The Nucleophilic Catalysed Decomposition of *N*-Methyl-*N*-nitroamides in Aqueous Buffers

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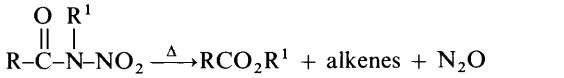
Rate constants for the decomposition of *N*-nitro-*N*-methylamides to *N*-nitro-*N*-methylamine and the corresponding carboxylic acid in aqueous buffer solutions are reported. For *N*-nitro-*N*-methylacetamide (**1a**) and *N*-nitro-*N*-methylbenzamide (**1b**), the pH-rate profiles indicate that below pH 5 the reaction is independent of $[H^+]$. At pH values >7 the reactions are strongly HO^- catalysed. Moreover, the basic component of the buffer also catalyses the decomposition reaction. Second-order rate constants, k_B, for this buffer catalysis are dependent on the structure of the base. Thus Brønsted plots of $\log k_B$ *versus* base pK_a for (**1a**) and (**1b**) yield slopes of 0.64 and 0.60, respectively, for nitrogen bases. The oxygen bases AcO^-, HPO_4^{2-} and HO^- appear to fall on another line of slope *ca.* 0.5. Solvent deuterium kinetic isotope effects for both the AcO^- and HO^- catalysed reactions are *ca.* 1, whereas that for the non-catalysed reaction is *ca.* 2. Catalysis is found to be nucleophilic in nature; thus, for each of the reactions of (**1b**) with morpholine, piperidine and 4-chlorophenol the corresponding benzoylated base could be isolated. Further, the observed first-order rate constants for the reaction of either (**1a**) or (**1b**) with imidazole reach a limiting value identical to that for *N*-acetylimidazole itself. For (**1a**), the ratios of k_B for piperidine to 2,2',6,6'-tetramethylpiperidine and for pyridine to acetate are *ca.* 300 and 100, respectively. Again, this is consistent with nucleophilic catalysis. The aromatic substituent effect for the HO^- catalysed reaction yields a Hammett ρ value +2.8, whereas for the non-catalysed reaction a value of 0.8 is obtained. The data are discussed in terms of a mechanism in which nucleophilic attack of the catalyst at the carbonyl C-atom to form a tetrahedral intermediate is rate-limiting. Lack of ^{18}O-exchange during hydrolysis is consistent with this proposal. This mechanism is unusual for amide hydrolysis and must reflect the enhanced nucleofugacity of the *N*-nitroamine fragment. The mechanism of the non-catalysed process is less clear. The substituent effects are much smaller than those for HO^-, and therefore unlikely to involve attack of H_2O at the carbonyl carbon. *N*-Methyl cleavage *via* H_2O attack or thermal rearrangement are possible candidates.

It is well known that carboxylic acid amides hydrolyse in aqueous solutions, giving the parent carboxylic acids and amines. The process involves the formation of a tetrahedral intermediate, which subsequently decomposes to products in a rate-limiting step that is subject to general acid-base catalysis.[1,2] However, amides with good leaving groups, *e.g.* *N*-acetylimidazolium ion and 1-acetyl-3-methylimidazolium ion, are known to decompose by a nucleophilic catalysed pathway.[2] Such a process has also been demonstrated for *N*-nitroso-2-pyrrolidone,[3] in which the presence of the *N*-nitroso group increases the leaving ability of the amino fragment, favouring nucleophilic catalysis.

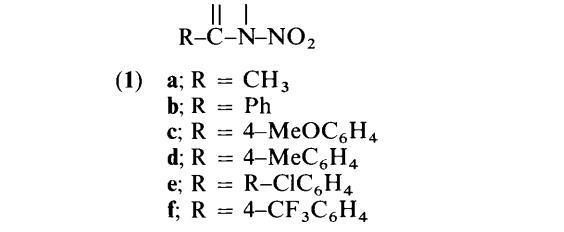
N-Nitroamides (**1**) are another type of amide in which cleavage of the C–N bond should be facilitated by the presence of a good leaving group. Garcia *et al.*,[4] have reported that the reaction of *N*-alkyl-*N*-nitroamides with amines in organic solvents yields amide products that result from the nucleophilic attack by the amine on the carbonyl group, followed by elimination of an *N*-nitroalkylamine. This process was observed even with weak nucleophiles such as anilines, implying that the *N*-nitro group also increases the electron deficiency of the amide carbonyl C-atom and promotes attack by nucleophiles. *N*-Nitroamides are also thermally labile and undergo pyrolysis with the expulsion of N_2O (Scheme 1) on heating, usually in



Scheme 1.

organic solvents.[5] White and Field[6] proposed a mechanism for these reactions involving ion-pair intermediates analogous to those for the thermal decomposition of *N*-nitrosamides.

To assess the susceptibility of *N*-nitroamides to nucleophilic reagents by either catalysed or thermal pathways, we have



(**1**) **a**; R = CH_3
b; R = Ph
c; R = 4-$MeOC_6H_4$
d; R = 4-MeC_6H_4
e; R = R-ClC_6H_4
f; R = 4-$CF_3C_6H_4$

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examined the hydrolysis of some *N*-methyl-*N*-nitroamides (**1**) both in aqueous buffers and in the presence of several base catalysts.

Experimental

Substrates and Reagents.—The *N*-methyl-*N*-nitroamides were prepared by known methods.[7–10] Carbonyl ^{18}O-labelled *N*-methyl-*N*-nitrobenzamide was prepared by nitration (with acetic anhydride/nitric acid) of ^{18}O-labelled *N*-methylbenzamide,[9] which was itself obtained by reaction of *N*-methylbenzimidoyl chloride with $H_2{}^{18}O$.

Analar CH_3COOH, CH_3COONa, Na_2HPO_4, $Na_2B_4O_7$, NaCl, $NaClO_4$, and $HClO_4$ were used without further purification, other than vacuum drying where appropriate. Pyridine, *N*-methylimidazole, morpholine, piperidine and 2,2′,6,6′-tetramethylpiperidine were vacuum distilled from KOH and then kept at −20 °C. Imidazole and *N*-acetylimidazole were recrystallised from benzene, 4-chlorophenol was recrystallised from light petroleum (60–80 °C) and all were vacuum dried. NaOH and HCl were BDH volumetric solutions.

Kinetics.—The hydrolysis of the *N*-nitroamides was generally followed by monitoring the decrease in u.v. absorbance of the substrate, at an appropriate wavelength, using Pye-Unicam SP1800 or SP8-500 spectrophotometers. Reactions were monitored continuously in thermostatted cells for *ca.* 10 half-lives to obtain accurate infinity readings and, except in the presence of imidazole (see below), good isobestic points were obtained. At the conclusion of each experiment the pH of the reaction was measured. In deuteriated solvents, values were calculated from the expression pD = pH + 0.4.[11] In all of the experiments the ionic strength was maintained at 0.75 mol dm^{-3} by addition of $NaClO_4$ or NaCl. The majority of the experiments were carried out at 25 ± 0.1 °C.

Reactions that were too fast to follow using conventional u.v. spectrophotometers were monitored using a High Tech Stopped Flow instrument and the output was fed directly into a Digital MINC minicomputer. For solubility reasons, reaction solutions used in these experiments contained 10% dioxane.

$$\text{Rate} = k_0[N\text{-Nitroamide}] \quad (1)$$

Pseudo first-order rate coefficients [equation (1)] were obtained from the slopes of plots ln $(A_t - A_\infty)$ *versus* time, where A_t, and A_∞ are the absorbance at time t and infinity, respectively; they were reproducible to ±13%. Values of k_2 [equation (2)] were obtained from plots of k_0 *versus* [Catalyst], where [Catalyst] refers to the concentration of the unprotonated base present, calculated from the experimental pH of the reaction solution and the catalyst pK_a.

$$\text{Rate} = k_2[\text{Substrate}][\text{Catalyst}] \quad (2)$$

Product Analysis.—Benzoic acid and *N*-methyl-*N*-nitroamine were isolated by extraction from large scale hydrolysis reactions of *N*-methyl-*N*-nitrobenzamide (**1b**) in phosphate buffer. When morpholine, piperidine or 4-chlorophenol were present, *N*-benzoylmorpholine, *N*-benzoylpiperidine and 4-chlorophenyl benzoate, respectively, were also isolated from the reaction mixture.

^{18}O *Exchange Experiments.*—Phosphate buffer (20 cm^3, KH_2PO_4 0.5 mol dm^{-3}, NaOH 0.375 mol dm^{-3}, NaCl 2.5 mol dm^{-3}) was added to a solution of carbonyl ^{18}O-labelled *N*-methyl-*N*-nitrobenzamide (0.09 g) in dioxane (10 cm^3) and made up to 100 cm^3 with water. Starting material was extracted using diethyl ether from aliquots of the reaction solution at timed intervals. In another experiment, the reaction was allowed to go to completion, acidified (H_2SO_4) and then extracted with diethyl ether. For both experiments, the ether extracts were dried, evaporated, and the residue, after recrystallization from light petroleum, was analysed for ^{18}O-content by mass spectrometry. There was no loss of ^{18}O from the starting material during reaction and the product of hydrolysis was found to be ^{18}O labelled benzoic acid with the same percentage of incorporation as the starting material.

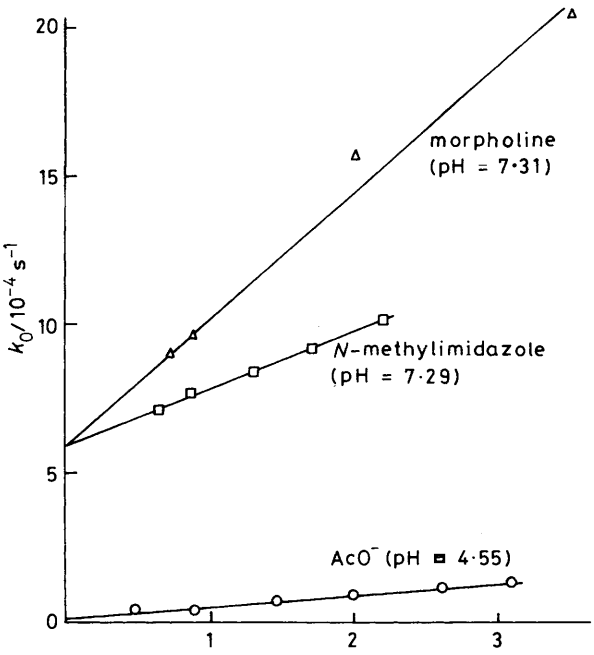


Figure 1. Hydrolysis of (**1a**) catalysed by various bases at 25 °C. [base]: × 10 for AcO^-, × 10^4 for *N*-methylimidazole, × 10^5 for morpholine.

Results and Discussion

Hydrolysis rates for the conversion of *N*-methyl-*N*-nitroamides (**1**) to the corresponding carboxylic acid and *N*-methyl-*N*-nitroamine (Scheme 2) were determined in various aqueous buffers

$$\text{R–C(=O)–N(Me)–NO}_2 + \text{H}_2\text{O} \longrightarrow \text{R–CO}_2\text{H} + \text{MeNHNO}_2$$

Scheme 2.

(acetate, phosphate, borate) and in the presence of several potential catalysts which had been added to the aqueous buffer solution. Thus, pyridine, imidazole and *N*-methylimidazole were studied in phosphate buffer, and morpholine, 4-chlorophenol, piperdine and 2,2′,6,6′-tetramethylpiperidine in borate buffer. This allowed the use of small amounts of powerful catalysts and avoided u.v. interference. Good linear correlations were found between values of the *pseudo* first-order rate coefficient (k_0) and the concentration of either the base component of the buffer system or the unprotonated catalyst present. Examples of such plots are presented in Figure 1. The plots indicate that the reactions contain at least two components; one reaction with, and/or catalysis by, HO^-, the other due to catalysis by buffer component, B.

The increase in both the intercept with increasing pH and the slope with increasing pK_a of the buffer material identifies HO^- and the conjugate base of the buffer as the major catalysts. For

Table 1. Second-order rate coefficients for the reaction of *N*-methyl-*N*-nitroacetamide (**1a**) and *N*-methyl-*N*-nitrobenzamide (**1b**) with base catalysts at 25 °C.

		(1a)		(1b)	
Catalyst	pK_a	Average pH	k_B/dm^3 mol^{-1} s^{-1}	Average pH	k_B/dm^3 mol^{-1} s^{-1}
Water	−1.7	—	0.000 01	—	0.000 025
Acetate	4.57	3.95; 4.55	0.000 37	4.65	0.000 99
Acetate(D_2O)	5.09	5.23[a]	0.000 29	—	—
Pyridine	5.2	7.26	0.12	6.94	0.044
Phosphate	6.9	6.30; 7.36	0.0032	6.93	0.0044
N-Methylimidazole	7.0	7.29	1.7	6.97	5.1
Imidazole	7.1	7.21	0.94	6.95	0.46
Morpholine	8.7	7.31	44.5	6.98	9.3
4-Chlorophenol	9.28	8.30; 8.86; 9.44	16.4	—	—
Piperidine	11.20	8.84	1533	—	—
2,2′,6,6′-Tetramethylpiperidine	11.07	8.85	20	—	—
Hydroxide (borate)	15.75	8.83–9.40	130	7.89–9.42	228
Deuteroxide (borate)	16.61	9.40–9.89[a]	131	9.40–9.89[a]	228

[a] pD values.

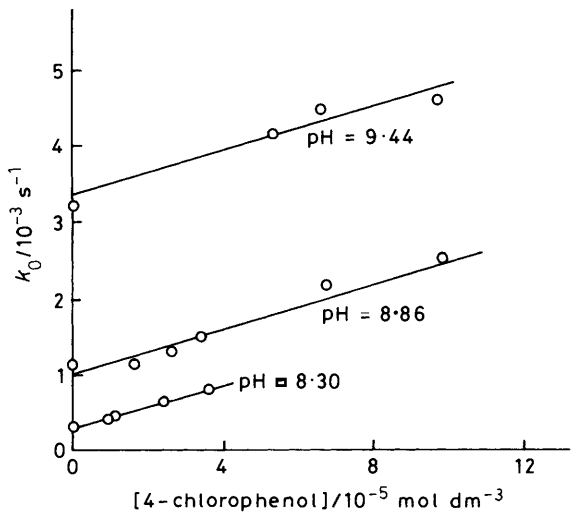


Figure 2. Hydrolysis of (**1a**) catalysed by 4-ClC_6H_4OH at three pH values.

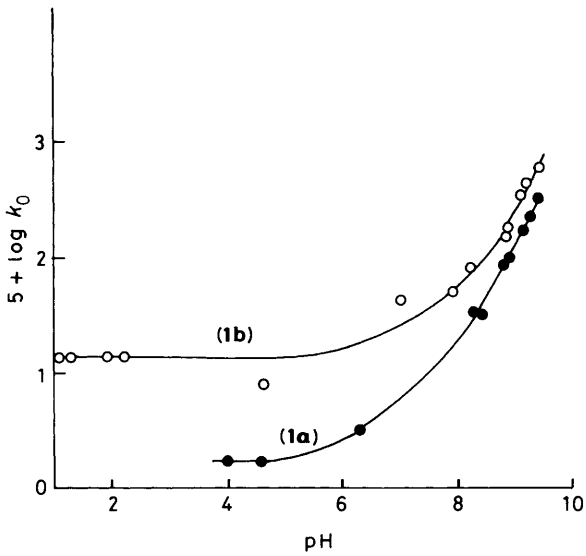


Figure 3. pH-rate profiles for the hydrolyses of (**1a**) and (**1b**) at 25 °C.

acetate, phosphate and 4-chlorophenol, reactions were also undertaken at different pH values. The slopes of the plots obtained were always parallel (Figure 2) which implies that the catalysis is only brought about by the conjugate base of the buffer. The second order rate coefficients, k_2, for each of the catalysts studied are shown in Table 1.

pH-*Rate Profile*.—For compounds (**1a**) and (**1b**), pH-rate profiles were constructed (Figure 3) using values of the intercepts (k_{1n}) from the plots of k_0 *versus* [Buffer]. At low pH values an uncatalysed reaction is observed which at higher pH values is overtaken by an HO^--catalysed process. The slope of the log k_{1n} *versus* pH plot in the HO^--catalysed region is 1.0. Thus, the observed *pseudo* first-order rate constant, k_0, includes contributions from all the bases present [Equation (3)].

$$k_0 = k_{H_2O} + k_{HO^-}[HO^-] + \sum_i k_{B_i}[B_i] \qquad (3)$$

The pH profiles of Figure 3 resemble that for ester hydrolysis, for which an HO^--catalysed process is seen at pH > 6–7. By analogy with esters, it seems probable that the hydrolysis of *N*-nitroamides involves formation of a tetrahedral intermediate which decomposes to products. The rate increase with increasing pH then arises from the enhanced nucleophilicity of HO^- over H_2O.

Solvent Deuterium Kinetic Isotope Effects.—The hydrolysis of (**1a**) and (**1b**) was also studied, using deuterium oxide as solvent, in acetate and borate buffers and in sodium deuteriooxide. The solvent deuterium kinetic isotope effects obtained from k_2 values for acetate, and HO^- were *ca.* 1, which indicates that for these reactions proton transfer is not kinetically important (Table 2). However, the solvent deuterium kinetic isotope effect which was obtained from both the intercepts of plots of k_0 *versus* [AcO^-] in H_2O and D_2O, and the intercepts of plots of k_0 *versus* [HO^-] and [DO^-] in borate buffers, is *ca.* 2.0. In both cases, these latter values relate to the uncatalysed reaction and they are consistent with the involvement of two water molecules. As the pH increases the deuterium solvent kinetic isotope effect decreases to *ca.* 1 as the reaction becomes dominated by catalysis by HO^-/DO^-.

Activation Parameters.—The variation of second order rate coefficients, k_2, with temperature for the HO^- catalysed

Table 2. Solvent deuterium kinetic isotope effects at 25 °C.

	Isotope effect	
	(1a)	(1b)
From slopes of AcO^- in H_2O and D_2O	1.3	1.0
From slopes of HO^- and DO^-	0.99	1.0
From intercept in acetate (borate)[a] buffers	2.2(2.1)	2.1(2.0)

[a] Data in parentheses refer to borate buffers.

Table 3. Temperature dependence of the second-order rate coefficients for the HO^- catalysed decomposition of (**1b**) and (**1c**).

	k_{HO^-} dm^3 mol^{-1} s^{-1}	
T/°C	(1b)	(1c)
24.8	66.7	18.9
30.2	121.4	26.4
34.9	151.3	34.0
40.4	186.2	37.1

Table 4. Rate coefficients (k_{HO^-} and k_{H_2O}) for the HO^- catalysed and noncatalysed hydrolysis of 4-substituted *N*-methyl-*N*-nitrobenzamides at 25 °C.

Compound	k_{HO^-}/dm^3 mol^{-1} s^{-1}	k_{H_2O}/10^{-4} s^{-1}
(1c)	37	0.59
(1d)	73	0.86
(1b)	228	1.25
(1e)	1024	1.57
(1f)	5561	2.5

hydrolysis of (**1b**) and (**1c**), is shown in Table 3. These data give rise to values for $\Delta S^{\ddagger}$ of -54 J K^{-1} mol^{-1} and -80 J K^{-1} mol^{-1} for (**1b**) and (**1c**), respectively. These values are typical of bimolecular processes.

Aromatic Substituent Effects.—The HO^- catalysed reaction was studied for several 4-substituted *N*-methyl-*N*-nitrobenzamides [(**1b–f**)] in borate buffer solutions at 25 °C. The second-order rate coefficients for each compound, shown in Table 4, correlate with Hammett σ_p values giving a value for ρ of $+2.8$ (Figure 4). Thus, electron-withdrawing substituents on the benzene ring increase the electron deficiency of the carbonyl C-atom and facilitate attack by the nucleophile. ρ Values of the same order of magnitude have been obtained for the HO^- catalysed hydrolysis of esters with very good leaving groups, *e.g.* 4-nitrophenyl benzoates.[12]

From the intercepts of the k_0 *versus* [HO^-] plots, the observed first-order rate constants for the non-catalysed process can be obtained (Table 4). The precision of these data is low ($\pm 25\%$) but is sufficient to establish that they correlate with Hammett σ_p values giving a ρ value of 0.8($\pm$0.2) (Figure 4). This value is significantly lower than that for HO^- catalysis and has important mechanistic consequences (see below).

The Buffer Catalysed Reaction.—When the reaction was carried out in the presence of secondary amines and phenols, stable products resulting from the nucleophilic attack of the base on the carbonyl carbon atom were isolated. For example, in the presence of either morpholine, piperidine or 4-chlorophenol, *N*-benzoylmorpholine, *N*-benzoylpiperidine or 4-chlorophenyl benzoate was isolated from reactions with (**1b**). With bases leading to the formation of unstable products by

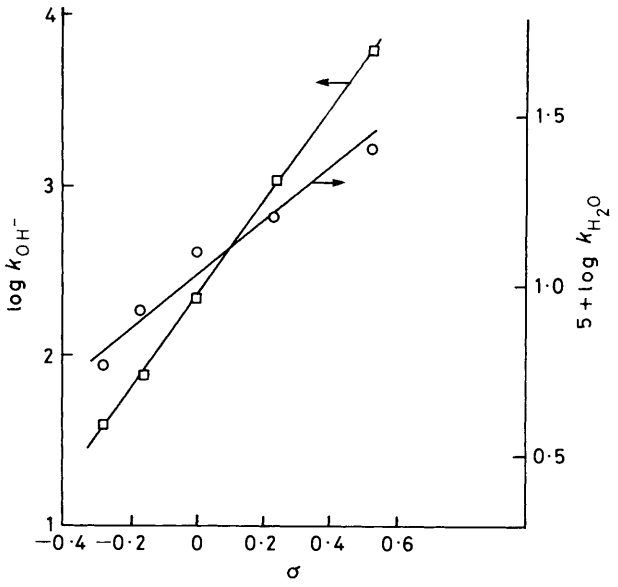


Figure 4. Hammett plot for the HO^--catalysed □ and non-catalysed hydrolysis ○ of (**1, b–f**) at 25 °C.

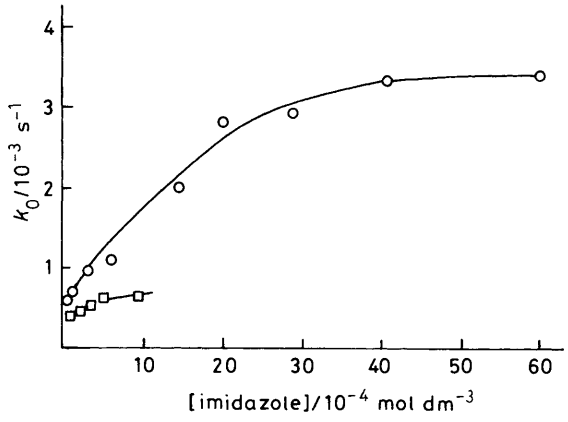


Figure 5. Effect of [Imidazole] on the observed rate constant for the hydrolysis of (**1a**), ○ and (**1b**), □ at 25 °C.

nucleophilic attack, only the corresponding carboxylic acid and *N*-nitroamine were found at the end of the reaction. When the reaction of (**1a**) was carried out in the presence of imidazole, the observed rate constant, k_0, attained a limiting value as [Imidazole] increased (Figure 5). Further, it was found that, at the higher imidazole concentrations, the u.v. spectra of the reaction solutions did not show the characteristic isobestic point. Since the reaction was followed at λ_{max} = 244 nm, and *N*-acetylimidazole, the product of nucleophilic attack on the *N*-nitroamide, is known to absorb at λ_{max} = 245 nm, this suggests that formation of *N*-acetylimidazole interferes with the rate measurements. Indeed, hydrolysis of an authentic sample of *N*-acetylimidazole, carried out under the same conditions as the hydrolysis of (**1a**), gave an observed rate constant identical to those obtained at high imidazole concentrations (Table 5). The detection of *N*-acetylimidazole as a transient intermediate with (**1a**), and *N*-benzoylmorpholine, *N*-benzoylpiperidine and 4-chlorophenyl benzoate with (**1b**) is evidence that in these cases the reaction proceeds by a nucleophilic catalysed pathway (Scheme 3).

Examination of the second-order bimolecular rate coefficients (k_2) for various catalysts in Table 1 provides convincing

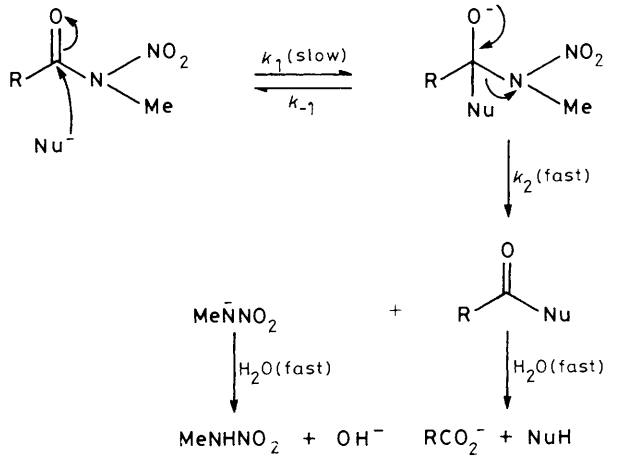
Table 5. Comparison of the rate of hydrolysis of acetylimidazole and *N*-methyl-*N*-nitroacetamide catalysed by high [Imidazole][a].

[Imidazole]/ mmol dm^{-3}	[(**1a**)]/ mmol dm^{-3}	[Acetylimidazole]/ mmol dm^{-3}	[*N*-Nitromethylamine]/ mmol dm^{-3}	$k_0/10^{-3}$ s^{-1}
10	1	0	0	3.2
9	0	**1**	1	3.3

[a] [KH_2PO_4] = 0.3 mol dm^{-3}; [NaOH] = 0.225 mol dm^{-3}; μ = 0.75 mol dm^{-3}; T = 25 °C

Table 6. Second-order catalytic rate coefficient ratios at 25 °C.

	(**1a**)	(**1b**)
$k_{MeIm}/k_{HPO_4^{2-}}$	794	1 416
k_{pyr}/k_{AcO^-}	310	44
k_{HO^-}/k_{MeIm}	77	40
$k_{pip}/k_{Me_4\text{-}pip}$	76	—



Scheme 3. Mechanism of the nucleophilic-catalysed hydrolysis of *N*-nitroamides.

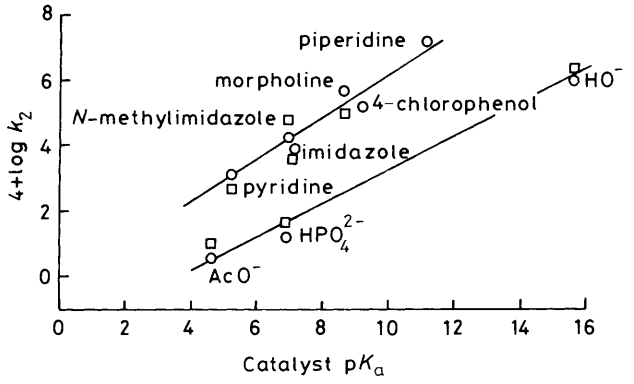


Figure 6. Brønsted plots for the hydrolysis of (**1a**), ○ and (**1b**), □ at 25 °C.

evidence for hydrolysis *via* a nucleophilic-catalysed rather than a base-catalysed pathway.

Thus, nucleophilicity determines the effectiveness of the catalysts. Ratios of rate coefficients for *N*-methylimidazole *versus* HPO_4^{2-}, *N*-methylimidazole *versus* HO^- and pyridine *versus* acetate are of the orders of magnitude expected for a nucleophilic catalysed hydrolysis pathway[13] (Table 6). This conclusion is further supported by the observation of significant steric effects for the catalysed hydrolysis of (**1a**). Thus, piperidine is a much more effective catalyst by a factor of *ca.* 100 than 2,2′,6,6′-tetramethylpiperidine (Table 1).

The correlation of the second-order catalytic rate coefficients (k_B) with the basicity of the catalyst is shown in Figure 6. Data for nitrogen bases lie on lines from which β values of 0.64 and 0.60 are obtained for compounds (**1a**) and (**1b**), respectively. Data for acetate, phosphate and HO^-, however, fall on a common line of slope *ca.* 0.51. The Brønsted relationship is often obeyed in nucleophilic catalysed hydrolysis reactions but different plots are obtained for different types of nucleophiles. These effects are clearly observed for the hydrolysis of *N*-nitroamides. Nevertheless, β values obtained for other nucleophilic catalysed reactions are usually higher (*e.g.* β = 0.8 for 4-nitrophenyl acetate[14]) than those for *N*-nitroamide hydrolysis. This suggests that *N*-nitroamides are electron deficient, less selective substrates.

The alternative, general base-catalysed hydrolysis reactions are usually associated with solvent deuterium kinetic isotope effects >2, whereas nucleophilic catalysed reactions normally have a lower isotope effect.[14] The solvent deuterium kinetic isotope effects observed for both the acetate and the HO^- catalysed hydrolyses of (**1a**) and (**1b**) are *ca.* 1, which is further evidence for a nucleophilic catalysed pathway.

Conclusions

In neutral and alkaline aqueous media, secondary *N*-nitroamides undergo decomposition (hydrolysis) by concurrent uncatalysed and nucleophilic-catalysed pathways. The products are the *N*-nitroamine and the acylated nucleophile, which may undergo further hydrolysis to the corresponding carboxylic acid.

The catalysed pathway (Scheme 3) is unusual for an amide hydrolysis under alkaline conditions insofar as the catalyst acts as a nucleophile, and its interaction with the carbonyl C-atom to form the tetrahedral intermediate is rate-limiting. These mechanistic conclusions are consistent with the negligible solvent deuterium kinetic isotope effects, the highly negative $\Delta S^{\ddagger}$ values, the substantial rate accelerations by aromatic electron-withdrawing substituents (Hammett ρ = +2.8) and the catalytic effect of various nucleophiles (*e.g.* Brønsted β *ca.* 0.6 and substantial steric effects). These mechanistic conclusions are also consistent with the absence both of significant ^{18}O-exchange during hydrolysis and additional second-order base-catalysis terms in the rate equation for hydrolysis. Both the nucleophilic catalysis and rate-limiting step must reflect the enhanced nucleofugacity of the *N*-nitroamine fragment. Generally, for carboxylic acid derivatives bearing a stable nucleofuge, (*e.g.* 4-nitrophenylacetate), hydrolysis proceeds *via* rate-limiting nucleophilic attack on the carbonyl C-atom. In this context, it is interesting to note the excellent correlation (Figure 7, slope = 1.1) between the catalytic rate coefficients for the hydrolysis of (**1a**) and 4-nitrophenylacetate.[14]

The mechanism(s) of the uncatalysed hydrolysis reaction is less clear; but it is unlikely to involve rate-limiting attack by H_2O on the carbonyl C-atom because substituent effects are much smaller than for the HO^--catalysed reaction. Our preferred mechanism, which does not conflict with any experimental observation, is *N*-methyl cleavage either thermally or *via* H_2O attack.

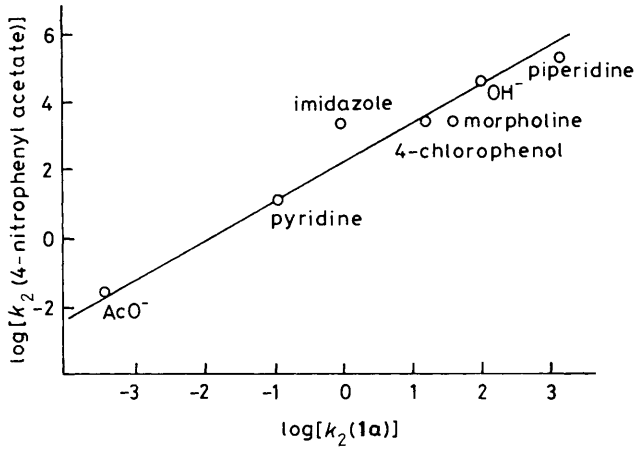


Figure 7. Correlation between catalytic rate coefficients for the hydrolysis of (**1a**) and 4-nitrophenyl acetate in aqueous buffers at 25 °C.

Acknowledgements

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