Solvent effects on aromatic nucleophilic substitution by the ANRORC mechanism. Hydrolysis of 2-chloro-3,5-dinitropyridine

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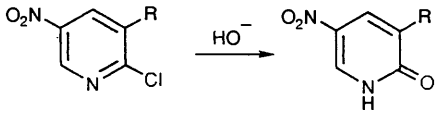
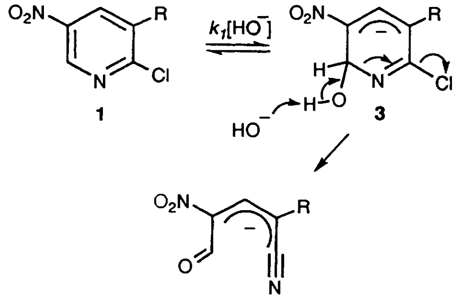
Added organic solvents (dimethyl sulfoxide is an exception) have opposite effects on the rates of formation and disappearance of the open-chain intermediate **4** (R = NO_2) involved in the hydrolysis of 2-chloro-3,5-dinitropyridine to the 2-pyridone by the nucleophilic ring-opening ring-closure mechanism. The ratio k_1/k_2 increases from 8 in water to over 1000 in 80% tetrahydrofuran at 25 °C and above. The effects are too complex to be analysed in terms of a single parameter, but an approach using the Kamlet–Taft solvatochromic parameters is applied successfully to six mixed aqueous solvent systems.

This paper reports solvent effects on the rates and thermodynamic activation parameters of the deceptively simple alkaline hydrolysis of 2-chloro-3,5-dinitropyridine ($\mathbf{1} \longrightarrow \mathbf{2}$, R = NO_2). The base-catalysed hydrolysis of the mono-nitro derivative 2-chloro-5-nitropyridine (**1**, R = H) to the pyridone (**2**, R = H) is thought to involve a complex mechanism involving ring-opening and subsequent ring-closure.[1,2] Hydroxide adds first to the unsubstituted 6-position to give an intermediate (**3**, R = H) which rapidly fragments to give the delocalised anion (**4**, R = H). This is long-lived in the absence of an excess of hydroxide. It has been isolated from the reaction in aqueous dimethyl formamide, and characterised spectroscopically both in solution[1] and as a yellow solid.[2] The mechanism gains further support from the observation[3] that the ammonolysis of **1** (R = H) with $^{15}NH_3$ leads to 2-amino-5-nitropyridine with extensive incorporation of the labelled nitrogen in the ring: a result which can only reasonably be explained by the S_N(ANRORC)[4,5] mechanism.

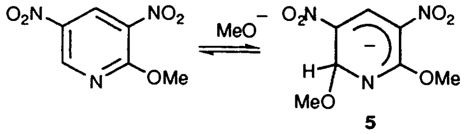


1 **2**



1 **3** **4**

The same mechanism may be expected to account for the hydrolysis of 2-chloro-3,5-dinitropyridine (**1**, R = NO_2). At UV concentrations (*ca.* 5 × 10^{-5} mol dm^{-3}), in aqueous solutions containing low concentrations (typically 10^{-3} mol dm^{-3}) of NaOH, we observe a strong yellow colour (λ_{max} 426 nm), which appears rapidly, then disappears relatively slowly. This is evidently the delocalised anion **4** (R = NO_2). It cannot be a Meisenheimer complex (**3**), at high dilution in a hydroxylic solvent. For comparison, the methoxide adduct from 2-methoxy-3,5-dinitropyridine (shown to have structure **5**, and not subject to the further reaction corresponding to $\mathbf{3} \longrightarrow \mathbf{5}$) has λ_{max} 455 nm and is not very stable in methanol (equilibrium constant of only 1.9 dm^3 mol^{-1}).[6] The 426 nm chromophore observed in the present work is formed from **1** (R = NO_2) from 8 to over 1000 times faster than it disappears under the standard conditions, so the consecutive reactions can be followed separately. Both are of the first order in both substrate and [HO^-], and we have measured rate constants for both processes under standard, pseudo-first order conditions, at a range of temperatures in mixed aqueous solvents. The results are summarised in the Figures and the Table.



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Discussion

The general effect of the addition of polar organic solvent on the rate of formation of the presumed intermediate **4** (R = NO_2) is to increase k_1 (Fig. 1). This is consistent with a transition state in which charge is more delocalised than in the ground state, and is the usual effect of polar aprotic solvents on nucleophilic substitutions of aromatic nitro-compounds,[7] in which the initial, addition, step is rate determining. The rate determining step in the formation of the presumed intermediate **4** (R = NO_2) is also presumed to be the addition of hydroxide to the aromatic ring, since the fragmentation of the dianion produced by the deprotonation of **3**, or the concerted base-catalysed fragmentation shown (**3**), would be second order in hydroxide concentration. Consistent with this conclusion is the entropy of activation, in the region of 100 J K^{-1} mol^{-1}, as expected for a bimolecular reaction; and a second order rate constant similar [actually less than twice as large (Table 1)] to that for the addition of hydroxide to the 2-position of 3,5-dinitropyridine (calculated to be 33.5 dm^3 mol^{-1} s^{-1} at 25 °C from the data of Chatrousse and Terrier).[8]

The disappearance of the intermediate (**4**) with the chromophore at 426 nm is of particular interest. **4** (R = NO_2), with two nitro-groups, reacts with hydroxide (~ 15 dm^3 mol^{-1} s^{-1} at 40 °C) some 260 times faster than the mono-nitro

Table 1 First-order rate constants for the appearance and disappearance at 25 °C of intermediate **4** (R = NO_2) in water and 50% mixed aqueous solvents containing 0.001 mol dm^{-3} NaOH

	Appearance (k_1)			Disappearance (k_2)			
Solvent	$k_1/10^2\ s^{-1}$	$\Delta H^‡$/ kJ mol^{-1}	$-\Delta S^{‡a}$/ J K^{-1} mol^{-1}	$k_2/10^4\ s^{-1}$	$\Delta H^‡$/ kJ mol^{-1}	$-\Delta S^{‡a}$/ J K^{-1} mol^{-1}	k_1/k_2
Water	5.63	38.8 ± 0.6	81 ± 2	68.2	44.7 ± 0.5	79 ± 2	8.25
EtOH aq.	8.49	35.0 ± 3.6	91 ± 12	58.7	38.7 ± 1.4	101 ± 5	14.5
DMSO aq.	31.1	27.7 ± 0.8	105 ± 3	130	39.0 ± 0.9	93 ± 3	23.9
Acetone aq.	20.6	28.5 ± 2.5	106 ± 9	12.6	35.2 ± 1.6	126 ± 5	127
Dioxan aq.	17.9	30.9 ± 3.5	99 ± 12	7.11	37.7 ± 4.0	122 ± 13	151
MeCN aq.	5.80	31.4 ± 6.7	106 ± 22	3.64	37.0 ± 3.6	129 ± 12	157
THF aq.	28.8	22.3 ± 3.7	124 ± 12	4.30	16.2 ± 3.0	198 ± 10	670

[a] Entropies of activation are calculated at 298 K using second-order rate constants measured at six different temperatures between 15 and 40 °C. (Rate constants are based on [NaOH] = 0.001 mol dm^{-3} and not corrected for the maximum of 5% of base consumed in step 1.) Second-order rate constants, obtained from measurements at six different NaOH concentrations between 2×10^{-4} and 2×10^{-3} mol dm^{-3} in water at 25 °C were: $k_1 = 61 \pm 1.2$ and $k_2 = 10.1 \pm 0.8$ dm^3 mol^{-1} s^{-1}.

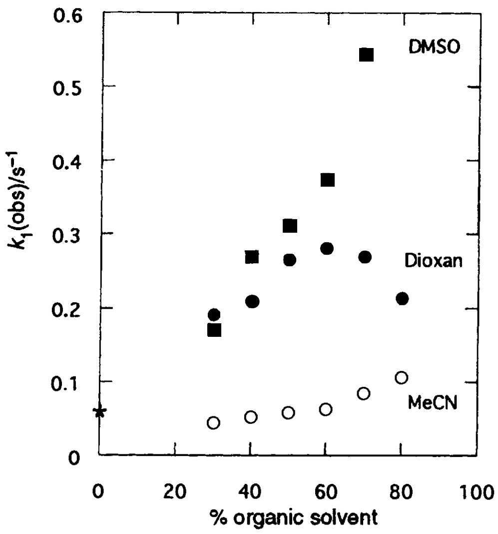


Fig. 1 Variation of the observed pseudo first-order rate constants k_1 for the appearance of the intermediate **4** (R = NO_2), as a function of the percentage of organic solvent in the mixed aqueous medium. Organic component as indicated. For solvents not shown: acetone behaves qualitatively like dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) like dioxan, and up to 80% of ethanol has little effect. Initial concentrations: substrate (**1**, R = NO_2) *ca.* 5×10^{-5}; NaOH 10^{-3} mol dm^{-3}.

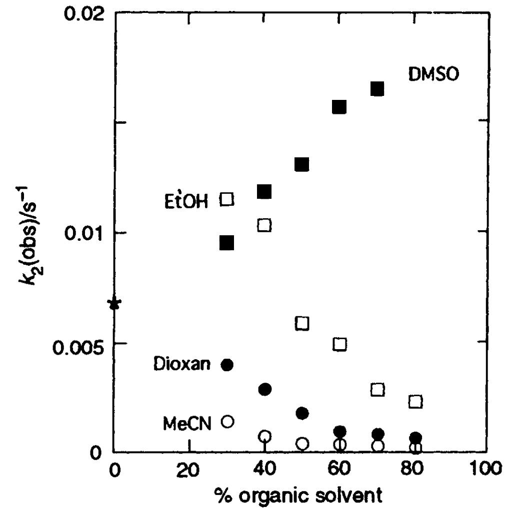
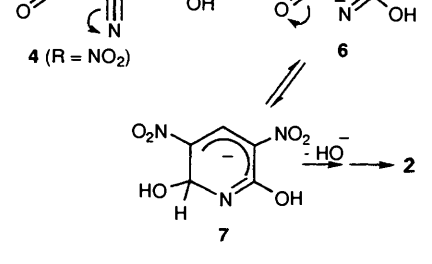


Fig. 2 Variation of the observed pseudo first-order rate constants k_2 for the disappearance of the intermediate **4** (R = NO_2), as a function of the percentage of organic solvent in the mixed aqueous medium. Organic component as indicated. For solvents not shown: acetone behaves qualitatively like dioxan, tetrahydrofuran (THF) like MeCN. For conditions see caption to Fig. 1.

derivative **4**, R = H (5.7×10^{-2} dm^3 mol^{-1} s^{-1} at 38 °C, ref. 1). The reaction[1,2] must involve the addition of hydroxide to the nitrile group of the delocalised anion (**4**). This step may be presumed to be rate determining, since the hydration of a nitrile is not reversible under basic conditions. The subsequent intramolecular cyclisation of the initial product (**6**) involves bond formation between two reactive centres in close proximity, and is a favourable pericyclic process. The net result of the addition of hydroxide ion to **4** (R = NO_2) is some further delocalisation of negative charge. However, the observed effect of increasing concentrations of organic solvent is in most cases a monotonic decrease in the rate of disappearance of **4** (R = NO_2: Fig. 2), paralleling the observations of Reinheimer *et al.*,[1] who also observed that the rate of disappearance of their intermediate **4** (R = H) was reduced when 40–60% of four organic solvents was added to the aqueous reaction solution. Exceptions are the reaction in aqueous ethanol, which is faster at low (30–40%) proportions of the organic solvent (Fig. 2), and shows a rate maximum at about 30% ethanol before the usual decrease in rate sets in: and dimethyl sulfoxide, which effects a monotonic increase in rate with increasing concentration. This effect is smaller than on the rate of formation of **4** (R = NO_2), and could be simply explained in terms of the competing effects of the organic cosolvent, stabilising the delocalised intermediate but increasing the activity of the hydroxide ion. In the case of dimethyl sulfoxide the latter effect wins for **4** (R = NO_2), though not for **4** (R = H, less extensive delocalisation), which reacts more slowly in the presence of



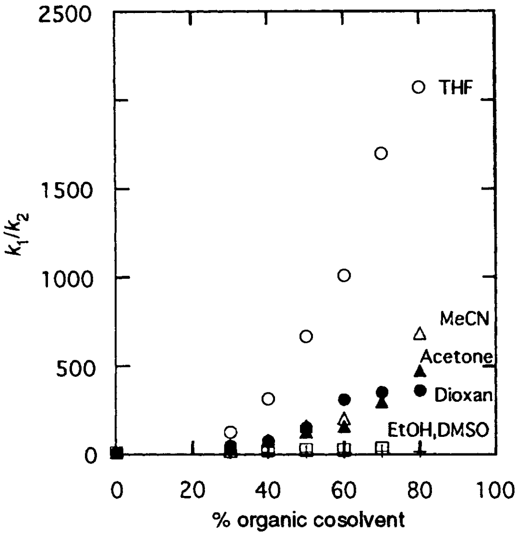


Fig. 3 Effect of varying the percentage (v/v) of organic solvent in the mixed aqueous medium on the ratio of rate constants k_1/k_2 for the formation and disappearance of the intermediate **4** (R = NO_2). Organic component as indicated: the ratio for DMSO (open squares) increases by a factor of less than two up to 70% of the organic component. The data are from Supplementary Tables S1–S7.

added dimethyl sulfoxide.[1] This interpretation is reasonable, but an over-simplification, as discussed below.

The generally opposite effects of added organic cosolvent, stabilising the intermediate **4** (R = NO_2) and thus increasing its rate of formation but slowing its disappearance, result in substantial increases in the ratio k_1/k_2: from 8.25 in water to over 1000 in 80% tetrahydrofuran at 25 °C and above (Fig. 3). Parallel modest decreases in $\Delta H^‡$ for both steps with increasing concentration of organic cosolvent are offset by compensating decreases in $\Delta S^‡$ (Table 1). These trends are exaggerated for tetrahydrofuran, to the point that the enthalpy of activation is actually smaller for the slower k_2 step. In compensation the entropy of activation is in this case extraordinarily large, at almost 200 J K^{-1} mol^{-1}: presumably reflecting specific solvation by the water in the mixed solvent of the intermediate **4** (R = NO_2), which has no less than six electronegative centres to be solvated.

Multiparameter analysis

The dependence on the composition of the aqueous solvent of the rates of the two reactions studied in this work is clearly too complex to be interpreted in terms of any single solvent parameter, such as the relative permittivity or Reichardt's $E_T(30)$.[9] Thus, dimethyl sulfoxide (DMSO), with the highest relative permittivity of the organic solvents used, is the most effective in increasing the rates of both reactions; but next most effective for k_1 are the least polar, ether solvents dioxan and tetrahydrofuran (THF), with ethanol the least effective: whereas for k_2 the order is reversed, with low concentrations of ethanol as effective as DMSO, while THF slows the reaction down. Thus only a multiparameter approach is likely to allow any sort of analysis of the data.

Since both reactions involve hydroxide ion as a reagent, and the starting material is heteroaromatic we expect both the hydrogen bonding capability and the polarisability of the medium to be relevant. We obtain reasonable correlations of our data in the solvent mixtures with Kamlet and Taft's solvatochromic parameters α, β and π* for the organic component.[9,10] These parameters, hydrogen bonding donor (HBD) capacity α, hydrogen bonding acceptor (HBA) capacity β, and solvent dipolarity and polarisability π*, specifically allow for these properties of the solvent, and are appropriate for the reactions under discussion because they are based on the properties (solvent shifts in the UV and visible spectra) of aromatic nitro compounds. They are not however available for the solvent mixtures used in this work. So we use the parameters for the pure organic solvent.

Multiple linear regression performed on the data for the binary mixtures containing the highest proportion of organic cosolvent (80% v/v) gives the following correlations (for six data sets in each case):

$$\log k_1 = -(0.95 \pm 0.22)\alpha + (0.24 \pm 0.47)\beta + (1.07 \pm 0.47)\pi^* - (1.40 \pm 0.47)$$

$$\log k_2 = (0.37 \pm 0.47)\alpha + (2.26 \pm 0.99)\beta + (2.90 \pm 1.03)\pi^* - (6.25 \pm 1.00)$$

The same analysis was carried out on the data for all the other solvent mixtures, with the following, encouraging results. (*i*) The two smallest coefficients, both of which are smaller than their standard deviations in the correlations above, do not change significantly as the proportion of water in the mixed solvent is increased. This is some confirmation that the parameters concerned, hydrogen bonding acceptor (HBA) capacity, β, and hydrogen bonding donor (HBD) capacity, α, are not significant for k_1 and k_2, respectively. (*ii*) The two largest coefficients fall in each case with decreasing proportions of the organic component, as would be expected, to become negligible in pure water. (*iii*) This decrease is close to linear in %H_2O added, so allows a crude extrapolation of the coefficients to 100% organic solvent. The results of this extrapolation are as follows (the absolute magnitudes of the coefficients are not important for the present discussion, but are of interest for comparisons with other reactions).

$$\log k_1 = -(1.17 \pm 0.04)\alpha + (1.48 \pm 0.13)\pi^*$$
(R 0.987 and 0.979, respectively)

$$\log k_2 = (2.72 \pm 0.21)\beta + (3.99 \pm 0.14)\pi^*$$
(R 0.937 and 0.994, respectively)

These correlations allow a more focused insight into the effects of solvent on the reactions of **1** and **4** with hydroxide. It is not unexpected that the hydrogen bonding acceptor capacity (β) of the solvent is unimportant for k_1, since the reactants and products are themselves bases. The signs and magnitudes of the two remaining coefficients indicate that the two major factors recognised above, desolvation of the hydroxide nucleophile (which depends primarily on the HBD capacity of the solvent) and stabilisation of the delocalised π-system of the transition state, are of comparable importance.

The parameters for k_2 are more intriguing. Clearly dominant is the large positive dependence on the dipolarity/polarisability parameter π*: this is expected since the transition state for the formation of the dianion **6** involves extensive delocalisation of the two full negative charges. The absence of a significant dependence on the HBD parameter α is at first sight surprising for any reaction involving the hydroxide ion; but this is simply explained if hydrogen-bonding stabilisation of the two reacting anions and of the doubly-charged transition state are comparable.

Most unexpected, in view of the absence of any effect on k_1, is the substantial positive dependence on the hydrogen-bond acceptor parameter β: increasing the basicity of the solvent strongly favours the k_2 reaction, though neither reactants nor transition state are expected to be important H-bond donors. A possible explanation in these mixed solvent systems is solvent–solvent interactions: selective (hydrogen-bonding) solvation of the more localised reactant anions by the water in the solvent mixture will be reduced by competition from good HBA solvents. It is not clear, however, why this effect should be so large when the direct effect of HBD solvation is negligible. Perhaps more likely is a less specific destabilisation of localised anions by more basic solvents: such an effect would be expected to overlap with dipolarity/polarisability effects, and to be observed only where there is—as here—a large dependence on π^*.

Experimental

2-Chloro-3,5-dinitropyridine, and the solvents used in the kinetic studies, were of reagent grade, and obtained from Aldrich Co. Solvent mixtures were prepared by making up a measured volume (20–80 ml) of distilled deionised water to 100 ml with the organic component.

Rate constants were measured in the thermostatted cell compartment of a Perkin-Elmer 330 UV-VIS spectrophotometer, as previously described.[11] Repetitive scans of reaction mixtures showed the appearance and subsequent disappearance of a single intermediate absorbing at 426 nm. The rates of the two consecutive reactions were always different enough for them to be followed independently at the wavelength corresponding to λ_{max} for the intermediate and good pseudo-first order kinetics were observed. (That the first stage was effectively complete before the second began was shown by the maximum in the absorbance at 426 nm, which was independent of $[OH^-]$.) Most of the (over 430) reactions were run at a fixed concentration (10^{-3} mol dm^{-3}) of NaOH: in water the reaction was accurately first order in NaOH, with k_1 and k_2 61.0 ± 1.2 and 10.1 ± 0.8 dm^3 mol^{-1} s^{-1}, respectively (from five runs at [NaOH] from 2×10^{-4} to 2×10^{-3} mol dm^{-3}). At high NaOH concentrations the reactions became too fast to follow manually. (We saw no sign of the green colour noted by Murto.[12]) The spectrum of the product was identical with that of 3,5-dinitro-2-pyridone. No 2-ethoxy-3,5-dinitropyridine product was observed in the ethanol–water mixtures, nor would any be expected: the ANRORC reaction is significantly faster than the ordinary S_NAr reaction, but is not possible when ethoxide is the nucleophile. Kamlet–Taft solvatochromic parameters α, β and π^* were taken from the compilation of Reichardt.[9] Multiple linear regressions were performed using the GraFit program: details appear in the Supplementary Data.[†,13]

Acknowledgements

H. Al-H. is grateful to the British Council, Riyadh for support under their Postdoctoral Summer Research Programme, sponsored by British Aerospace. We thank also Professor J. B. F. N. Engberts for helpful discussions, and Claus Beckmann for performing the multiple linear regressions.

[†] The Supplementary Data contain tables of observed rate constants and coefficients of multiple linear regression analysis, and have been deposited under the Supplementary Publications Scheme. For details of the scheme, see 'Instructions for Authors (1995)', *J. Chem. Soc., Perkin Trans. 2*, 1995, issue 1 [Supp. Pub. No. 57091 (9 pp.)].

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Paper 5/01475A
Received 9th *March* 1995
Accepted 22nd *March* 1995