N-Hydroxy-compounds as Acyl Transfer Agents. Part 2.[1] Kinetics and Mechanism of Hydrolysis and Aminolysis of 1-Hydroxypyrazole and 1-Hydroxyimidazole Esters

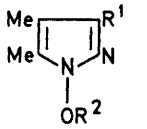
By **Daniel G. McCarthy** and **Anthony F. Hegarty,*** Chemistry Department, University College, Cork, Ireland

Benzoate esters of 3-(alkyl or aryl)-1-hydroxy-4,5-dimethylpyrazole (1) and 1-hydroxy-4,5-dimethyl-2-phenylimidazole (2) react with hydroxide ion, water (*via* acid catalysis), and primary amines in aqueous dioxan at 25°, but at a much slower rate than the corresponding esters of 1-hydroxybenzotriazole. Hydrolysis of the pyrazole esters (1a and b) shows specific acid and base catalysis, giving Hammett ρ values of 1.1 and 1.5 respectively. For the acid-catalysed process, protonation of the heterocyclic ring rather than the carbonyl oxygen is invoked. Acid-catalysed hydrolysis of the imidazole ester (2a) occurs at about the same rate, but the hydroxide ion-catalysed process is much slower (k_{OH^-} 8.32 l mol^{-1} s^{-1}). The rate of hydroxide attack on (1a and b) and (2a) has a lower sensitivity to the pK_a of the leaving group ($\beta_{l.g.}$ −0.2), than phenyl acetates ($\beta_{l.g.}$ −0.33). Only one pK_a (7.22) could be measured for (1e), in contrast to two pK_a values reported previously (6.1 and 5.5). The reaction of (1a) with primary amines gives β_{nuc} 0.89, and general base catalysis was observed with ethylenediamine monocation and glycine ethyl ester (k_{gb} = 61.6 × 10^{-3} l^2 mol^{-2} s^{-1} and 5.3 × 10^{-3} l^2 mol^{-2} s^{-1}). With amines the imidazole ester (2a) shows β_{nuc} 0.80 and no general base-catalysed process was observed. Above pH 9, 2-phenyloxazolin-5-one (12) was observed as an intermediate in the hydrolysis and aminolysis of the hippurate ester (1c). The ester (1d) reacts with nucleophiles by a $B_{AC}2$ mechanism at all pH. Compounds (1e and 1f) and (2b) and 1-hydroxybenzotriazole catalyse the decomposition of *p*-nitrophenyl acetate, but the latter two compounds show a 50-fold negative deviation from structure–reactivity correlations (log k_n *versus* pK_a).

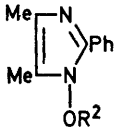
THE kinetics of deacylation of 1-hydroxybenzotriazole esters have been described.[1] In view of the high reactivity of this compound as an acyl transfer agent, it was of interest to determine if other heterocyclic *N*-hydroxy-compounds behaved similarly. Furthermore, the observation of a large water-catalysed reaction and the absence of an acid-catalysed reaction suggested that acidic catalysis might be observed with a more basic

[1] Part 1, D. G. McCarthy, A. F. Hegarty, and B. J. Hathaway, preceding paper.

heterocyclic system. In this case protonation of one of the heterocyclic nitrogens in the ester would give a neutral leaving group in the *N*-oxide form thus greatly facilitating hydrolysis. We have investigated the hydrolysis and aminolysis of esters of 3-(alkyl or aryl)-1-hydroxy-4,5-dimethylpyrazoles (1) and 1-hydroxy-4,5-dimethyl-2-phenylimidazole (2).



(1)



(2)

	R^1	R^2
a;	Me	COAr
b;	Ph	COAr
c;	Me	$COCH_2NHCOPh$
d;	Me	$COCH_2NHCO_2CH_2Ph$
e;	Me	H
f;	Ph	H

a; R^2=COAr
b; R^2=H

RESULTS AND DISCUSSION

Benzoate esters of 1-hydroxypyrazoles (1a and b) undergo hydrolysis in aqueous dioxan at 25 °C to give benzoic acids and the 1-hydroxypyrazole as the only products. Variation of the pH of the reaction medium shows two general patterns of reactivity (Figure 1). Above pH 8, log k_{obs} is directly proportional to pH, consistent with a bimolecular mechanism involving hydroxide ion and the ester. The 3-phenyl ester (1b; Ar = Ph) reacts faster than the 3-methyl compound, as expected on the basis of the lower pK_a for the

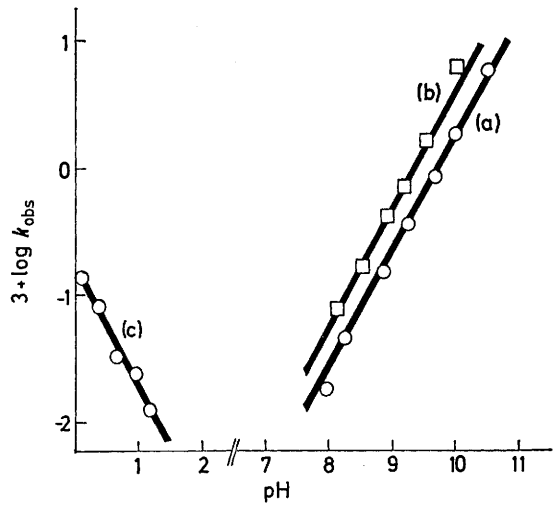
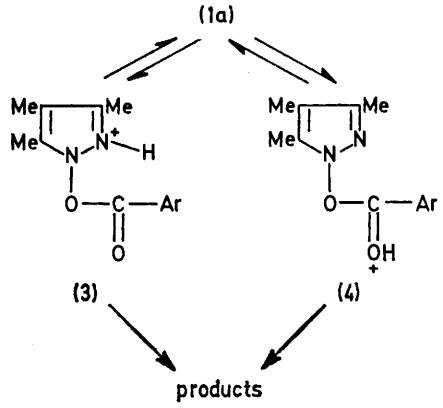


FIGURE 1 Plot of the log of the observed rate constant *versus* pH for the hydrolysis of (a) (1a); (b), (1b); (c) (1a; Ar = 4-ClC_6H_4) in 1 : 4 dioxan–H_2O at 25° (μ 1.0; $NaClO_4$)

hydroxypyrazole leaving group in this case. Electron-withdrawing substituents in the benzoate residue increase the rate of hydroxide ion attack on the ester of the trimethyl compound; thus for (1a; Ar = *p*-ClC_6H_4 and *p*-$NO_2C_6H_4$) the observed first-order rate constants at pH 9 are 0.36×10^{-3} and 2.49×10^{-3} s^{-1}, respectively. Using normal σ values a Hammett ρ of *ca.* +1.5 can be calculated for the HO^- -catalysed reaction.

At low pH (<2), a slow pH dependent rate of hydrolysis was observed; a plot of log k_{obs} *versus* pH is linear with a slope −1.0. This indicates specific acid catalysis with pre-equilibrium formation of the protonated ester (3) or (4), followed by rate-determining water attack on this to give the observed products. Electron-withdrawing substituents in the aryl ring increase the rate of the acid-catalysed process, but the rate is not as sensitive to substituents as is the base-catalysed process. At pH 0.15, the rates of reaction of the three esters (1a; Ar = Ph, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$) are k_{obs} 0.087×10^{-3}, 0.15×10^{-3}, and 0.61×10^{-3} s^{-1}, respectively. An approximate Hammett ρ of +1.1 may be calculated for the acid-catalysed process. Acid-catalysed ester hydrolysis, involving pre-equilibrium protonation of the carbonyl oxygen, followed by water attack on this generally shows a low sensitivity to substituents in the acyl



SCHEME 1

function (ρ *ca.* 0).[2] In view of the higher ρ obtained here an alternative mechanism is favoured. This requires initial protonation of one of the pyrazole nitrogens [(3)] (whose pK_a ≤0) with subsequent water attack on the carbonyl oxygen. In this case a neutral *N*-oxide leaving group would result. The basicity of the pyrazole ring nitrogens would not be expected to be very sensitive to substituents in the benzoate ring of the ester. Thus the overall ρ for hydrolysis (which would be the sum of the separate values for protonation and water attack) would be expected to approach that for water attack on the ester. We have previously observed [1] a ρ of +1.39 for water attack on 1-benzoyloxybenzotriazoles.

In basic solution the 1-hydroxyimidazole ester (2a; Ar = Ph), reacts similarly to give benzoic acid and the 1-hydroxyimidazole (2b). The rate of reaction is dependent on the pH of the reaction medium (Table 1), and a plot of log k_{obs} *versus* pH is linear with slope +1.0,

[2] J. Shorter, 'Correlation Analysis in Organic Chemistry,' Clarendon Press, Oxford, 1973, ch. 3.

indicating a specific base catalysed process. The *p*-chloro-ester reacts faster than the unsubstituted compound (k_{obs} 2.47 × 10^{-3} s^{-1} at pH 10.0). In acid solution, no enhanced rate of reaction is observed for the imidazole esters; thus at pH 0.6 the *p*-chlorobenzoate ester of the hydroxyimidazole reacts at about the same

TABLE 1

Observed pseudo-first-order rate constants (s^{-1}) for hydrolysis of (2a) in 1 : 4 dioxan–water at 25 °C (μ 1.0; $NaClO_4$)

pH	9.73	10.0	10.85	10.97	11.4	11.78
10^3 k_{obs} [a]	0.283	0.832	2.40	6.46	15.85	46.76

[a] Determined at 316 nm with Cary 14 pH stat assembly.

TABLE 2

Observed pseudo-first-order rate constants (s^{-1}) for hydrolysis of ester (1c) in 1 : 4 dioxan–water at 25 °C (μ 1.0; $NaClO_4$)

pH	8.8 [a]	9.3 [a]	12.5 [b]
10^3 k_{obs}/s^{-1}	130	167	33
10^3 k_{obs}/s^{-1} [c]	140	170	31

[a] In 10^{-2}M-borax buffer. [b] Sodium hydroxide buffer. [c] Observed rate constants for the hydrolysis of 2-phenyloxazolin-5-one (12).

TABLE 3

Second-order rate constants for reaction of *N*-hydroxy-compounds with *p*-nitrophenyl acetate at 25 °C (μ 1.0; $NaClO_4$)

Nucleophile	pK_a	k/l mol^{-1} s^{-1} [e]
1-Hydroxybenzotriazole	7.4 [a]	0.13
(1e)	7.22 [c]	0.63
	(6.6) [b]	
(1f)	6.8 [c]	0.708
(2b)	10.04 [c]	1.44
	(4.32) [d]	

[a] Calculated from data in F. T. Boyle and R. A. Y. Jones, *J.C.S. Perkin II*, 1973, 160. [b] Measured in water. [c] Measured in 1 : 4 dioxan–water (v/v). [d] pK_{a2} (protonation of N-3). [e] Measured at 400 nm in sodium carbonate or *N*-ethylmorpholine buffers (1 × 10^{-2}M).

rate (k_{obs} 0.05 × 10^{-3} s^{-1}) as the corresponding *N*-hydroxypyrazole ester. Although the hydroxyimidazole is a much poorer leaving group than the hydroxypyrazoles (ΔpK_a *ca.* 3), the imidazole ring is more basic, so that a greater proportion of the protonated imidazole ester will be present at a particular pH (assuming protonation of the imidazole ring N-3 takes place). Thus the opposing effects of greater basicity of the ester and poor leaving group ability of the alcohol portion of the molecule cancel each other and result in no change in the rate of reaction compared with the pyrazole system.

Figure 2 shows a plot of the log of the second-order rate constant for hydroxide ion attack on the *N*-hydroxy-esters, *versus* the pK_a of the leaving group. For comparison purposes data [3] for alkaline hydrolysis of phenyl acetates are included on the same plot. It is clear that the *N*-hydroxy-compounds react faster than phenyl acetates by a factor of 3—7. The still higher reactivity of 1-hydroxybenzotriazole esters is also evident. For steric reasons phenyl acetates react faster with nucleophiles than phenyl benzoates,[3,4] so that the acetate esters of (2) and (3) would be expected to react 20—30 times faster than phenyl acetates. The enhanced reactivity of active peptide esters of *N*-hydroxy-compounds towards nucleophiles has been attributed to the electronegativity of the nitrogen atom of the N–O bond.[5] Inspection of molecular models indicates that

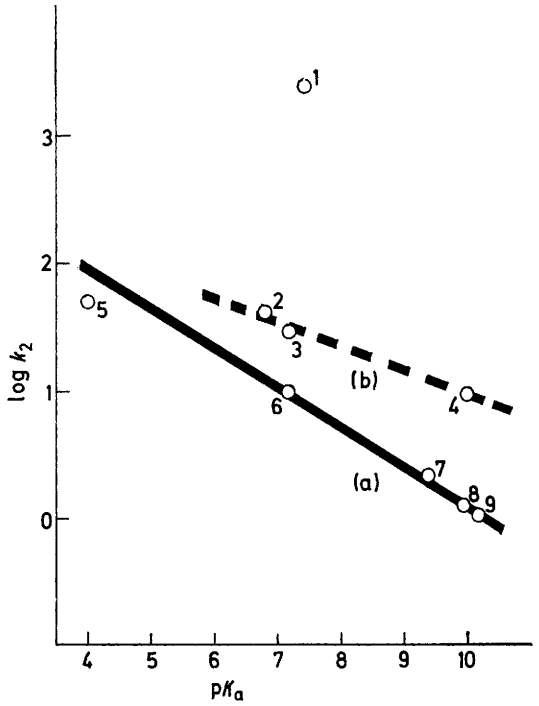


FIGURE 2 Plot of log of second-order rate constants (k_2) for HO^- attack on (a) phenyl acetates, (b) benzoate esters of *N*-hydroxy-compounds against the pK_a of the conjugate acid of the leaving group. Esters: 1, 1-benzoyloxybenzotriazole; 2, (1b); 3, (1a); 4, (2a); 5, 2,4-dinitrophenylacetate; 6, 4-nitrophenyl acetate; 7, 4-chlorophenyl acetate; 8, phenyl acetate; 9, 4-methoxyphenyl acetate

the carbonyl carbon of the pyrazole esters is less hindered than that of a phenyl benzoate, but, for the imidazole ester, no steric advantage can be seen, largely due to the proximity of the 2-phenyl and 5-methyl groups to the reaction site. The alkaline hydrolysis of phenyl acetates shows a leaving group sensitivity ($\beta_{l.g.}$ −0.33),[3] while for the *N*-hydroxy-esters a $\beta_{l.g.}$ of *ca.* −0.2 can be obtained from the data, suggesting that the hydrolysis of these esters has very little carbon–oxygen bond cleavage in the transition state. If a tetrahedral intermediate is formed in the reaction, nucleophilic attack of hydroxide ion would be rate determining rather than loss of the leaving group for these compounds. However, in view of the structural differences between the pyrazole and imidazole leaving groups, it may not be valid to place both groups of compounds on the same

[3] J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, 1964, **86**, 837.

[4] J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, 1968, **33**, 127.

[5] P. G. Sammes, *J. Chem. Soc.*, 1965, 6609.

line. Deviations from structure–reactivity correlations for steric and electronic reasons are known.[6]

The pK_a values of the *N*-hydroxy-compounds were determined under the kinetic conditions. For 1-hydroxy-3,4,5-trimethylpyrazole, two pK_a values are reported,[7] 6.1 (ionization of OH group), and 5.5 (ionization of protonated *N*-hydroxy-compound). In view of the low reactivity of the benzoate esters of this compound towards acid catalysis, and the absence of any evidence for the 2-nitrogen participating as an intramolecular general base, the ionization of this *N*-hydroxy-compound was reinvestigated under the kinetic conditions. Repetitive scans of the u.v. spectrum of this compound over the pH range 0—9 showed two spectral changes at pH *ca.* 2 and 7. A spectrophotometric titration of the latter ionization gave a pK_a of 7.22. In order to check that the spectrophotometric titration curve did not contain two closely spaced pK_a values, a potentiometric measurement gave a similar pK_a (7.25), and showed that only one equivalent of base per equivalent of substrate was used for the titration. Further evidence that the ionization involves the OH group was obtained by observing that the pK_a changed to 6.8 on going from 1 : 4 dioxan–water to pure water. Thus an increase in acidity on increasing the ionizing power of the medium, suggests that a process involving charge separation is taking place. Data for the other compounds are given in Table 3.

Aminolysis Reactions.—The reactions of the esters (1a; Ar = Ph) and (2a; Ar = Ph) with primary amines were investigated. Aminolysis reactions were studied in amine buffer solutions under pseudo-first-order conditions at concentrations 10^{-1}—1.0M for the slower reacting amines, and 10^{-2}—10^{-1}M for the more reactive amines (glycine and ethylamine), and usually at the pK_a of the conjugate acid of the amine. The reaction products in each case were the corresponding amide and *N*-hydroxy heterocycle (1 and 2; $R^2 = H$). With ethylamine some hydroxide ion attack on the ester accompanied aminolysis. The first-order rate constants were directly proportional to the concentration of free amine except for reactions of the pyrazole ester with glycine ethyl ester and ethylenediamine monocation, where curved plots of k_{obs} *versus* amine concentration were obtained. For these amines the second- and third-order rate constants were obtained by standard graphical techniques,[8] using equation (1).[9] The third-order rate

$$k_{obs} = k_{OH}[HO^-] + k_{H_2O}[H_2O] + k_n[am] + k_{gb}[am]^2 + k_{ga}[am][amH^+] + k[HO^-][am] \quad (1)$$

constants (k_{gb}) obtained were 61.6×10^{-3} and 53×10^{-3} l^2 mol^{-2} s^{-1} respectively. Brønsted plots for the aminolysis of each ester are shown in Figure 3. These show that both esters react at approximately the same rate with primary amines, but the pyrazole ester is more sensitive to the pK_a of the conjugate acid of the amine (β_{nuc} 0.89; *r* 0.995, *s* 0.09), than is the imidazole ester (β_{nuc} 0.8; *r* 0.997, *s* 0.06).

The current understanding of the mechanism of ester aminolysis [10] suggests that for alkyl and phenyl acetates, the formation of a tetrahedral intermediate $T^{\pm}$ (5) is rapid and reversible for all esters except those with very good leaving groups (2,4-dinitrophenol and 4-methoxypyridine *N*-oxide). On the basis of the pK_a values of the leaving groups, the *N*-hydroxypyrazole (1; $R^1 = CH_3$) would be expected to behave similarly to *p*-nitrophenol, while the hydroxyimidazole would be similar to *p*-methoxyphenol. Thus in the case of the pyrazole ester, the mechanism can be described in terms of initial formation of a tetrahedral intermediate $T^{\pm}$ (5), followed by rate-determining breakdown of this in the case of uncatalysed aminolysis (or removal of a proton

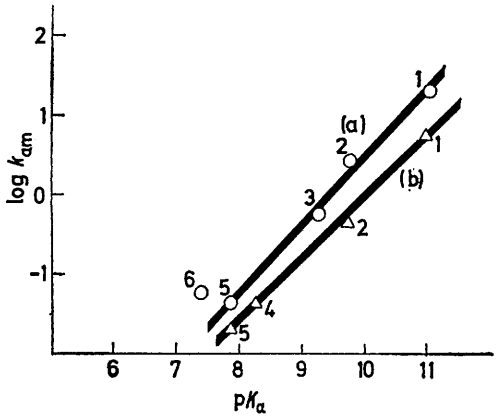
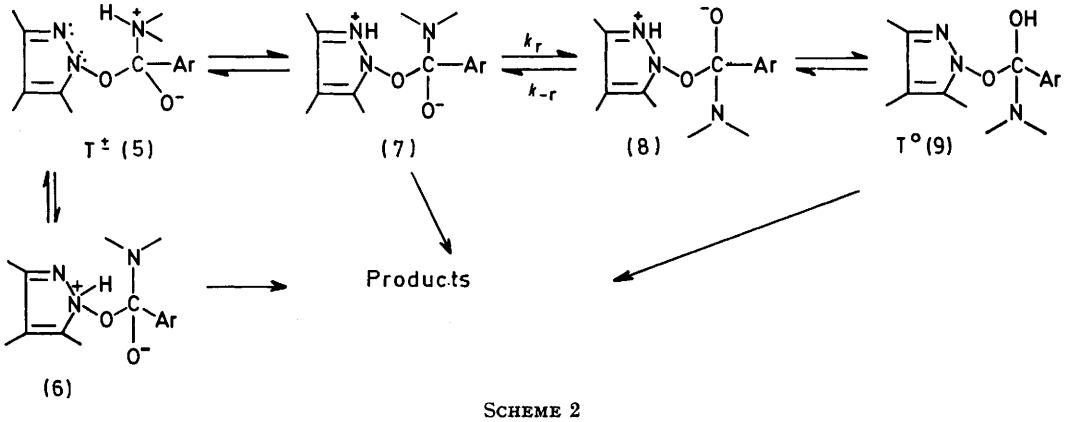


FIGURE 3 Brønsted plot of the second-order rate constants (k_{am}) for the reactions of primary amines with (a) (1a), and (b) (2a). Amines: 1, ethylamine; 2, glycine; 3, ammonia; 4, glycylglycine; 5, glycine ethyl ester; 6, ethylenediamine monocation

from $T^{\pm}$ by water). The amine-catalysed reaction would represent rate determining proton removal from $T^{\pm}$ to give T^-, followed by fast decomposition of the latter to products, the catalyst serving to trap $T^{\pm}$ and prevent it from reverting to starting materials. In the case of the pH and buffer independent aminolysis, the role of the 1- or 2-nitrogen of the pyrazole ring must be considered. These nitrogens could remove a proton for the ammonium group of $T^{\pm}$ to give an equivalent of T^- [(6) or (7)] which would then collapse to products, and in this case the leaving group would be the neutral *N*-oxide. Participation of the 2-nitrogen would be more favourable as this would involve a six-membered transition state, whereas for involvement of the 1-nitrogen, the transition state would be five-membered. The participation of the 1-nitrogen in the reaction of amines with esters of 1-hydroxypiperidine has been

[6] C. D. Johnson, 'The Hammett Equation,' Cambridge University Press, London, 1973.
[7] F. T. Boyle and R. A. Y. Jones, *J.C.S. Perkin II*, 1973, 164.
[8] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, ch. 11.
[9] T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, 1967, **89**, 2106.
[10] (*a*) A. C. Satterthwait and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 7019; (*b*) P. Y. Bruice and T. C. Bruice, *ibid.*, p. 5533.

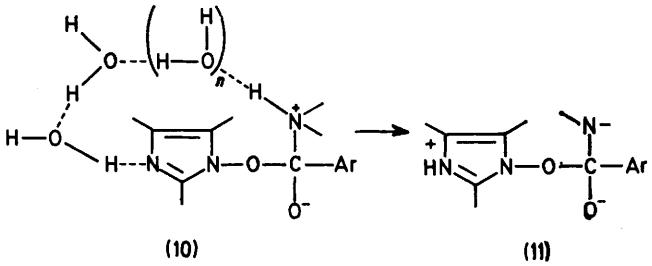
suggested by Young.[11] Catalysis could also arise through the 2-nitrogen acting as a catalyst for proton transfer from the ammonium group to the oxide anion of $T^{\pm}$ ($T^{\pm} \longrightarrow T^{0}$). This would involve initial protonation of the 2-nitrogen [(7)], followed by rotation about the O–C bond to give a conformation where O^- is in a position to remove the proton from the 2-nitrogen [(8)].



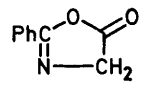
SCHEME 2

Formation of products from a neutral tetrahedral intermediate (T^0) has been suggested to involve a lower energy pathway than from a zwitterionic intermediate $T^{\pm}$.[10b] The overall proton transfer would be energetically favourable as the ammonium group of $T^{\pm}$ is a stronger acid than the alcohol group of T^0, the difference being 3 pK_a units,[12] but the mechanism would be dependent on the basicity of the 2-nitrogen of the pyrazole. Participation of the 1-nitrogen of the hydroxyimidazole ester as an intramolecular general base catalyst would provide the only mechanism of intramolecular catalysis to account for the observed behaviour of these esters. For the uncatalysed reactions of phenyl acetates with amines, the leaving group sensitivity is usually $\beta_{l.g.}$ -1.0,[10a] this corresponding with a β_{nuc} of 0.9. With ethylamine a $\beta_{l.g.}$ of *ca.* -0.25 can be estimated for the two esters studied, which is in disagreement with the value of -1.0 suggested for rate-determining loss of the leaving group from $T^{\pm}$. It is possible that the two leaving groups should not be classified together in view of their differing structures. For a leaving group with a pK_a >10, a mechanism of aminolysis has been suggested [10a] (involving rate-determining proton transfer through water ($T^{\pm} \longrightarrow T^{0}$), followed by conversion of T^0 to T^- and rapid loss of the leaving group from T^-. This mechanism shows a positive deviation from structure–reactivity relationships (log *k versus* pK_a of leaving group), and exhibits a $\beta_{l.g.}$ of 0.2. In the case of the imidazole ester this possibility would represent proton transfer through water (stepwise or concerted), from the ammonium group of $T^{\pm}$ (10) to the 3-nitrogen of the imidazole ring (11), giving a neutral *N*-oxide leaving group. Heterocyclic *N*-oxides can exist in solution as two tautomers, *N*-hydroxy or *N*-oxide, or as an equilibrium mixture of the two,[13] although in the present case it is not known which tautomer is preferred.

Oxazolinone Formation.—Active esters of *N*-hydroxy-compounds are widely used in peptide synthesis,[14] largely due to their ability to form peptides in high yields and reduce racemization (due to oxazolinone formation). Thus it was of interest to determine if an *N*-acylamino-acid ester of (1) or (2) would form an oxazolinone at high pH or undergo deacylation by a



normal $B_{Ac}2$ mechanism. When the hippurate ester (1c) was added to an aqueous buffer above pH 9 a rapid increase in optical density was observed at 340 nm. This absorption has previously been attributed to the anion of 2-phenyloxazolin-5-one,[15] and was found to decay rapidly under the reaction conditions used. Formation of an oxazolinone intermediate in this case was confirmed by observing that an authentic sample of (12) showed the same reactivity under the conditions



(12)

used (Table 2). From the agreement of the two sets of data it is clear that the oxazolinone (12) is present in the hydrolysis of the hippurate ester (1c). At high pH

[11] B. O. Handford, J. H. Jones, G. T. Young, and T. F. N. Johnson, *J. Chem. Soc.*, 1965, 6814.
[12] J. P. Fox and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 1436.
[13] A. R. Katritzky and J. M. Lagowski, 'Chemistry of the Heterocyclic *N*-Oxides,' Academic Press, London, 1971.
[14] D. T. Elmore, 'Peptides and Proteins,' Cambridge University Press, London, 1968, ch. 4.
[15] J. de Jersey, P. Willadsen, and B. Zerner, *Biochemistry*, 1969, **8**, 1959.

(12.5), the rate of hydrolysis of (12) and the intermediate agree with the data of Zerner.[15] The mechanism of aminolysis of hippurate esters is dependent on the pH of the reaction medium; [16] at high pH the mechanism proceeds through the oxazolinone, while at lower pH a greater proportion of the reaction proceeds by normal displacement at the ester carbonyl group. Thus with glycine (0.01M, pH 9.8), the reaction of (1c) proceeds largely through the oxazolinone, which then reacts with the amine (k_2 3.26 × 10^3 l mol^{-1} s^{-1}), giving the same product as would be observed by the direct displacement mechanism. The glycine ester (1d) reacts with hydroxide ion (k_2 585 l mol^{-1} s^{-1}) and glycine (k_2 30.4 l mol^{-1} s^{-1}) *via* a normal displacement mechanism rather than *via* oxazolinone formation.

Nucleophilicity towards Acyl Centres.—The enhanced nucleophilicity of hydroximate anions, hydroxamic acids, and other compounds containing the N–O group towards saturated and acyl carbon centres is well established.[17] This is attributed to the operation of the 'α-effect.' [18] To complete the present study the nucleophilic reactivity of the compounds (1e), (1f), and (2b) and 1-hydroxybenzotriazole towards *p*-nitrophenyl acetate (PNPA) was examined. The triazole could, in small concentrations serve as a catalyst for the decomposition of PNPA in view of the high rate of hydrolysis of esters of this compound. Generally where *N*-hydroxy-compounds have been used as catalysts for decomposition of PNPA, the slow step was the hydrolysis of the intermediate ester.[19] In the presence of an excess of the hydroxy-compounds (1e and f) and (2b) and 1-hydroxybenzotriazole (10^{-2}—10^{-1} mol l^{-1}), an efficient release of *p*-nitrophenol was observed at 25 °C in water. For each compound the pseudo-first-order rate constants were directly proportional to the nucleophile concentration, and increased with increasing pH, indicating that the anionic form of the nucleophile is the reactive species. Data for 1-hydroxybenzotriazole at two pH values are shown in Figure 4. The initial products were the *O*-acylated hydroxylamine derivatives, and with the exception of 1-hydroxybenzotriazole these were the final products; for 1-hydroxybenzotriazole the intermediate ester hydrolysed rapidly under the reaction conditions to give acetic acid and regenerate the catalyst. Jencks and Carriuolo [17b] have obtained a wide range of kinetic data for the reactions of nucleophiles including *N*-hydroxy-compounds towards *p*-nitrophenyl acetate. The latter group show a positive deviation from the Brønsted line for primary amines, the difference corresponding to a 100-fold greater reactivity, and a β_{nuc} of 0.7 may be calculated for these compounds from the data presented. For the four nucleophiles used here, the data for the two *N*-hydroxypyrazoles fits on the line established by Jencks, whereas the other two compounds deviate considerably from the line, corresponding to a 50-fold slower rate of reaction; however all the *N*-hydroxy compounds do react faster than phenoxides with PNPA. The deviations could be due to steric effects of the 2-phenyl and 5-methyl groups in the *N*-hydroxyimidazole, and due to the 7-hydrogen in 1-hydroxybenzotriazole. Another possibility is that these compounds act as nucleophiles through the 3-nitrogen. In this case the imidazole would not be expected to show an 'α-effect,' but the hydroxybenzotriazole would, due to the lone pair of electrons on the 2-nitrogen. The negative deviation shown by this compound is similar to that shown by methoxyamine, which, though it exhibits an 'α-effect' reacts through a nucleophilic nitrogen. In the presence of an excess of PNPA (10^{-3}M), at low concentrations (10^{-5}M) of (1e) or (2b), no catalytic decomposition of the ester was observed (at pH 8) largely due to the slow rate of hydrolysis of the intermediate ester. For 1-hydroxybenzotriazole which would be expected to show catalytic activity under the same conditions, the experiments were not successful due to the fact that the buffer solutions which had to be used were more efficient catalysts for the release of *p*-nitrophenol than the *N*-hydroxy-compound.

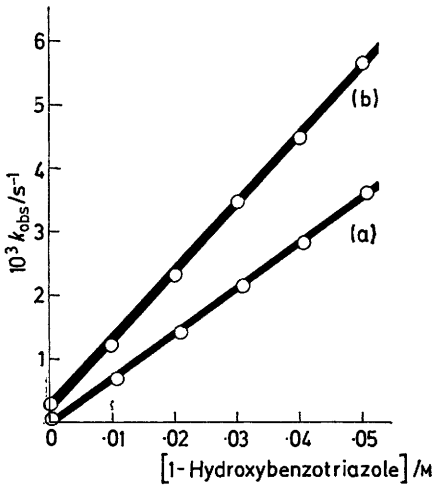


FIGURE 4 Plot of the observed first-order rate constants for the release of *p*-nitrophenoxide ion from *p*-nitrophenyl acetate *versus* total concentration of 1-hydroxybenzotriazole concentration: (a) pH 7.5; (b) pH 8.2 at 25° in H_2O, μ 1.0 ($NaClO_4$); pH maintained by *N*-ethylmorpholine

EXPERIMENTAL

The general experimental and kinetic procedures used are as given in Part 1.[1]

Substrates.—*p*-Nitrophenyl acetate,[20] *N*-benzyloxycarbonylglycine,[21] and 2-phenyloxazolin-5-one [22] were prepared by standard procedures. 1-Hydroxy-4,5-dimethyl-3-phenylpyrazole was prepared by the method of Freeman

[16] A. Williams, *J.C.S. Perkin II*, 1975, 947.
[17] (*a*) R. J. MacConaill and F. L. Scott, *J. Chem. Soc.* (*C*), 1971, 584 and references therein; (*b*) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1773.
[18] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1962, **84**, 16.
[19] T. Kunitake and S. Horie, *Bull. Chem. Soc. Japan*, 1975, **48**, 1304 and references therein.
[20] F. D. Chattaway, *J. Chem. Soc.*, 1931, 2495.
[21] M. Bergman and L. Zervas, *Ber.*, 1932, **65**, 1192.
[22] M. Crawford and W. T. Little, *J. Chem. Soc.*, 1959, 129.

and Gannon [23] and had m.p. 165—167 °C (lit.,[23] 167—168 °C). 1-Hydroxy-3,4,5-trimethylpyrazole was made by a modification of Freeman's method. 1-Hydroxy-3,4,5-trimethylpyrazole 2-oxide (2.13 g, 0.015M) was added to a solution of sodium dithionate (3.0 g, 0.015 mol; 85% $Na_2S_2O_4$), in deionised water (100 ml) and the mixture was refluxed for 1 h. On cooling a white precipitate was obtained, and this was recrystallised from 95% ethanol to give the 1-hydroxypyrazole, m.p. 183—184 °C (lit.,[23] 183—184 °C), δ ([$^2H_6$]dimethyl sulphoxide) 1.81 (3 H, s), 1.98 (1 H, s), and 2.04 (1 H, s). Using Freeman's method [23] for this compound the only product obtained was 3,4,5-trimethylpyrazole. 1-Hydroxy-4,5-dimethyl-2-phenylimidazole monohydrate was obtained by the procedure of Diels [24] and had m.p. 115—117 °C (lit.,[24] 120—122 °C), δ ([$^2H_6$]dimethyl sulphoxide) 8.05 (2 H, m), 7.3 (3 H, m), 2.01 (3 H, s), and 2.05 (3 H, s).

1-*Benzoyloxy*-3,4,5-*trimethylpyrazole*.— Dicyclohexylcarbodi-imide (1.03 g, 5 mmol) in dry tetrahydrofuran (10 ml) was added to a cold solution of benzoic acid (0.61 g, 5 mmol), and 1-hydroxy-3,4,5-trimethylpyrazole (0.63 g, 5 mmol) in tetrahydrofuran (20 ml). The solution was kept at 0° for 24 h. Removal of the urea by filtration, followed by evaporation of the solvent gave a yellow oil. This was dissolved in dry ether and a further quantity of the insoluble urea removed. Removal of the ether followed by distillation of the residue gave a light yellow *liquid*, b.p. 126—128 °C at 0.03 mmHg; $\nu_{max.}$ ($CHCl_3$) 1 775 (C=O) cm^{-1} (Found: C, 67.4; H, 6.1; N, 12.1. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%).

1-p-*Chlorobenzoyloxy*-3,4,5-*trimethylpyrazole*.— 1-Hydroxy-3,4,5-trimethylpyrazole (0.126 g, 1.0 mmol) was dissolved in 1N-sodium hydroxide solution (1 ml) and water (20 ml) was added. To this was added *p*-chlorobenzoyl chloride (0.18 g, 1.0 mmol) and the solution was shaken vigorously for 5 min. The white precipitate which formed was washed with water (3 × 50 ml), dried over P_2O_5, and recrystallised from chloroform–hexane (1 : 2) to give the ester as white clusters, m.p. 90—92° (Found: C, 59.05; H, 4.0; N, 10.6. $C_{13}H_{13}ClN_2O_2$ requires C, 59.0; H, 5.1; N, 10.7%), $\nu_{max.}$ (KBr) 1 780 (C=O) cm^{-1}; δ (CCl_4) 8.05 (2 H, d, *J* 8.5 Hz), 7.4 (2 H, d, *J* 9.5 Hz), 2.1 (3 H, s), 2.02 (3 H, s), and 1.9 (3 H, s). The *p*-nitro-ester was prepared in a similar fashion, m.p. 137—138.5 °C (lit.,[23] 137—139 °C).

1-*Benzoyloxy*-4,5-*dimethyl*-3-*phenylpyrazole* was prepared by adding benzoyl chloride (0.4 g) to the hydroxypyrazole (0.28 g, 1.5 mmol) in dry pyridine at 0 °C. The solution was stirred at 0 °C for 5 min and then at room temperature for 2 h. On pouring into ice water (50 ml) an emulsion formed. On saturation of the solution with sodium chloride a precipitate was obtained. This was washed with water (3 × 50 ml), dried, and recrystallised from benzene–hexane (1 : 4) to give the ester as needles, m.p. 77—79 °C, $\nu_{max.}$ (KBr) 1 780 (C=O) cm^{-1} (Found: C, 75.3; H, 5.9; N, 9.6. $C_{18}H_{16}N_2O_2$ requires C, 75.0; H, 5.5; N, 9.4%).

N-*Benzyloxycarbonylglycine* 1-*Hydroxy*-3,4,5-*trimethylpyrazole Ester*.—This was prepared by the dicyclohexylcarbodi-imide method as for the benzoate ester, and had m.p. 96—98 °C [chloroform–light petroleum (b.p. 60—80 °C) 1 : 1] (Found: C, 60.4; H, 6.25; N, 12.7. $C_{16}H_{19}N_3O_4$ requires C, 60.6; H, 6.0; N, 13.2%), δ (KBr) 3 220 (NH), 1 810 (ester C=O), and 1 720 (carbamate C=O) cm^{-1}, δ ($CDCl_3$) 7.33 (5 H, m), 5.11 (2 H, s), 3.95 (2 H, d, *J* 2 Hz), 2.14 (3 H, s), 2.08 (3 H, s), and 1.88 (3 H, s).

N-*Benzoylglycine* 1-*Hydroxy*-3,4,5-*trimethylpyrazole Ester*.—This was prepared by the mixed anhydride method using isobutyl chloroformate in dry tetrahydrofuran and was recrystallised from chloroform–light petroleum (1 : 4), m.p. 144—145 °C (Found: C, 63.7; H, 6.15; N, 14.2. $C_{15}H_{17}N_3O_3$ requires C, 63.5; H, 5.8; N, 14.3%), $\nu_{max.}$ (KBr) 3 295 (NH), 1 810 (ester C=O), and 1 665 (amide NH) cm^{-1}, δ ([$^2H_6$]acetone) 7.9 (2 H, q), 7.5 (3 H, m), 4.1 (2 H, d, *J* 6 Hz), 2.0 (3 H, s), 1.88 (3 H, s), and 1.83 (3 H, s).

1-*Benzoyloxy*-4,5-*dimethyl*-2-*phenylimidazole*.—This was prepared by the pyridine method above, and had m.p. 105—107 °C (cyclohexane) (Found: C, 70.2; H, 5.45; N, 9.5. $C_{18}H_{16}N_2O_2$ requires C, 70.55; H, 5.5; N, 9.6%), $\nu_{max.}$ (KBr) 1 770 (C=O) cm^{-1}, δ ([$^2H_6$]acetone) 8.2 (2 H, q, J_o 8, J_m 2 Hz), 7.73 (5 H, m), 7.3 (3 H, m), 2.19 (3 H, s), and 2.15 (3 H, s). The *p*-chlorobenzoate ester was obtained similarly, m.p. 95—97 °C (chloroform–pentane 1 : 1) (Found: C, 66.45; H, 4.9; N, 8.7. $C_{18}H_{15}ClN_2O_2$ requires C, 66.2; H, 4.6; N, 8.6%), $\nu_{max.}$ 1 780 (C=O) cm^{-1}.

pK_a *Determinations*.—Ionization constants were determined both by spectrophotometric and potentiometric methods; for the latter the procedure of Albert and Sergeant [25] was used. For the spectrophotometric method the Cary 14 pH stat assembly [26] was used to obtain values of optical density (O.D.) of the substrate as a function of pH, at intervals of 0.5 pH unit (0.1 unit close to the pK_a of the compounds). The pK_a values were obtained by comparing the experimental titration curve with theoretical titration curves plotted using equation (2). In all cases

$$(O.D.)_{obs} = (O.D.)_{max.}K_a/(a_{H^+}+K_a) \qquad (2)$$

the solvent was 1 : 4 dioxan–water, at 25 °C, with μ 1.0 ($NaClO_4$).

Product Analysis.—Reaction products were determined by a number of methods: (i) by comparing the u.v. spectrum at the end of a reaction with a spectrum of a mixture of the expected products under the same conditions (concentration, solvent, *etc.*) and (ii) by performing the reaction on a preparative scale and identifying the products either by t.l.c. on silica gel (Merck HF_{254}) or by isolation and comparison with authentic samples. Typical examples follow.

(a) *Hydrolysis of* (2a). The ester (0.3 g) in dioxan (2 ml) was added slowly to a 10^{-3}M solution of NaOH in water (20 ml), and the resulting solution stirred at room temperature for 3 h. The solution was acidified with 2N-HCl to pH 1. T.l.c. (methanol–ethyl acetate 1 : 1) of the aqueous solution showed that only benzoic acid and 1-hydroxy-4,5-dimethyl-2-phenylimidazole were present. On standing overnight the imidazole derivative precipitated in 62% yield, and was identical with an authentic sample.

(b) *Hydrolysis of the pyrazole esters* (1a *and* b). This was conducted similarly except that in this case the products were identified by t.l.c. only (methanol–ethyl acetate 6 : 1).

(c) *Aminolysis of* (2a). The ester (0.25 g) in dioxan (2 ml) was added dropwise to a 0.5M-glycine solution (20 ml) in water at pH 9.8. The resulting solution was

[23] J. P. Freeman, J. J. Gannon, and D. L. Surbey, *J. Org. Chem.*, 1969, **34**, 194.
[24] O. Diels, *Ber.*, 1918, **51**, 965.
[25] A. Albert and E. P. Sergeant, 'The Determination of Ionization Constants,' Chapman and Hall, London, 1971.
[26] A. F. Hegarty, P. J. Moroney, A. Moynihan, and F. L. Scott, *J.C.S. Perkin II*, 1972, 1892.

stirred for 1 h at room temperature, acidified with 2N-HCl, and extracted with chloroform (3 × 25 ml). The extract, on drying and evaporation of the solvent gave *N*-benzoylglycine (70%). T.l.c. (methanol) of the aqueous solution showed that the *N*-hydroxyimidazole was present. A similar procedure was used for glycine ethyl ester (pH 7.9).

(d) *Aminolysis of* 1-*benzoyloxy*-3,4,5-*trimethylpyrazole*. This was conducted in a similar manner except that t.l.c. only was used to identify the products (ether–ethyl acetate 1 : 1).

D. G. McC. is grateful to the Irish Government for a State Maintenance Award for Research.

[6/675 *Received*, 7*th April*, 1976]