaction times: (B) t = 30 s; (C) t = 60 s; (D) t = 75 min; (E) t = 7 h 13 min.

The kinetics of the slow process of the reaction of **3** in 60% 1,4-dioxane/H_2O were studied at 25 °C and 0.2 M ionic strength with NaOH between 0.01 and 0.2 M. As was previously observed at reflux,[7] two products were formed: 2,4,6-trinitrophenol (**4**) and 5,7-dinitro-2-propyl-1*H*-benzimidazole 3-oxide (**5**) [Equation (1)]. The reaction was followed by measuring the decrease in absorbance at 435 nm, the $\lambda_{\max}$ of the intermediate species formed.

The observed rate constants k_{obs}, the molar fractions of **4** and **5**, and the pseudo-first-order rate constants k_P and k_N for the formation of the products **4** and **5**, respectively, are listed in Table 4. It can be seen that the relative yields of the products depend on the HO^- concentration and that the relative amount of **4** increases with HO^- concentration; this behaviour is similar to that found with **1** in 10% 1,4-dioxane/H_2O at 25 °C.[6]

Note that k_N, the observed pseudo-first-order rate constant for the formation of **5**, is nearly independent of NaOH concentration. On the other hand, the observed rate constants k_{obs} increase with NaOH concentration, as shown in Figure 7.

We attempted to follow the fast process of the reaction of **3** with NaOH in 60% 1,4-dioxane/H_2O in a stopped-flow spectrophotometer by measuring the change in absorbance at 440 and 500 nm, but the kinetic profiles had too much noise and were not reproducible. This may be due to the large number of intermediates involved in the reaction leading to the formation of **4** and **5**.

When the reaction was followed in a conventional spectrophotometer at 480 nm with 0.20 M NaOH for up to 5000 s, a two-exponential decay in absorbance was observed. By fitting these data to Equation (2), a value of 3.7×10^{-5} s^{-1} was calculated for the second process; this

Table 4. Rate constants and product yields for the reaction of *N*-butyl-2,4,6-trinitroaniline (**3**) in 60% 1,4-dioxane/water at 25 °C.[a]

[NaOH]/ M	k_{obs}/ 10^{-5} s^{-1}	*X*(**4**)[b]	k_P/ 10^{-5} s^{-1}[c]	*X*(**5**)[d]	k_N/ 10^{-5} s^{-1}[e]
0.010	0.57	0.345	0.20	0.655	0.373
0.020	0.62	0.495	0.31	0.505	0.313
0.040	0.64	0.472	0.30	0.528	0.338
0.060	0.98	0.575	0.56	0.425	0.416
0.079	1.16	0.637	0.74	0.363	0.421
0.090	1.30	0.669	0.87	0.331	0.431
0.100	1.30	0.669	0.87	0.331	0.431
0.100	1.58	0.695	1.10	0.305	0.482
0.119	1.55	0.698	1.08	0.302	0.468
0.120	1.90	0.751	1.43	0.249	0.473
0.130	2.20	0.741	1.63	0.259	0.570
0.132	1.94	0.734	1.42	0.266	0.515
0.149	2.22	0.749	1.66	0.251	0.556
0.149	1.92	0.819	1.57	0.181	0.347
0.170	2.24	0.844	1.89	0.156	0.349
0.170	2.56	0.774	1.90	0.227	0.580
0.180	2.42	0.847	2.05	0.153	0.369
0.189	2.65	0.831	2.12	0.169	0.448

[a] Ionic strength $I = 0.2$ M (NaCl); $[\mathbf{3}]_0 = (5.11–7.97)\times10^{-5}$ M. [b] Molar fraction of phenol **4**. [c] Pseudo-first-order rate constants for the formation of **4**. [d] Molar fraction of *N*-oxide **5**. [e] Pseudo-first-order rate constants for the formation of **5**.

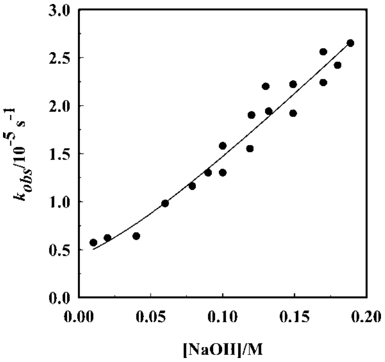


Figure 7. Plot of k_{obs} versus [NaOH] for the reaction of **3** with NaOH at 25 °C in 60% 1,4-dioxane/H_2O. $[\mathbf{3}]_0 = 7\times10^{-5}$ M. The line was drawn using Equation (14).

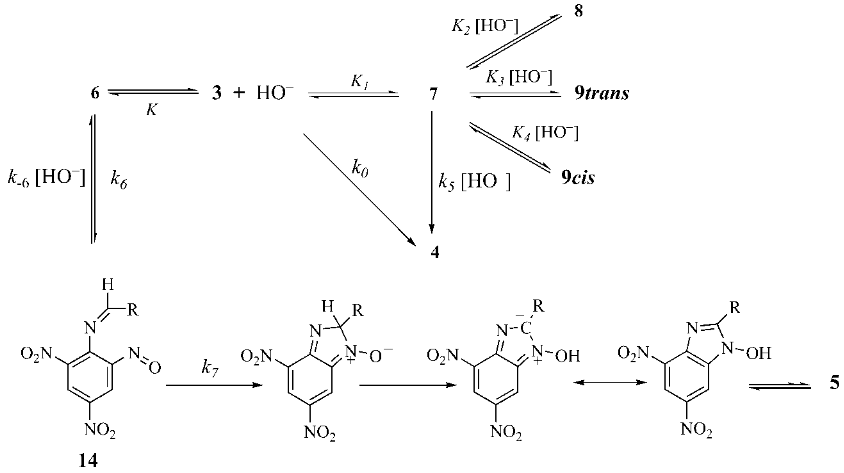
value is similar to that obtained at the same NaOH concentration measured for the slow process leading to the formation of **4** and **5** (Table 4). We tried to follow the reaction of **3** with 0.04 M < [NaOH] < 0.20 M at 25 °C and 0.20 M ionic strength at 480 nm for up to 500 s in a conventional spectrophotometer; two kinetic processes were observed under these conditions, but the results were not reproducible and no further attempts to measure them were made.

On the basis of the mechanism proposed for the formation of **4** in 10% 1,4-dioxane/H_2O (Scheme 4) and the mechanism for the formation of *N*-oxides from **1**[6] and *N*-(dinitrophenyl) amino acid derivatives,[9] we suggest the mechanism shown in Scheme 5 for the reaction of **3** with NaOH in 60% 1,4-dioxane/H_2O. The anion of the substrate and some of the σ complexes proposed as intermediates were detected when the reaction of **3** was conducted in 60% $[D_8]$1,4-dioxane/D_2O and was followed by ^{1}H NMR spectroscopy (see below).

The first step in the formation of **5** is the ionization of the substrate as was previously demonstrated with related compounds;[6,8,9] formation of an *N*-alkylidene-2-nitrosoaniline-type intermediate like **14** was previously discussed in the reactions of *N*-(dinitrophenyl) amino acid derivatives.[9] The observed rate constant for the mechanism depicted in Scheme 5 is given by Equation (10).

$$k_{obs} = k_P + k_N \tag{10}$$

The mechanism for the formation of **4** is the same as that proposed for the reaction in 10% 1,4-dioxane/H_2O shown in Scheme 4; thus, k_P is given by Equation (9). The stability of the dianionic complexes **8** and **9** should diminish with a decrease in solvent polarity as a result of poorer solvation.[25] Thus, we expected parameter $K_1(K_2 + K_3 + K_4)$ for the reaction in 60% 1,4-dioxane/H_2O to be less than in 10% 1,4-dioxane/H_2O and therefore can be neglected for the reactions in the former medium. On the basis of these assumptions, the expression for the pseudo-first-order rate constant for the formation of **4** under these conditions is given by Equation (11).



Scheme 5.

$$k_P = \frac{k_0\left[HO^-\right] + k_5 K_1 \left[HO^-\right]^2}{1 + \left(K + K_1\right)\left[HO^-\right]} \qquad (11)$$

For the mechanism for the formation of **5** shown in Scheme 5, we can derive the expression for k_N given in Equation (12), assuming that the steps after cyclization are faster than the others and by considering **13** as a steady-state intermediate.

$$k_N = \frac{K k_6 k_7 \left[HO^-\right]}{\left(k_{-6}\left[HO^-\right] + k_7\right)\left(1 + \left(K + K_1\right)\left[HO^-\right] + K_1\left(K_2 + K_3 + K_4\right)\left[HO^-\right]^2\right)} \qquad (12)$$

The quadratic term in the denominator of Equation (12) can be neglected as in Equation (11), and if $k_{-6}[HO^-] >> k_7$, Equation (12) reduces to Equation (13).

$$k_N = \frac{K K_6 k_7}{1 + \left(K + K_1\right)\left[HO^-\right]} \qquad (13)$$

By substituting k_P and k_N from Equation (11) and Equation (13) into Equation (10) and rearranging, Equation (14) is obtained.

$$k_{obs} = \frac{K K_6 k_7 + k_0\left[HO^-\right] + K_1 k_5 \left[HO^-\right]^2}{1 + \left(K + K_1\right)\left[HO^-\right]} \qquad (14)$$

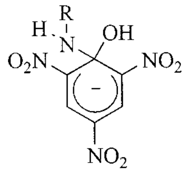
A good fit of the data to Equation (14) can be obtained with $K + K_1 = 1–10\ \text{M}^{-1}$ (Figure 7); the parameters calculated are summarized in Table 5 in which it can be seen that, except for the parameter of the quadratic term, the others are nearly the same for $K + K_1 = 1$ or $10\ \text{M}^{-1}$.

Table 5. Calculated rate constants for the reaction of *N*-butyl-2,4,6-trinitroaniline (**3**) with NaOH in 60% 1,4-dioxane/water at 25 °C.

KK_6k_7/s^{-1}	$(3.8 \pm 0.7) \times 10^{-6}$	$(4.4 \pm 0.6) \times 10^{-6}$
$k_5K_1/\text{M}^{-2}\ \text{s}^{-1}$	$(2.5 \pm 0.4) \times 10^{-4}$	$(1.5 \pm 0.4) \times 10^{-3}$
$k_0/\text{M}^{-1}\ \text{s}^{-1}$	$(1.00 \pm 0.07) \times 10^{-4}$	$(1.00 \pm 0.07) \times 10^{-4}$
$K + K_1/\text{M}^{-1}$	1	10

The good fit of the data to the proposed mechanism suggests that the rate-determining step for the formation of **5** is the cyclization of intermediate **13**. The results presented here can be interpreted by the same mechanism previously proposed for *N*-oxide formation from other 2-nitroaniline derivatives but with a different rate-determining step.[9]

Note that the steps that lead to **4** in Scheme 5, namely k_0 and k_5, are not elementary steps and must involve the attack of the HO⁻ ion on the carbon atom bearing the amine with the formation of intermediates **15** and **16**.



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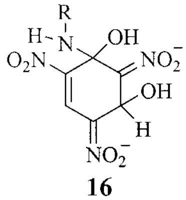

16

The Hughes–Ingold rules of solvent effects on reactions between an ion and a neutral molecule and between ions of like charges[26] predict that k_0 increases and k_5 decreases with an increase in dioxane percentage. An increase in the rate of hydrolysis when the solvent changes from 10 to 60% 1,4-dioxane/H_2O was observed with phenyl ethers of 2,4-dinitrophenol.[27] In contrast, our experimental results indicate that the rate of formation of **4** decreases in the less polar solvent due to a decrease in k_0 as well as in k_5K_1 (compare data from Table 3 and Table 5). The same effect was observed in the reaction of **1** at 25 °C which gives a mixture of 2,6-dinitrophenol and **2** in 10% 1,4-dioxane/H_2O and only **2** in 60% 1,4-dioxane/H_2O.[6] The decrease in k_0 when changing to a less polar solvent, that is, from 10% to 60% 1,4-dioxane/H_2O, may be attributed to a decrease in the contribution of the more reactive conformation of the substrate. It has previously been shown (see above) that the conformation of the substrate in the initial state is an important factor in determining the reactivity of aromatic amines.

We conclude that the increase in dioxane content in the solvent produces a decrease in the reaction rate of the substitution reaction enabling competition with the cyclization reaction that leads to *N*-oxide **5**. The rate of this reaction has low sensitivity to the polarity of the solvent.[6]

The mechanism proposed for the formation of benzimidazole *N*-oxides from 2-nitroaniline derivatives involves the reduction of a nitro to a nitroso group.[6,9,28] The reduction of nitro to nitroso groups of benzene derivatives in basic solution is a well-documented reaction that depends on the oxygen content of the reaction media.[29,30] In addition, the yield of 7-nitro-2-propyl-5-(trifluoromethyl)-1*H*-benzimidazole 3-oxide obtained from *N*-butyl-2,6-dinitro-4-(trifluoromethyl)aniline increases when the reaction is carried out under N_2.[8] Thus, we investigated the effect of N_2 on the kinetics and product distribution of the reaction of **3** with NaOH in 60% 1,4-dioxane/H_2O.

The reactions of **3** at 25 °C in 60% 1,4-dioxane/H_2O under N_2 were studied in NaOH concentrations ranging from 0.040 to 0.191 M. The reactions were followed by measuring the decrease in absorbance at 435 nm; in the spectra of the reaction mixture recorded at different reaction times no isosbestic point was observed. The observed pseudo-first-order rate constants were greater than those obtained in similar conditions in air, but the results were not reproducible and values in the range of $(1.63–9.97) \times 10^{-5}\ \text{s}^{-1}$ were obtained in successive runs. We think that the influence of traces of oxygen may be important for the reaction but we did not find the appropriate methodology to carry out the experiments in the total absence of oxygen. Besides, spectrophotometric quantification of the reaction products showed the presence of an additional product along with **4** and **5**. This unknown product is not a decomposition product of the other two as a solution of a mixture of authentic samples of **4** and **5** under the same reaction conditions does not change with time.

It has been reported that in the reaction of nitrobenzene derivatives[29,30] and *o*-nitroanilines[9,28,31] in basic media, azoxybenzene derivatives are formed. Therefore, it is possible that azoxybenzene compounds are formed in our reaction system under N_2. However, this product should not be an intermediate in the formation of **4** and **5** because the relative amounts of these two compounds do not change significantly in the absence of oxygen. Besides, the addition of O_2 to the reaction media has no effect on the kinetics and product distribution because when the reaction was carried out with 7.5×10^{-5} M **3** and 0.138 M NaOH in 60% 1,4-dioxane/H_2O at 25 °C while O_2 was bubbled through the solution, the observed pseudo-first-order rate constant, that is, 2.3×10^{-5} s^{-1}, and the relative yields of **4** and **5** were similar to the values observed in air under the same conditions.

NMR Studies

In order to confirm the identities of the products as well as to identify the intermediates formed in the reaction of **3** with NaOH in 60% 1,4-dioxane/H_2O, the reaction was followed by ^{1}H NMR spectroscopy in 60% [D$_8$]dioxane/D_2O at room temperature with NaOD.

The NMR spectrum of **3** in 60% [D$_8$]dioxane/D_2O shows four signals at high fields with relative intensities of 3:2:2:2 corresponding to aliphatic protons and one signal at low field corresponding to the chemically equivalent aromatic protons at δ = 9.14 ppm (Figure 8, a). The addition of 0.178 M NaOD causes a shift of the aliphatic signals to higher fields and various signals appear between δ = 6 and 9 ppm (Figure 8, b,c). The three doublets at δ = 6.36, 6.25 and 6.19 ppm may be attributed to the presence of σ complexes formed by addition of one and two HO^- ions to unsubstituted ring positions and the anion of substrate **3**.[9,11,32,33]

The products formed under these conditions were phenol **4** and *N*-oxide **5** as can be inferred by comparison of the spectrum taken at infinity (Figure 8, e) with that of a mixture of authentic samples of **4**, **5** (80:20) and butylamine. The chemical shifts of compounds **3**, **4** and **5** are summarized in Table 6.

When the reaction was conducted in the presence of 0.018 M NaOH only signals attributable to monoanionic complexes were observed (Figure 9). This is in agreement with previous reports on the reaction of **3** with butylamine in DMSO.[11] The final spectrum of this reaction is of a mixture of **4**, **5** (50:50) and butylamine as was corroborated with authentic samples of the products in the same reaction media.

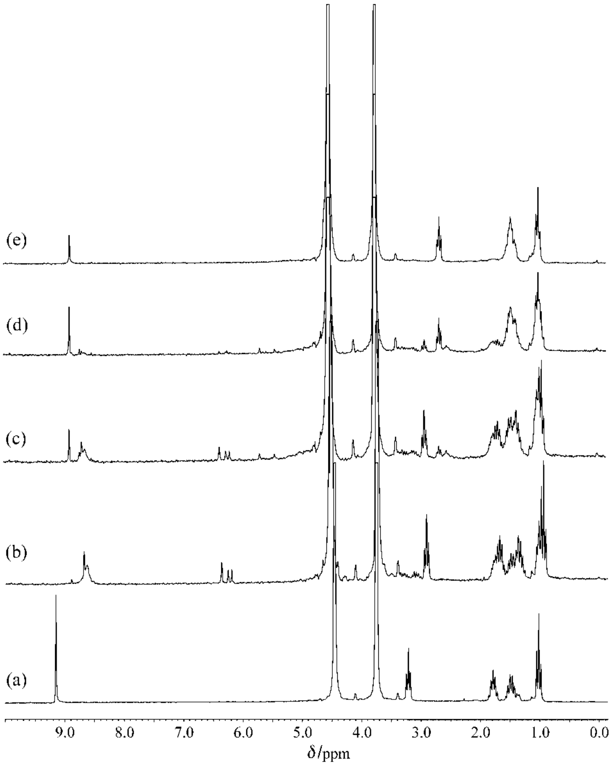

Figure 8. 200-MHz ^{1}H-NMR spectra of (a) **3** (8.06×10^{-3} M) recorded in 60% [D$_8$]1,4-dioxane/D_2O at room temperature and at various times after the addition of 0.178 M NaOD: (b) t = 10 min, (c) t = 63 min, (d) t = 193 min, (e) at infinity.

Table 6. ^{1}H NMR spectroscopic data for compounds **3**, **4** and **5** in 60% 1,4-[D$_8$]dioxane/D_2O at room temperature.

	^{1}H NMR shifts /ppm Ar-H	Alkyl-H
3	9.146 (s)	3.211 (t),1.79 (m),1.46 (m), 1.02 (t)
4	8.86 (s)	
5	8.88 (d), 8.82 (d)	3.07 (t), 1.92 (m), 1.08 (t)

The spectra of both reactions recorded at infinity revealed that the relative intensities of the aliphatic signals corresponding to butylamine and the aromatic protons of **4** were higher than expected. This is attributed to isotopic exchange of an aromatic proton with deuterium. A similar exchange has been reported for 1,3,5-trinitrobenzene[34] and 1,3-dinitrobenzene[35] in basic media. For the reaction of 1,3,5-trinitrobenzene with NaOD in D_2O/DMF, the exchange of an aromatic proton by deuterium was suggested as a competing pathway to the addition of DO^- to an unsubstituted ring position.[34] We could confirm that this exchange was taking place in our system because a decrease in the aromatic signal relative to the aliphatic signals of butylamine was observed in the spectra of a mixture of **4** and butylamine in 60% [D$_8$]dioxane/D_2O and 0.20 M NaOD recorded at different times.

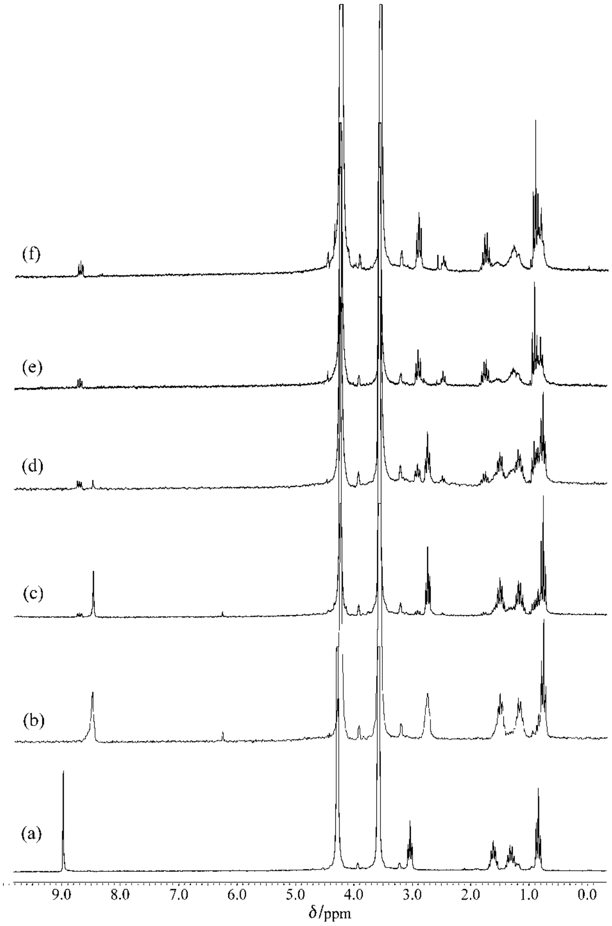

Figure 9. 200-MHz ^{1}H-NMR spectra of: (a) **3** (8.48×10^{-3} M) recorded in 60% [D$_8$]dioxane/D$_2$O at room temperature and at various times after the addition of 0.018 M NaOD: (b) *t* = 8 min, (c) *t* = 4 h, (d) *t* = 22 h, (e) *t* = 70 h, (f) at infinity.

Conclusions

The reaction of *N*-butyl-2,4,6-trinitroaniline (**3**) with NaOH depends strongly on the reaction media. Whereas in 10% 1,4-dioxane/H$_2$O the amino group is easily substituted to give 2,4,6-trinitrophenol (**4**) quantitatively, in 60% 1,4-dioxane/H$_2$O 5,7-dinitro-2-propyl-1*H*-benzimidazole 3-oxide (**5**) is formed along with **4** in yields that depend on NaOH concentration. This difference in behaviour is a consequence of a decrease in the rate constant of the hydrolysis reaction produced by the decrease in the polarity of the reaction media on going from 10 to 60% 1,4-dioxane/H$_2$O which is not accompanied by a similar change in the rate of *N*-oxide formation. In previous work we have shown that the observed rate constant for *N*-oxide formation from **1** at 0.2 M NaOH is 1.26×10^{-5} s^{-1} in 10% 1,4-dioxane/H$_2$O and 1.4×10^{-5} s^{-1} in 60% 1,4-dioxane/H$_2$O.[6]

The presence of σ complexes in the reaction media could be established by UV/Vis and ^{1}H NMR spectroscopy. The σ complex formed by the addition of one HO$^-$ ion to C3 of the aromatic ring provides a pathway to the phenol that competes with the substitution of the amino group with similar energetic requirements.

Our kinetic results for *N*-oxide formation in 60% 1,4-dioxane/H$_2$O can be explained on the basis of the mechanism previously proposed[6,9] provided that the rate-determining step is the cyclization of the *N*-alkylidene-2-nitrosoaniline-type intermediate.

Experimental Section

Materials: *N*-Butyl-2,4,6-trinitroaniline (**3**) and 5,7-dinitro-2-propyl-1*H*-benzimidazole 3-oxide (**5**) were available from previous work.[7]

1,4-Dioxane was purified as described previously.[3] Water purified in a Millipore Milli-Q apparatus was used throughout. All of the inorganic reagents were of analytical-reagent grade and were used without further purification. Methanol (HPLC grade) was used for HPLC analysis. The NaOH concentrations are expressed in terms of the total solvent volume (1,4-dioxane/H$_2$O).

UV spectra and kinetic measurements were measured with a Shimadzu UV-2101 PC spectrophotometer. An Applied Photophysics SF 17MV stopped-flow spectrofluorimeter was used to measure the fastest processes. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded with a Bruker ACE 200 instrument. Chemical shifts in 60% [D$_8$]1,4-dioxane/D$_2$O are referenced to the dioxane signal.

Thin-layer chromatography (TLC) was carried out using silica gel 60 F$_{254}$ (Merck) and the spots were visualized by UV light. Silica gel (60 mesh, 0.063–0.200 nm, Merck) was used for column chromatography.

Kinetic Procedures: Reactions were initiated by adding the substrate dissolved in 1,4-dioxane to a solution containing all the other constituents. The reaction temperature was 25 ± 0.01 °C and NaCl was used throughout as compensating electrolyte. For the reactions in 10% v/v 1,4-dioxane/H$_2$O the ionic strength was 1 M, whereas for those in 60% 1,4-dioxane/H$_2$O, it was 0.2 M.

All kinetic runs were carried out under pseudo-first-order conditions with substrate concentrations of about $(5–8)\times10^{-5}$ M. The slow process in 10% 1,4-dioxane/H$_2$O that leads to the quantitative formation of **4** was followed by measuring the increase in absorbance at 359 nm, the λ maxima of picrate ion. The spectra of the solutions at infinity were compared with solutions of **4** under the same reaction conditions.

The reactions in 60% 1,4-dioxane/H$_2$O were followed by measuring the decrease in absorbance of the reaction mixture at 435 nm, which is the wavelength maximum of the first species formed. The final spectra of the solutions at infinity were compared with solutions of authentic samples of **4** and **5** available from previous work[7] under the same reaction conditions. The yields of **4** and **5** were determined spectrophotometrically from the absorbance of solutions after around 10 half-lives by recording the absorbance in basic media at 320 and 376 nm. At 320 nm the extinction coefficients are 5583 and 12555 cm^{-1}M^{-1} for **4** and **5**, respectively, whereas at 376 nm the extinction coefficient for **4** is 16322 cm^{-1}M^{-1} and for **5** is 5227 cm^{-1}M^{-1}.

In a typical stopped-flow experiment, two solutions in 10 or 60% 1,4-dioxane/H$_2$O of twice the concentration required for the final solution were prepared; one of them contained the substrate and the other the nucleophile and NaCl. The reaction was initiated by mixing equal volumes of both solutions. All relaxation times represent average values from 15 determinations.

Reactions under N$_2$: The kinetics of the reactions in N$_2$ were studied by using the freeze-pump-thaw technique.[36] This procedure was carried out in two flasks, one containing **3** (7×10^{-5} M) in 1,4-dioxane and the other the rest of the constituents of the reaction mixture; both solutions were mixed under positive N_2 pressure.

For the reaction of **3** in 60% 1,4-dioxane/H_2O at reflux under N_2 the method previously described was used;[8] **3** (3.5×10^{-3} M) and NaOH (0.14 M) were refluxed until no substrate was detected by TLC. The reaction products **4** and **5** were isolated by column chromatography on silica gel by eluting with variable amounts of hexane/EtOAc and were identified by TLC by comparison with an authentic sample.

Acknowledgments

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