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AMINES AS LEAVING GROUPS IN NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS. III.* HYDROLYSIS OF 1-AMINO-2,4-DINITROBENZENES

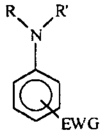
ELBA BUJÁN DE VARGAS,† M. VIRGINIA REMEDI AND RITA H. DE ROSSI†

Instituto de Investigaciones en Fisicoquimica de Córdoba, INFIQC, Departamento de Quimica Orgánica, Facultad de Ciencias Quimicas, Universidad Nacional de Córdoba. C.C. 61, Suc. 16, 5016 Córdoba, Argentina

The kinetic study of the reaction of 1-pyrrolidino-2,4-dinitrobenzene, 1-piperidino-2,4-dinitrobenzene and 1-morpholino-2,4-dinitrobenzene with NaOH in the presence and absence of the amine leaving group was carried out in aqueous solutions at 25 °C, giving 2,4-dinitrophenol as the only product. A mechanism involving the formation of σ complexes by addition of HO^- or the amine to the unsubstituted positions of the aromatic ring is proposed. These complexes were found to react faster than the original substrates.

INTRODUCTION

Although aromatic amines with general structure **1** are fairly resistant to elimination of the amino group, we have reported some special cases where the substitution of the amino group by a nucleophile is possible.[1–3] It seems that a low interaction of the nitrogen lone pair of electrons with the π system is necessary so that substitution of the amino group occurs.



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There are also several reports that deal with easy amine–amine exchange in 1-amino derivatives of 2,4-dinitronaphthalene, 2,4,6-trinitrobenzene and 2,4-dinitrobenzene in dimethyl sulphhoxide (DMSO).[4]

We have previously found that the addition of a nucleophile (HO^- or an amine) to C-3 of 1-piperidino-2,4-dinitrobenzene (**2**) or 1-morpholino-2,4-dinitrobenzene (**3**),[1] and the addition of one and two HO^- groups to C-3 and C-5 of 1-piperidino-2,4,6-trinitrobenzene (**4**) or 1-morpholino-2,4,6-trinitrobenzene (**5**),[2] activate the substitution of the amine by HO^-.

We report here our results regarding the reaction of 1-pyrrolidino-2,4-dinitrobenzene (**6**) with NaOH in water at 25 °C together with new results from the reactions of **2** and **3**.

RESULTS

1-Pyrrolidino-2,4-dinitrobenzene (6)

The reaction of **6** in water containing 2% dioxane at HO^- concentrations up to 1 M in the presence and absence of pyrrolidine leads quantitatively to the formation of 2,4-dinitrophenol, as evidenced by comparison of the product with a mock solution of 2,4-dinitrophenol. A good isosbestic point is obtained when the spectra of the solution are taken at different reaction times (Figure 1).

The observed rate constant, k_{obs}, was determined by measuring the disappearance of **6** at 387 nm and the values obtained can be fitted to an equation of third-order in $[HO^-]$ (Table 1, Figure 2):

$$k_{obs} = k_1[HO^-] + k_2[HO^-]^2 + k_3[HO^-]^3 \qquad (1)$$

In the presence of 0·2 M pyrrolidine, k_{obs} increases by as much as two orders of magnitude, showing the same dependence with $[HO^-]$ (Table 2, Figure 3) but with higher values of k_2 and k_3 (Table 3). At constant HO^- concentration, the reaction is linearly dependent on pyrrolidine concentration (Table 2).

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* For Part II, see Ref. 2.

† Authors for correspondence.

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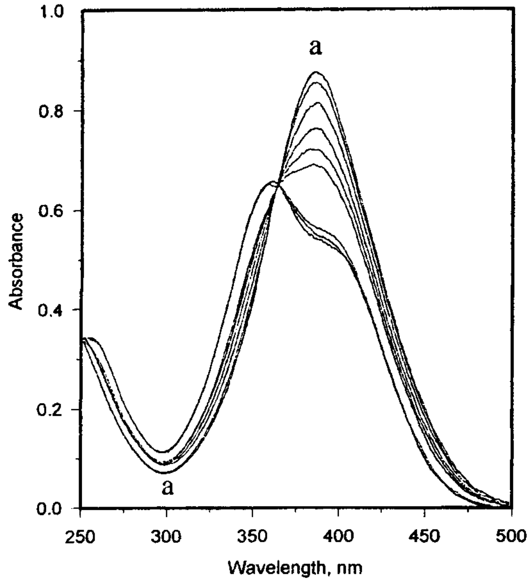


Figure 1. Absorbance of **6** in the presence of 0·81 M NaOH at different reaction times. $[\mathbf{6}]_0 = 4\times10^{-5}$ M. First cycle (a), 1 min. Total reaction time, 11 h

Table 1. Observed rate constants for the hydrolysis of 1-pyrrolidino-2,4-dinitrobenzene (**6**), 1-piperidino-2,4-dinitrobenzene (**2**) and 1-morpholino-2,4-dinitrobenzene (**3**) in water at 25 °C and dependence on hydroxide ion concentration

Substrate	[NaOH] (M)	10^5k_{obs} (s^{-1})
6	0·100	0·042
	0·200	0·146
	0·300	0·255
	0·391	0·410
	0·500	0·570
	0·601	0·770
	0·701	1·26
	0·794	1·74
	0·897	2·40
	0·939	2·56
	0·999	3·10
2	0·505	2·49
	0·697	5·10
	0·779	6·30
	0·902	8·90
	0·984	11·1
3	0·574	4·00
	0·697	5·90
	0·779	7·70
	0·820	8·80
	0·861	9·80
	0·902	11·0
	0·984	13·0

[a] Solvent contained 2% dioxane; ionic strength $\mu = 1$ M (NaCl); $[\text{substrate}]_0 = 4\times10^{-5}$ M.

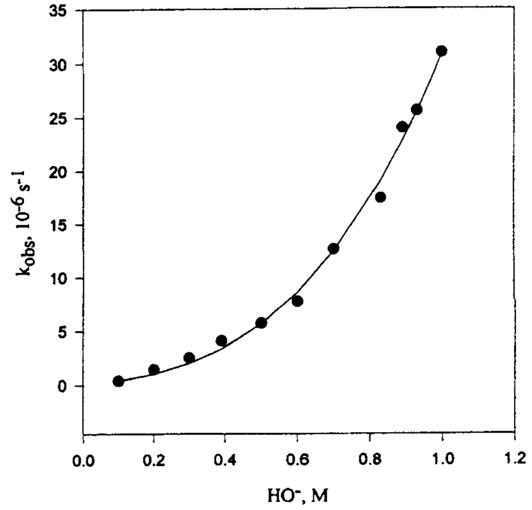


Figure 2. Plot of k_{obs} vs $[\text{HO}^-]$ for the formation of 2,4-dinitrophenol from **6** in the absence of pyrrolidine at 25 °C. Solvent, 2% dioxane–water

Table 2. Observed rate constants for the hydrolysis of 1-pyrrolidino-2,4-dinitrobenzene (**6**), 1-piperidino-2,4-dinitrobenzene (**2**) and 1-morpholino-2,4-dinitrobenzene (**3**) in water at 25 °C and dependence on hydroxide ion and amine concentrations[a]

Substrate	[NaOH] (M)	[Amine] (M)	10^4k_{obs} (s^{-1})
6	0·214	0·216	1·01
	0·197	0·473	1·56
	0·197	0·709	2·20
	0·197	0·946	2·94
	0·299	0·216	1·80
	0·384	0·216	3·20
	0·427	0·216	5·00
	0·598	0·216	8·40
	0·683	0·216	12·0
	0·810	0·216	17·1
	0·980	0·216	31·0
2	0·197	0·242	0·94
	0·197	0·324	1·42
	0·197	0·404	1·70
	0·197	0·485	1·74
	0·197	0·607	2·40
	0·400	0·240	3·34
	0·492	0·240	5·60
	0·656	0·240	11·4
	0·820	0·240	16·6
	0·980	0·240	29·4
3	0·197	0·228	2·40
	0·197	0·320	1·90
	0·197	0·411	2·40
	0·197	0·457	3·25
	0·197	0·823	5·40
	0·197	1·03	6·45
	0·492	0·228	7·00
	0·738	0·228	16·0
	0·902	0·228	31·0
	0·984	0·228	36·0

[a] Solvent contained 2% dioxane; $\mu = 1$ M (NaCl); $[\text{substrate}]_0 = 4\times10^{-5}$ M.

Table 3. Calculated values of the third-order coefficient of equation (1) for the reactions of compounds **2**, **3** and **6**

Coefficient	**6**	**2**	**3**
k_3 (in the presence of amine)	$(1{\cdot}9\pm0{\cdot}2)\times10^{-3}$	$(1{\cdot}9\pm0{\cdot}3)\times10^{-3}$	$(2{\cdot}6\pm0{\cdot}4)\times10^{-3}$
k_3 (without amine)	$(2{\cdot}3\pm0{\cdot}3)\times10^{-5}$	$(6{\cdot}1\pm0{\cdot}8)\times10^{-5}$	$(5{\cdot}2\pm0{\cdot}8)\times10^{-5}$

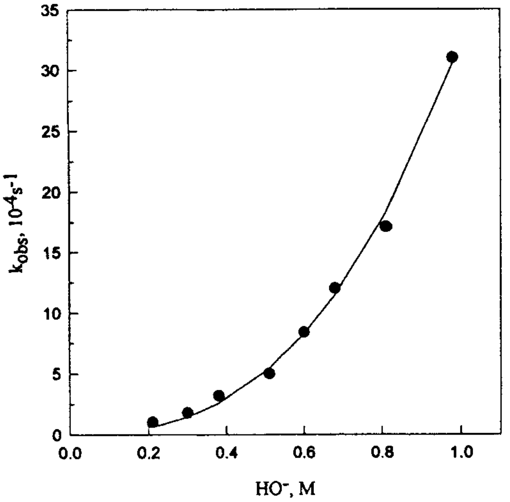


Figure 3. Plot of k_{obs} vs $[HO^-]$ for the formation of 2,4-dinitrophenol from **6** in the presence of 0·22 M pyrrolidine at 25 °C. Solvent, 2% dioxane–water

1-Piperidino-2,4-dinitrobenzene (2) and 1-morpholino-2,4-dinitrobenzene (3)

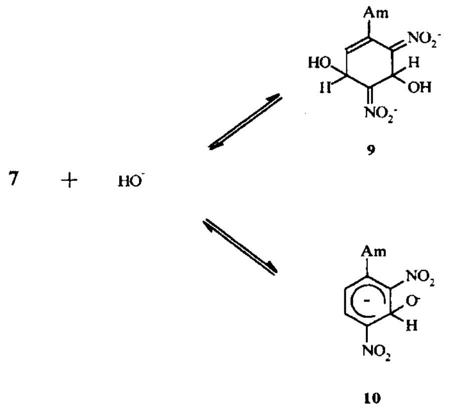
In order to compare the results for the hydrolysis of **6** with those of **2** and **3**, which were previously studied under the same conditions but at lower HO^- concentration (0·01–0·4 M), the reactions of these two substrates were studied at HO^- concentrations up to 1 M (Tables 1 and 2). The whole set of data can also be fitted by an equation of the form of (1).

DISCUSSION

We have previously suggested the mechanism in Scheme 1 for the hydrolysis of substrates **2** and **3**.[1] This mechanism takes account of the possibility of substitution of the amine (Am) within the 3-hydroxy σ complex **7** and the 3-amine σ complex **8**. Kinetic evidence for the substitution of other leaving groups (NO_2, MeO and Cl) within 1,3-σ complexes has been reported.[5,6]

The observed rate constant for this mechanism is in agreement with the experimentally determined rate law, provided that $K_1[HO^-]+K_{1A}[HO^-][Am]<1$, and we estimated that this was the case under the reaction conditions used. At the concentrations of HO^- used in this study, a term third order in HO^- is found. The coefficient of this term [k_3 in equation (1)] is different in the presence and absence of the amine, as can be seen in Table 3. There are two orders of magnitude difference between the values under the two sets of conditions.

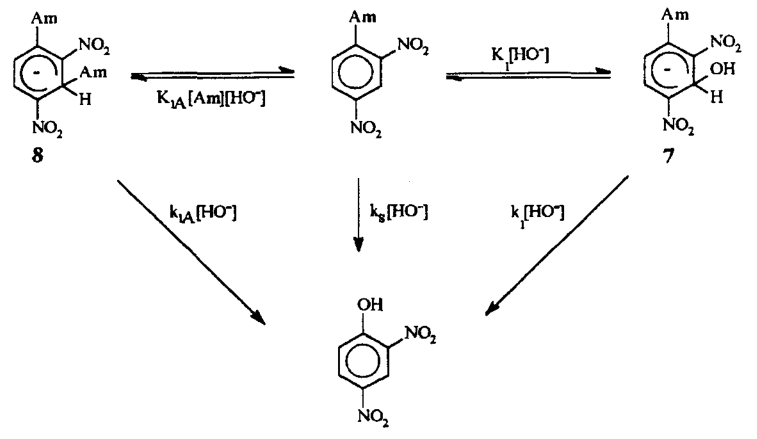
The third-order term in equation (1) could be accounted for by the formation of either complex **9** or **10**. The ionization of Meisenheimer complexes at high base concentration is known,[6–9] and based on those results we estimated that the equilibrium constant for reaction (2) should be <10 M^{-1}.



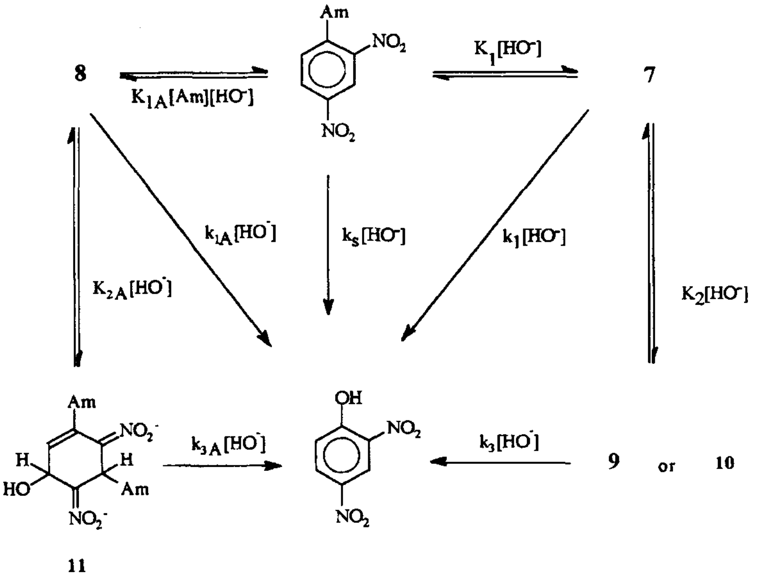
(2)

On the other hand, the equilibrium constant for the formation of **9** can be estimated to be 1 M^{-1}. This value is obtained considering the equilibrium constant for the addition of two HO^- groups to **4** namely $7{\cdot}5\times10^2$ M^{-1},[2] and taking into account the decrease in stability expected for a compound with one less nitro group as indicated below. Therefore, both compounds are expected to have similar stability and might be present under our reaction conditions. However, if **9** and **10** were fully responsible for the third-order coefficient in the rate law, it should be independent of the amine concentration, which is not the case. We therefore suggest the mechanism indicated in Scheme 2.

The formation of intermediate **11** requires one amine molecule and two HO^- and can account for the amine dependence of the k_3 term in equation (1).

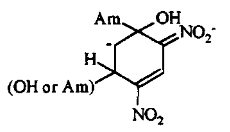


Scheme 1



Scheme 2

Addition of HO$^-$ to the substrate may occur also at position 5, but formation of the product from this intermediate is expected to be less favourable than for **7** or **8** because in the pathway to the products, intermediate **12** would form instead of **13**.



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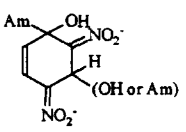

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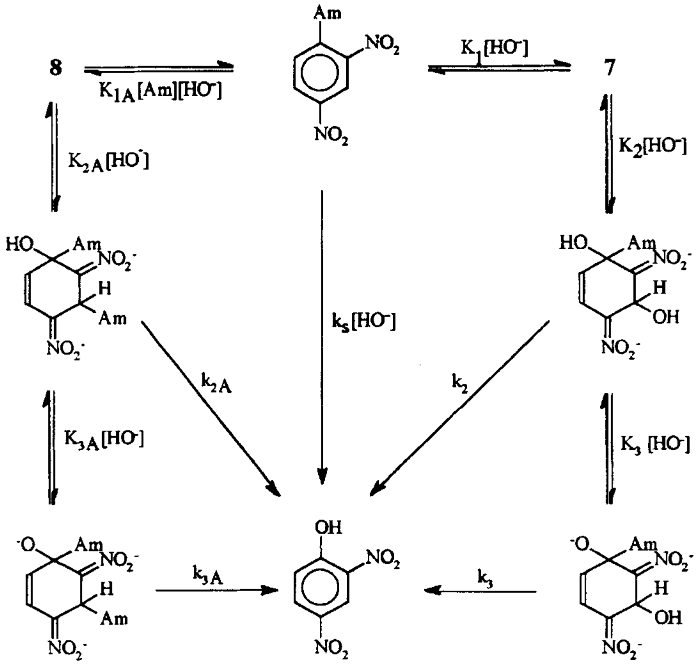
Another alternative which could explain the third-order term is shown in Scheme 3. The mechanisms in Schemes 2 and 3 are kinetically equivalent and the differences are that for Scheme 3 the third-order dependence is due to ionization of the OH group in the 1 : 2 σ complexes and that the rate-determining step is the leaving of the amine, whereas in Scheme 2 the amines may or may not be rate determining (see below).

Available data do not allow an easy differentiation of the two mechanisms, but we prefer that in Scheme 2 on the grounds that with substrates **4** and **5** we did not find evidence for the reaction pathway shown in Scheme 3.



Scheme 3

Further, the second- and third-order rate coefficients are similar for the three substrates and, if the leaving of the amines were rate determining, larger differences would be expected for these rate constants.

The observed rate constant for the mechanism shown in Scheme 2 is given by equation (3), provided that all the intermediates are present in very low concentration.

$$k_{obs} = k_s[HO^-] + (k_{1A}K_{1A}[Am] + k_1K_1)[HO^-]^2 + (K_{1A}K_{2A}k_{3A}[Am] + K_1K_2k_3)[HO^-]^3 \quad (3)$$

It was very difficult to fit the rate data and obtain good values for the coefficients of first, second and third order in HO^- concentration, because in most of the range studied the third-order term predominated, especially when amine was present. Therefore, we used the data at concentrations lower than 0·3 M to calculate k_s from the intercept of a plot of $k_{obs}/[HO^-]$ vs $[HO^-]$, and with this value and using a non-linear least-squares fit (calculations were carried out using the curve-fitting procedure of Sigmaplot[10]) we calculated the second- and third-order coefficients. The data without amine present provides the values of k_1K_1, and $K_1K_2k_3$, whereas the data in the presence of amine combined with those just mentioned provide the values of $K_{1A}k_{1A}$ and $K_{1A}K_{2A}k_{3A}$, which are given in Table 4.

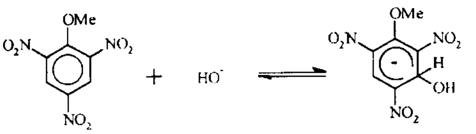
The values of the ratio $k_{1A}K_{1A}/K_1k_1$ are 909, 124 and 117 and those of $K_{1A}K_{2A}k_{3A}/K_1K_2k_3$ are 500, 152 and 176 for the reactions of **6**, **2** and **3**, respectively. The ratio K_{1A}/K_1 represents the stability ratio of the 1 : 1 σ complexes of the amine and HO^- with the substrate. The equilibrium constants for the addition of pyrrolidine and piperidine to trinitrobenzene have been measured[11] and also those for the addition of HO^- to the same compound.[12] The ratio of these equilibrium constants is 342 and 136 for pyrrolidine and piperidine, respectively, which are very similar to the values of the rate ratios $k_{1A}K_{1A}/K_1k_1$ and $K_{1A}K_{2A}k_{3A}/K_1K_2k_3$ for the catalysis by morpholine and piperidine, respectively, indicating that the reactivity of the intermediate 1,3-σ complexes is independent of the nucleophile bonded to C-3 as found previously.[1,2] The catalysis by the amine is relatively more efficient in the reactions of **6** than in those of **2** and **3**.

The ratios k_1K_1/k_s are 1·29, 9·43 and 4·17 for **6**, **2** and **3**, respectively. The value of $K_1 < 3 \times 10^{-2}$ can be estimated, considering the values of the equilibrium constant for the addition of HO^- to picryl piperidine, which is 19·6,[2] and the effect of removing one nitro group from the aromatic ring. This effect can be estimated from the values of K for equations (4) and (5).[12]

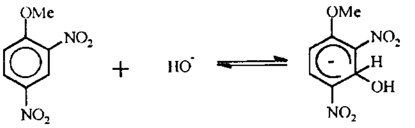
Table 4. Calculated rate constants for the hydrolysis of 1-pyrrolidino-2,4-dinitrobenzene (**6**), 1-piperidino-2,4-dinitrobenzene (**2**) and 1-morpholino-2,4-dinitrobenzene (**3**) in water at 25 °C

Parameter	**6**	**2**	**3**
$k_s \times 10^6$ ($\mathrm{M^{-1}\,s^{-1}}$)[a]	$3{\cdot}4 \pm 0{\cdot}4$	$5{\cdot}3 \pm 0{\cdot}5$	$12{\cdot}7 \pm 0{\cdot}6$
$k_1K_1 \times 10^5$ ($\mathrm{M^{-2}\,s^{-1}}$)[b]	$0{\cdot}44 \pm 0{\cdot}3$	$5{\cdot}0 \pm 0{\cdot}7$	$5{\cdot}3 \pm 0{\cdot}6$
$k_{1A}K_{1A} \times 10^3$ ($\mathrm{M^{-3}\,s^{-1}}$)[c]	4 ± 1	$6{\cdot}2 \pm 0{\cdot}2$	$6{\cdot}2 \pm 0{\cdot}5$
$K_{1A}K_{2A}k_{3A} \times 10^3$ ($\mathrm{M^{-4}\,s^{-1}}$)[c]	$11{\cdot}5 \pm 0{\cdot}9$	$9{\cdot}2 \pm 1{\cdot}4$	$13 \pm 0{\cdot}2$
$K_1K_2k_3 \times 10^5$ ($\mathrm{M^{-3}\,s^{-1}}$)[b]	$2{\cdot}3 \pm 0{\cdot}3$	$6{\cdot}0 \pm 0{\cdot}8$	$7{\cdot}4 \pm 0{\cdot}7$

[a] Calculated from data of $k_{obs}/\mathrm{HO^-}$ vs $[\mathrm{HO^-}]$ with data at $\mathrm{HO^-}$ concentrations lower than 0·25 M.
[b] Calculated from data of k_{obs} vs $\mathrm{HO^-}$.
[c] Calculated from data of k_{obs} vs $[\mathrm{HO^-}]$ in the presence of 0·2 M amine.



(in water) $K = 0{\cdot}83\ \mathrm{M^{-1}}$



(in 60% DMSO–water) $K = 1{\cdot}3 \times 10^{-3}\ \mathrm{M^{-1}}$

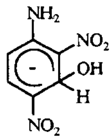
The value of K_1 (Scheme 2) is expected to be lower than the estimated value because the equilibrium constant for equation (5) has been determined in 60% DMSO–water and it is known that DMSO greatly stabilizes σ complexes.[7,8,13]

Considering the estimated value for K_1, it follows that the 1 : 1 σ complex is more than 300 times more reactive than the substrate itself. Similar results has been reported previously.[2,12]

We previously suggested that the increase in the rate of addition of $\mathrm{HO^-}$ to the 1,3-σ complex compared with the rate of addition of $\mathrm{HO^-}$ to the substrate may be due to the fact that in complexes **7** and **8** the nitrogen of the amino group is rotated out-of-plane in order to favour the planarity of the two nitro groups with the cyclohexadienyl ring.[1-3] To support this proposal, we carried out semi-empirical calculations using the AM1 method to determine the more stable conformation of substrates and intermediates.

The calculations indicated that for substrate **6**, the dihedral angle formed by the two rings of the molecule is 87·4°. The *o*-nitro group is also rotated out of the plane of the aromatic ring with an angle of 56·2°.

Owing to limited computer capacity we could not perform calculations of the structure of intermediates **7**, **9** and **10**; therefore, we used model compounds **14** and **15** and compared them with 2,4-dinitroaniline (**16**).



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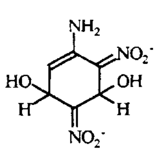

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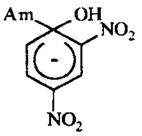
We found that the electronic density of C-1 decreases slightly in **14** compared with **16**, and the C-1—N distance is greater in **14** and **15** than in **16**. A decrease in the electronic density of C-1 in **7** compared with the substrate would facilitate the attack of a $\mathrm{HO^-}$ group in this position,in spite of the fact that complex **7** already has a negative charge. Besides, an increase in C-1—N bond length on formation of complexes **7**, **9** or **10** (or **11**) would favour the departure of the amine.

It should be noted that all the rate constants are quite similar for the three substrates; only k_1K_1 is approximately ten times smaller for **6** than for the other substrates. All the steps that lead to the product in Scheme 2 must involve the attack of $\mathrm{HO^-}$ to the carbon bearing the amine substituent and therefore the formation of intermediates **13**, **17** and **18**. Depending on the rate of bond rupture for C—N and C—O in intermediates **13**, **17** and **18**, the formation or decomposition of the intermediate should be rate determining.



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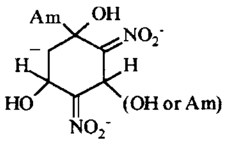
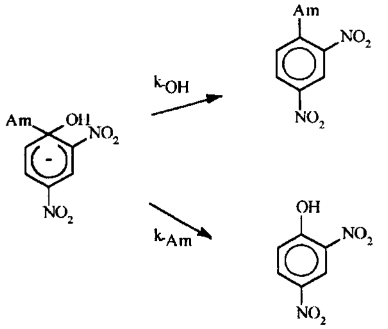


18

The reaction of 2,4-dinitrophenylphenyl ether with piperidine in 10% dioxane is catalysed by $\mathrm{HO^-}$,[14] whereas the same reaction with pyrrolidine is not;[15]

these reactivity differences were attributed to much higher ratios of the rate constants for leaving group expulsion from the σ complex intermediate for the reaction of pyrrolidine than for the piperidine derivative. The reactions to be compared in our system are shown in equation (6), and k_{-OH}/k_{-A} should be much higher for pyrrolidine than for piperidine or morpholine and therefore formation of the intermediate might be rate determining for the last two compounds and not for the former, and consequently the lower values of k_s and K_1k_1 found for **6** could be explained on this basis. However, all the other rates are similar for the three compounds and then the relative values of k_{-A} and k_{-OH} should be strongly dependent on whether the starting compound is 1 : 1 σ complex or the other highly charged intermediates.



(6)

CONCLUSIONS

The amines can be replaced by nucleophiles in the aromatic ring. The addition of a nucleophile to an unsubstituted position of the aromatic ring favours the displacement due to rotation of the amine group from the mean ring plane, which decreases the interaction of the nitrogen electron lone pair with the π system of the aromatic ring and so it increases the C—N bond length.

Higher concentrations of nucleophiles lead to highly charged σ complex intermediates by addition of nucleophiles to unsubstituted ring positions, which also react faster than the substrate itself.

EXPERIMENTAL

Materials. 1-Pyrrolidino-2,4-dinitrobenzene, m.p. 93–94 °C (lit.[4b] m.p. 101·5–102·5 °C), 1-piperidino-2,4-dinitrobenzene, m.p. 92–93 °C (lit.[14] m.p. 92–93 °C) and 1-morpholino-2,4-dinitrobenzene, m.p. 117–118 °C (lit.[16] m.p. 118 °C) were prepared by the method used previously.[17] The identity of 1-pyrrolidino-2,4-dinitrobenzene was confirmed by ^{1}H NMR (200 MHz, CCl_4), δ 2·058 (t, 4H), 3·344 (t, 4H), 6·900 (d, 1H), 8·188 (dd, 1H), 8·658 (d, 1H), and by ^{13}C NMR (200 MHz, $CDCl_3$), δ 25·57, 51·03, 115·46, 123·88, 127·56, 135·50, 143·53.

Dioxane was purified as described previously.[3a] Pyrrolidine was dried over KOH, refluxed for 24 h over sodium and distilled. Piperidine and morpholine were purified as before.[1]

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.

UV spectra were recorded on a Shimadzu UV-260 spectrophotometer and the change in absorbance during a kinetic run was measured on the same instrument and on a Beckman 24 spectrophotometer. NMR spectra were recorded on a Brucker ACE 200 instrument.

Kinetic procedures. Reactions were initiated by adding the substrate dissolved in dioxane to a solution containing all the other constituents. The total dioxane concentration was 2% in all reactions, the temperature was 25 °C and the ionic strength was 1 M. NaCl was used as compensating electrolyte.

All kinetic runs were carried out under pseudo-first-order conditions, with substrate concentrations of about 4×10^{-5} M.

In all cases the reactions were followed up to 90% conversion and good pseudo-first-order plots were obtained. Aliquots of the reaction mixture were taken at different times and made acidic with 3·7 M H_2SO_4 in 50% ethanol–water. The concentration of the substrate was then determined by reading the absorbance at the wavelength maximum of the particular substrate, that is, 387 nm for 1-pyrrolidino-2,4-dinitrobenzene, 400 nm for 1-piperidino-2,4-dinitrobenzene and 378 nm for 1-morpholino-2,4-dinitrobenzene.

The pseudo-first-order coefficient for the disappearance of the substrate, k_{obs}, was obtained from the slope of the plot of ln A_t vs time.

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