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# Steric and electronic substituent effects in hydrolysis and aminolysis of 4-alkyl-4-methyl-2-aryl-4,5-dihydro-1,3-oxazol-5-ones†

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ABSTRACT: The kinetics and mechanism of the acid-catalysed hydrolysis of substituted 4-alkyl-4-methyl-2-aryl-4,5-dihydro-1,3-oxazol-5-ones to the corresponding 2-alkyl-2-benzoylaminopropanoic acids were studied. The Taft correlation of rate constants of the acid-catalysed hydrolysis with alkyl substitution at the 4-position of the 1,3-oxazol-5-one ring is non-linear. In the Hammett correlation, the value of $\rho$ decreases with increasing steric demand of the alkyl substituent. With the 4-isopropyl and *tert*-butyl derivatives, $\rho = -0.63$ and $-0.32$, respectively. The protonated 4-isopropyl and *tert*-butyl derivatives undergo nucleophilic attack by water at the carbonyl carbon atom at the 5-position of the 1,3-oxazol-5-one ring to the extents of ca 70% and 60%, respectively. Another reaction path consists in nucleophilic attack by water at the 2-position of the 1,3-oxazol-5-one ring. The reaction kinetics of aminolyses of substituted 4-isopropyl-4-methyl-2-phenyl-1,3-oxazol-5(4*H*)-ones (**1a**, **1b**, **1f**) giving substituted *N*-{1,2-dimethyl-1-[(propylamino)carbonyl]-propyl}benzamides (**3a**, **3b**, **3f**, **4a**) was studied in aqueous propylamine buffers. In the case of the aminolysis of **1a** and **1b** with propylamine, the rate-limiting step consists in the decomposition of the intermediate $\mathbf{In}^{\pm}$ catalysed by both the acidic and the basic buffer components. The base-catalysed route is four times faster in both cases. In the case of the aminolysis of **1f** with propylamine and that of **1a** with ethylenediamine, the rate-limiting step is the formation of the intermediate $\mathbf{In}^{\pm}$, the subsequent reaction step being accelerated by substitution and/or intramolecular catalysis. Copyright © 2005 John Wiley & Sons, Ltd.
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KEYWORDS: hydrolysis; aminolysis; substituent effects; azlactones

## INTRODUCTION

Substituted 4,5-dihydro-1,3-oxazol-5-ones (azlactones) belong among significant five-membered heterocyclic compounds having a wide variety of applications. For instance, they can serve as a precursors in the synthesis of substituted 4,5-dihydro-1*H*-imidazol-5-ones, which are important herbicides,[1] pharmaceuticals[2] and chiral[3] ligands. The 4-monoalkyl-substituted[4,5] 4,5-dihydro-1,3-oxazol-5-ones are derived from acylated natural amino acids as their anhydrides. In addition to synthetic applications of 4,5-dihydro-1,3-oxazol-5-ones, there are several reports on the kinetics and/or mechanism of their hydrolysis[6–8] or phenolysis.[8,9] However, these papers only concern 4-unsubstituted or 4-monoalkyl 4,5-dihydro-1,3-oxazol-5-ones, the hydrolysis of which is connected with racemization.[7] Only one paper[10] describes the determination of the aminolysis rates of 4,4-dimethyl-2-phenyl-4,5-dihydro-1,3-oxazol-5-one by ethyl esters of $\alpha$-amino acids catalysed by acetic acid in a non-aqueous medium.

The aim of the present work was to study the effect of substitution in both the aromatic moiety of the molecule and at the 4-position of the 2-aryl-4,5-dihydro-1,3-oxazol-5-one ring on the kinetics and mechanism of their hydrolysis and aminolysis (Scheme 1). Our products (if optically pure) have the advantage of containing a quaternary asymmetric carbon atom, which prevents racemization[7] via cleavage of the $\alpha$-hydrogen atom.

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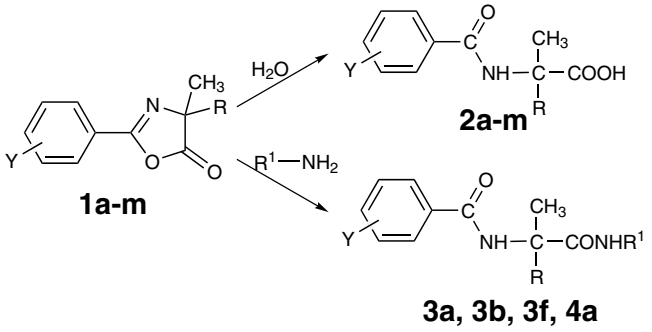
## EXPERIMENTAL

### Materials

The new dialkyl-2-aryl-4,5-dihydro-1,3-oxazol-5-ones were prepared by a known method[11] of ring closure and




| 1–2 | a | b | c | d | e | f | g | h | i | j | k | l | m |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Y** | H | 4-$OCH_3$ | 4-$CH_3$ | 3-Cl | 3-$NO_2$ | 4-$NO_2$ | 4-$NO_2$ | 4-$NO_2$ | $NO_2$ | H | 4-Cl | 4-$OCH_3$ | 4-$CH_3$ |
| **R** | *i*-$C_3H_7$ | *i*-$C_3H_7$ | *i*-$C_3H_7$ | *i*-$C_3H_7$ | *i*-$C_3H_7$ | *i*-$C_3H_7$ | $CH_3$ | $C_2H_5$ | *t*-$C_4H_9$ | *t*-$C_4H_9$ | *t*-$C_4H_9$ | *t*-$C_4H_9$ | *t*-$C_4H_9$ |

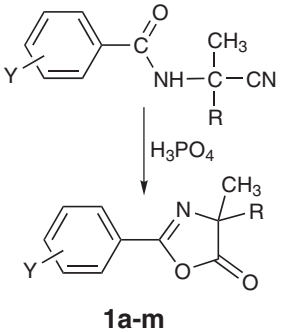
| | 3a | 3b | 3f | 4a |
|---|---|---|---|---|
| **Y** | H | 4-$OCH_3$ | 4-$NO_2$ | H |
| **R** | *i*-$C_3H_7$ | *i*-$C_3H_7$ | *i*-$C_3H_7$ | *i*-$C_3H_7$ |
| $\mathbf{R^1}$ | n-$C_3H_7$ | n-$C_3H_7$ | n-$C_3H_7$ | $CH_2CH_2NH_2$ |

**Scheme 1**

subsequent hydrolysis of substituted *N*-(1-cyano-1,2-dialkylpropyl)benzamides **1a**–**m** (Scheme 2).

### Kinetic measurements

The kinetic measurements were carried out on a Hewlett-Packard UV–VIS 8453 diode-array apparatus in 1 cm closable cells at 25 °C. First a suitable wavelength was chosen for the kinetic measurements on the basis of the spectra scanned from 200 to 1000 nm. Then the cell was charged with 2 ml of aqueous HCl or amine buffer solution. After attaining the chosen temperature (with maximum deviation ± 0.1 °C), 10 µl of methanolic solutions of the substrates **1a**–**m** were added so that the resulting substrate concentration would be about $5 \times 10^{-4}$ mol $l^{-1}$.




**Scheme 2**

The synthesis and characterization of compounds **1a**–**m**, **2a**–**m**, **3a**, **3b**, **3f** a **4a** are available as Supplementary material in Wiley Interscience.

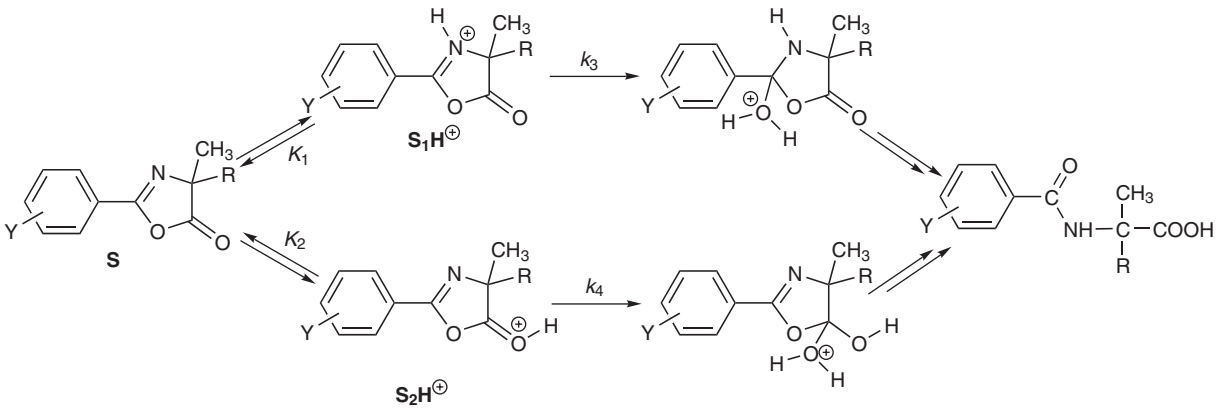
## RESULTS AND DISCUSSION

### Acid-catalysed hydrolysis

The kinetics of the acid-catalysed hydrolyses of 4-alkyl-2-aryl-4-methyl-4,5-dihydro-1,3-oxazol-5-ones **1a**–**m** were studied in aqueous solutions of hydrochloric acid (0.01–1 mol $l^{-1}$) under conditions of pseudo-first-order reaction at 25 °C. The hydrolysis was monitored spectrophotometrically and the spectra showed well-developed isosbestic points.

In principle, the mechanism of acid-catalysed hydrolysis can take two routes, both being preceded by a common fast protonation. This protonation can take place either at the more basic nitrogen ($pK_a \approx 0$; Ref. 8) to give the conjugated acid $\mathbf{S_1H^+}$ or at the less basic carbonyl group ($pK_a \approx -6$; Ref. 12) to give $\mathbf{S_2H^+}$. Both the conjugated acids formed undergo rate-limiting addition of a water molecule and, after a series of proton transfers, they give a single product, i.e. the corresponding carboxylic acid. The route via $\mathbf{S_2H^+}$ can formally be identified with an acid hydrolysis by the $A_{Ac}2$ mechanism (Scheme 3).

The factors that determine which of the routes will be preferred involve in particular the electronic effects of



**Scheme 3**

substituents in the benzene ring, but also the steric influence of alkyl group(s) near the carbonyl group.

A study of the acid hydrolysis of oxazolin-5-ones having no alkyl groups at the 4-position has been described.[5] A report[8] states that in this case the reaction only takes the route of nucleophilic attack of carbonyl group by a water molecule.

The site of attack can be diagnosed[13] by means of the Hammett and Taft correlation of the hydrolysis rate constants as depending on the substituent Y on the aromatic ring and substituent R at the 4-position of the oxazolin- 5-one nucleus. The hydrolysis rate monitored under pseudo-first-order conditions obeys the rate Eqn (1), where $k_{obs}$ ($s^{-1}$) is the observed rate constant and $c_S$ ($mol\,l^{-1}$) is the concentration of substrate **S** (**1a**–**m**):

$$v = k_{obs} c_S \qquad (1)$$

On the basis of the mechanism suggested, it is possible to derive Eqn (2) for the observed rate constant:

$$k_{obs} = \frac{k'_3 K_1 [H^+] + k'_4 K_2 [H^+]}{1 + (K_1 + K_2)[H^+]} = \frac{kK[H^+]}{1 + K[H^+]} \qquad (2)$$

where $k'_3 = k_3[H_2O]$, $k'_4 = k_4[H_2O]$ and $K = K_1 + K_2$.

Figure 1 presents the measured dependences of observed rate constant, $k_{obs}$, on the concentration of hydrochloric acid, $c_{HCl}$ ($mol\,l^{-1}$), for derivatives **1f–i** differing in substitution at the 4-position of the oxazoline ring (R = $CH_3$, $C_2H_5$, *i*-$C_3H_7$, *t*-$C_4H_9$).

All the dependences are linear throughout the concentration range measured, which means that the term $(K_1 + K_2)[H^+]$ in Eqn (2) is much less than 1 and the hydrolysis obeys the simplified kinetic equation

$$k_{obs} = k'_3 K_1 [H^+] + k'_4 K_2 [H^+] = kK[H^+] \qquad (3)$$

From the dependences found, it follows that the hydrolysis of derivative **1i** (R = *t*-$C_4H_9$) is the slowest and that of **1g** (R = $CH_3$) is the fastest. When plotting the logarithm of the product *kK* for the individual derivatives

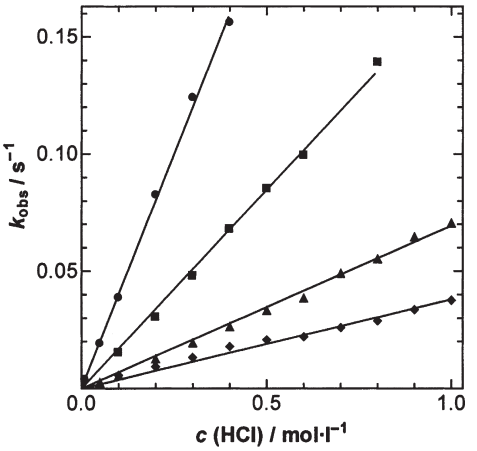



**Figure 1.** Dependences of observed rate constant, $k_{obs}$ ($s^{-1}$), of hydrolysis of derivatives **1f** (▲), **1g** (●), **1h** (■) and **1i** (◆) on concentration of hydrochloric acid ($mol\,l^{-1}$)

against the Taft steric constant[14,15] $E_S$, we obtain a non-linear dependence (Fig. 2).

The distinct acceleration of hydrolysis of derivative **1i** (R = *t*-$C_4H_9$), which should have reacted much more slowly owing to steric shielding of carbonyl group, can

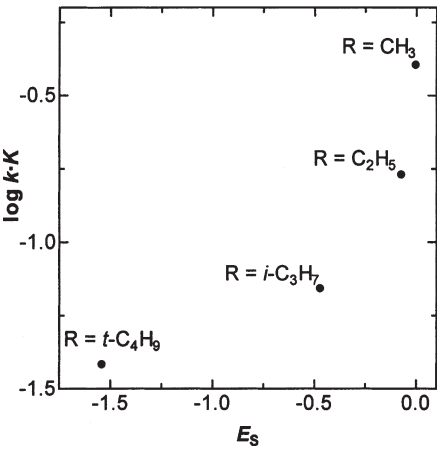



**Figure 2.** Taft correlation of log *kK* vs $E_S$ for derivatives **1f–i**

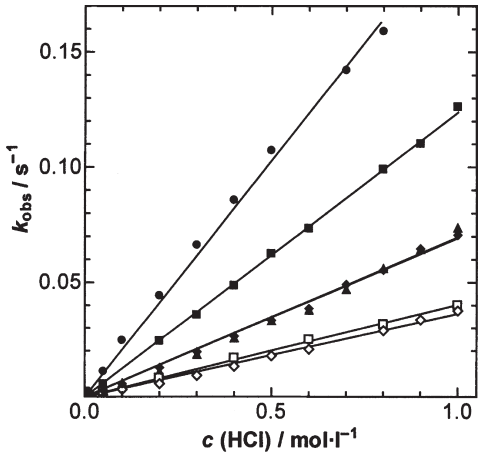



**Figure 3.** Dependences of observed rate constant, $k_{obs}$ ($s^{-1}$), of hydrolysis of derivatives **1a** (●), **1d** (■), **1e** (▲), **1f** (◆), **1k** (□) and **1i** (◇) on hydrochloric acid concentration (mol $l^{-1}$)

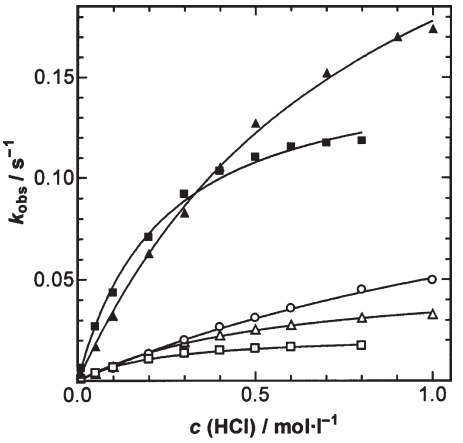



**Figure 4.** Dependences of observed rate constant, $k_{obs}$ ($s^{-1}$), of hydrolysis of derivatives **1b** (■), **1c** (▲), **1j** (○), **1m** (△) and **1l** (□) on hydrochloric acid concentration (mol $l^{-1}$)

be interpreted as a manifestation of the second reaction route proceedings via the conjugated acid $\mathbf{S_2H^+}$, in which the steric effect of alkyl groups does not make itself felt. The non-linear character of the Taft correlation indicates a gradual change in the reaction centre operating in the individual derivatives.

However, substitution of the benzene ring (Y) also strongly affects the site of nucleophilic attack, which is why we also studied the hydrolyses of substituted 2-phenyl-4-methyl-4-isopropyloxazol-5-ones **1a–f** and 2-phenyl-4-methyl-4-*tert*-butyloxazol-5-ones **1i–m**.

Figure 3 presents the dependences of observed rate constants on hydrochloric acid concentration for derivatives **1a**, **1d–f**, **1i** and **1k**; they are linear within the whole range measured and the observed rate constant ($k_{obs}$) obeys Eqn (3).

In the cases of derivatives **1b**, **1c**, **1j**, **1l** and **1m**, we obtained non-linear dependences (Fig. 4): the slope of dependence decreases with increasing concentration of hydrochloric acid, and in the limiting case (when all the substrate is present in its protonated form) is equal to zero.

The experimentally found values of rate constants given in Fig. 4 were fitted with curves corresponding to Eqn (2). Optimization gave the following values for the individual derivatives: **1b**, $k = (1.56 \pm 0.01) \times 10^{-1}\,\mathrm{l\,mol^{-1}\,s^{-1}}$ and $K = 4.22 \pm 0.03$ ($pK_a = -0.63$); **1c**, $k = (3.13 \pm 0.2) \times 10^{-1}\,\mathrm{l\,mol^{-1}\,s^{-1}}$ and $K = 1.24 \pm 0.01$ ($pK_a = -0.10$); **1j**, $k = (1.43 \pm 0.01) \times 10^{-1}\,\mathrm{l\,mol^{-1}\,s^{-1}}$ and $K = 0.55 \pm 0.07$ ($pK_a = +0.26$); **1m**, $k = (5.25 \pm 0.02) \times 10^{-2}\,\mathrm{l\,mol^{-1}\,s^{-1}}$ and $K = 1.79 \pm 0.16$ ($pK_a = -0.25$); **1l**, $k = (2.25 \pm 0.01) \times 10^{-2}\,\mathrm{l\,mol^{-1}\,s^{-1}}$ and $K = 4.49 \pm 0.34$ ($pK_a = -0.65$).

By plotting log *kK* of 2-phenyl-4-isopropyl-4-methyl-4,5-dihydro-1,3-oxazol-5-ones **1a–f** and 2-phenyl-4-*tert*-butyl-4-methyl-4,5-dihydro-1,3-oxazol-5-ones **1i–m** against the $\sigma$ constants of individual substituents[13] on the benzene ring, we obtained the Hammett relationships given in Fig. 5.

The values obtained for the product *kK* correspond to two processes, *viz.* reversible protonation of the oxazolin-5-one at both its centres of basicity ($K_1$ and $K_2$), giving the respective conjugated acids, and their subsequent reaction with water. Hence the value of $\rho$ must reflect the relative contributions of individual reaction routes. For the oxazolin-5-ones having no 4-alkyl substituent, it is claimed[8] that $\rho$ has a value of about $-1.25$ (Fig. 5); in addition, experiments with these compounds that had been isotopically labelled showed that the attack by a water molecule takes place only at the carbonyl group. In our case, it was found that substitution at the 4-position by a methyl and isopropyl group lowered the value of $\rho$ by about half ($\rho = -0.63$), and that by a *tert*-butyl group and methyl group by as much as three-quarters

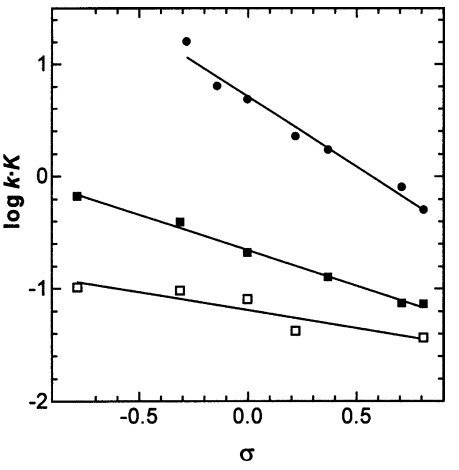



**Figure 5.** Hammett correlation of hydrolysis of isopropyl derivatives **1a–f** (■), *tert*-butyl derivatives **1i–m** (□), and 2-aryl-4,5-dihydro-1,3-oxazol-5-ones (taken from Ref. 5) with $\sigma$ and $\sigma^-$ constants

($\rho = -0.32$). If the reaction proceeded purely as an attack of C-2 carbon by a water molecule, then the value of $\rho$ should be about +1 (protonation $\rho \approx -1$, and nucleophilic attack itself $\rho \approx +2$). A similar value (+0.9) was reported[8] for the base hydrolysis of oxazolin-5-ones by the *E*1*cB* mechanism, where the rate-limiting step consists in the rupture of the C-2—O bond. From what has been said above, it follows that in the cases of the isopropyl and *tert*-butyl derivatives, the attack at the C-2 carbon atom operates to extents of 30 and 40%, respectively.

The increasing proportion of C-2 attack also follows from the fact that the faster reacting derivatives (4-OMe and 4-Me) require application[13] of the $\sigma^-$ constants. In these cases there is direct conjugation between the substituent and the reaction centre.

## Aminolysis

The rates of aminolyses of **1a**, **1b** and **1f** were measured under pseudo-first-order conditions in aqueous solutions of propylamine buffer used in excess, the substrate concentration being $c_S = 10^{-4}\,\mathrm{mol\,l^{-1}}$. The spectra show well-developed isosbestic points, and the aminolysis rates also obey the kinetic Eqn (1). The general kinetic Scheme 4 can be suggested for the aminolysis of oxazolinones **1a**, **1b** and **1f**; it can formally be identified with that of aminolysis of $\beta$-lactams.[16–19]

The first reaction step involves addition of amine to the carbonyl group of oxazoline giving the tetrahedral zwitterionic intermediate $\mathbf{In}^{\pm}$. Generally, the decomposition of the intermediate can be assisted by the basic or acidic buffer component, or the intermediate can decompose spontaneously and very rapidly in a non-catalysed way.[16]

Figures 6 and 7 show the dependences of the observed rate constant, $k_{obs}$ ($s^{-1}$), (involving the aminolysis with simultaneously proceeding hydrolysis) measured in propylamine buffers with derivatives **1a** and **1b** on the buffer concentration, $c_{Buffer}$ ($\mathrm{mol\,l^{-1}}$), with various ratios of the acidic to basic buffer components (pH 10.30–11.28). The dependences obtained are linear, and the observed rate constant can be expressed by Eqn (4):

$$k_{obs} = k_{OH}[OH^-] + k_{Buffer}[Buffer] \qquad (4)$$

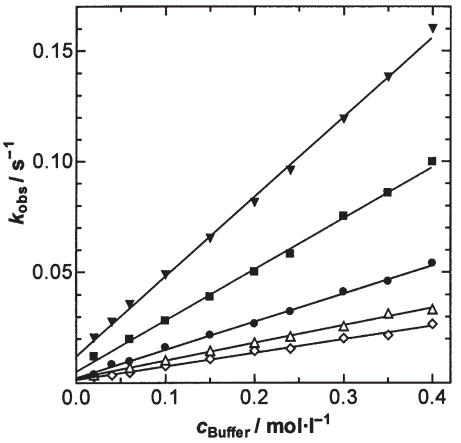



**Figure 6.** Dependences of observed rate constant, $k_{obs}$ ($s^{-1}$), of aminolysis of derivative **1a** on concentration of propylamine buffer, $c_{buffer}$ ($\mathrm{mol\,l^{-1}}$), at various pH values: 10.30 (1:4a, ◆); 10.42 (1:3a, ○); 10.66 (1:2a, ●); 10.89 (1:1, Δ); 11.28 (2:1b, ▼)

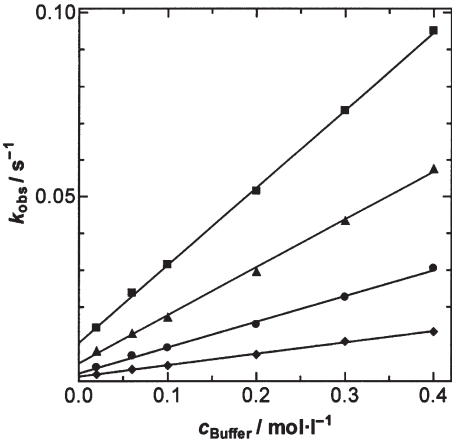
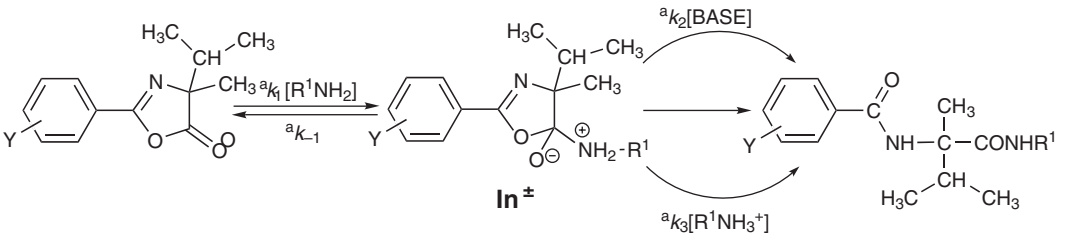



**Figure 7.** Dependences of observed rate constant, $k_{obs}$ ($s^{-1}$), of aminolysis of derivative **1b** on concentration of propylamine buffer, $c_{buffer}$ ($\mathrm{mol\,l^{-1}}$) at various pH values: 10.30 (1:4a, ◆); 10.66 (1:2a, ●); 10.89 (1:1, ▲); 11.28 (2:1b, ■)

The intercepts on the ordinate in Figs 6 and 7 represent the values of product $k_{OH}[OH^-]$, from which we determined the values of the rate constant of hydroxide ion-catalysed hydrolysis for **1a** as $k_{OH} = 6.90 \pm 0.12\,\mathrm{l\,mol^{-1}\,s^{-1}}$ and for **1b** $k_{OH} = 4.04 \pm 0.19\,\mathrm{l\,mol^{-1}\,s^{-1}}$. The ratios of the populations of products of aminolysis and those of




**Scheme 4**

base-catalysed hydrolysis **2a/3a** and **2b/3b** depend on the pH values of the buffers and the buffer concentrations. These ratios can be calculated from Eqn (4) or found graphically from Figs 6 and 7. For instance, with the buffer (2:1b, pH = 11.2, $c_{\text{Buffer}} = 0.4\ \text{mol}1^{-1}$), the molar ratio of products **2a/3a** is equal to 14. By plotting the values of $k_{\text{Buffer}}$ against the molar fraction of amine in buffer, $\alpha$ ($\alpha = [R^1NH_2]/[\text{Buffer}]$; $[\text{Buffer}] = [R^1NH_2] + [R^1NH_3^+]$), we obtained quadratic dependences only describing the aminolysis (Fig. 8), expressed by Eqn (5):

$$k_{\text{Buffer}} = a\frac{[\text{RNH}_2][\text{RNH}_3^+]}{[\text{Buffer}]} + b\frac{[\text{RNH}_2]^2}{[\text{Buffer}]} \qquad (5)$$

If the concentration ratios in Eqn (5) are expressed by the respective values of the molar fraction $\alpha$, then Eqn (5) becomes.

$$k_{\text{Buffer}} = [\alpha^2(b-a) + \alpha a][\text{Buffer}] \qquad (6)$$

Optimization of the quadratic dependence [Eqn (6), Fig. 8] gave values of the ratios of coefficients for **1a** of $b/a = 4.1$ and for **1b** of $b/a = 3.9$. The physico-chemical meaning of the coefficients $a$ and $b$ can be derived from Scheme 4. As the aminolysis is accelerated also by the acidic buffer component, the kinetic equation [Eqn (7a)] applies (according to Scheme 4) to the acid-catalysed decomposition of $\mathbf{In}^{\pm}$ ($k_{\text{ac}}$):

$$k_{\text{ac}} = \frac{{}^{a}k_1\ {}^{a}k_3\ [R^1NH_2]\ [R^1NH_3^+]}{{}^{a}k_{-1} + {}^{a}k_3\ [R^1NH_3^+]} \qquad (7a)$$

The analogous kinetic equation [Eqn (7b)] applies to the base-catalysed decomposition of $\mathbf{In}^{\pm}$ ($k_{\text{base}}$):

$$k_{\text{base}} = \frac{{}^{a}k_1\ {}^{a}k_2\ [R^1NH_2]\ [\text{Base}]}{{}^{a}k_{-1} + {}^{a}k_2\ [\text{Base}]} \qquad (7b)$$

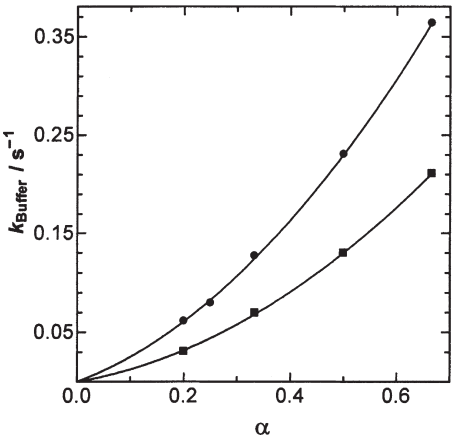



**Figure 8.** Dependence of $k_{\text{Buffer}}$ on molar fraction $\alpha$ of propylamine in buffer for **1a** (●) and **1b** (■)

If in the rate-limiting step of decomposition of intermediate $\mathbf{In}^{\pm}$ both acidic and basic buffer components are operating simultaneously, it can be presumed that ${}^{a}k_{-1} \gg {}^{a}k_3[R^1NH_3^+]$ and ${}^{a}k_{-1} \gg {}^{a}k_2[\text{Base}]$. The base concentration in amine buffer is given as the sum of all the basic components present, i.e. $[\text{Base}] = [R^1NH_2] + [OH^-]$. At pH in the range 10–12, $[OH^-]$ is more than one order of magnitude lower than the concentration of amine, hence $[\text{Base}] \approx [R^1NH_2]$. With these presumptions, Eqns (7a) and (7b) are simplified to

$$k_{\text{ac}} = \frac{{}^{a}k_1\ {}^{a}k_3}{{}^{a}k_{-1}}[R^1NH_2]\ [R^1NH_3^+] \qquad (8a)$$

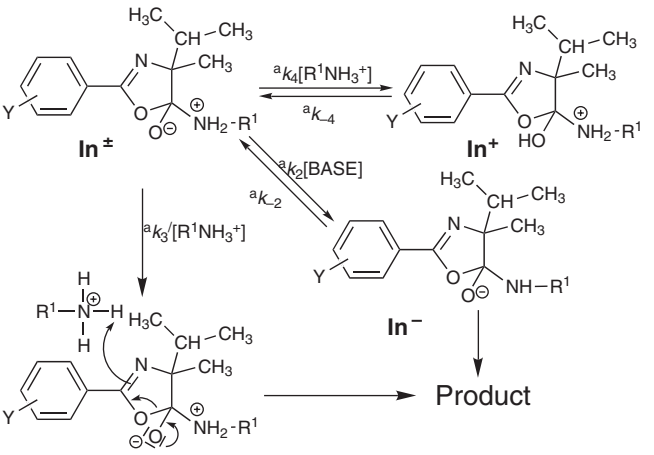
$$k_{\text{base}} = \frac{{}^{a}k_1\ {}^{a}k_2}{{}^{a}k_{-1}}\left[R^1NH_2\right]^2 \qquad (8b)$$

From Eqns (5), (8a) and (8b) it is possible to see the meaning of the coefficients $a$ and $b$, since the ratio $b/a$ expresses ${}^{a}k_2/{}^{a}k_3$, i.e. the ratio of the decomposition rates of the intermediate ($\mathbf{In}^{\pm}$) by the base- and acid-catalysed routes:

$$\frac{b}{a} = \frac{{}^{a}k_1\ {}^{a}k_2}{{}^{a}k_{-1}} \times \frac{{}^{a}k_{-1}}{{}^{a}k_1\ {}^{a}k_3} = \frac{{}^{a}k_2}{{}^{a}k_3} \qquad (9)$$

From what has been said, it clearly follows that the rate-limiting step of aminolysis of derivatives **1a** and **1b** by propylamine involves both proton transfer from $\mathbf{In}^{\pm}$ to the basic buffer component and proton transfer from the acidic buffer component to $\mathbf{In}^{\pm}$. The base-catalysed decomposition (${}^{a}k_2/{}^{a}k_3$) proceeds about four times faster than acid-catalysed decomposition, which applies to both the derivatives **1a** and **1b**. The proton transfer from acidic buffer components can be directed to the negatively charged oxygen atom in $\mathbf{In}^{\pm}$ giving $\mathbf{In}^{+}$ (Scheme 5).

Since $\mathbf{In}^{+}$ practically does not decompose to the product, this route can be considered a 'blind alley'. The




**Scheme 5**

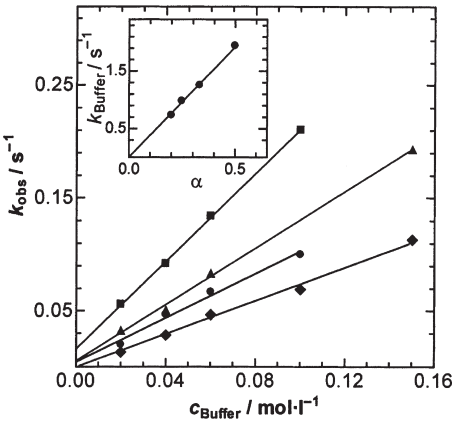



**Figure 9.** Dependence of observed rate constant, $k_{obs}$ ($s^{-1}$), of aminolysis of derivative **1f** on concentration of propylamine buffer, $c_{Buffer}$ ($mol\,l^{-1}$), at various pH values: 10.30 (■); 10.42 (▲); 10.66(●) and 10.89 (◆). Inset: dependence of $k_{Buffer}$ for **1f** on molar fraction, $\alpha$, of propylamine in buffer

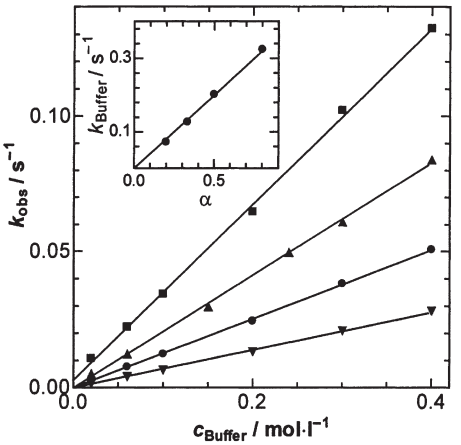



**Figure 10.** Dependence of observed rate constant, $k_{obs}$ ($s^{-1}$), of aminolysis of derivative **1a** on concentration of ethylenediamine buffer, $c_{Buffer}$ ($mol\,l^{-1}$), at various pH values: 11.26 (■); 11.03 (▲); 10.76(●); and 10.42 (◆). Inset: dependence of $k_{Buffer}$ for **2a** on molar fraction, $\alpha$, of ethylenediamine in buffer

route leading to the product involves a synchronous proton transfer directly to the nitrogen atom of the 1,3-oxazol-5-one ring $\mathbf{In}^{\pm}$ ($^{a}k'_3[R^1NH_3^+]$, $^{a}k_3 = {}^{a}k'_3 - {}^{a}k'_4\,{}^{a}k_{-4}$), in analogy with the acid-catalysed aminolysis of $\beta$-lactams[18] (Scheme 5).

Figure 9 presents the dependences of the observed rate constant of aminolysis, $k_{obs}$ ($s^{-1}$), of the nitro derivative **1f** on concentration of propylamine buffer, $c_{Buffer}$ ($mol\,l^{-1}$), for various ratios of the acidic and basic buffer components (pH 10.30–10.89). The dependences measured are linear, and the observed rate constant can be expressed by Eqn (5).

The intercepts on the ordinate in Fig. 9 represent the product $k_{OH}[OH^-]$, from which we could determine the value of the rate constant of $OH^-$ ion-catalysed hydrolysis, $k_{OH} = 13.10 \pm 0.03\,l\,mol^{-1}\,s^{-1}$. By plotting the values of $k_{Buffer}$ against the molar fraction $\alpha$ of amine in buffer (Fig. 9, inset), we obtained a linear dependence crossing the origin of coordinates, from which it follows that $k_{obs}$ depends only on the concentration of basic buffer components, i.e. propylamine and $OH^-$ [Eqn (10)]:

$$k_{obs} = k_{OH}[OH^-] + {}^{a}k_1[R^1NH_2] \qquad (10)$$

This different course of the dependence, compared with that for derivatives **1a** and **1b**, can be interpreted by a change in the rate-limiting step of the aminolysis. The nitro group in derivative **1f** causes an overall acceleration of the aminolysis ($k_{obs}$); however, particularly accelerated is the subsequent decomposition of $\mathbf{In}^{\pm}$. This means that the catalysis of decomposition of $\mathbf{In}^{\pm}$ by the acidic or basic buffer components will not make itself felt. In this case, the rate-limiting step consists of the addition of propylamine to carbonyl group, i.e. formation of $\mathbf{In}^{\pm}$, and the rate constant of aminolysis is $^{a}k_1 = 3.81 \pm 0.14\,l\,mol^{-1}\,s^{-1}$.

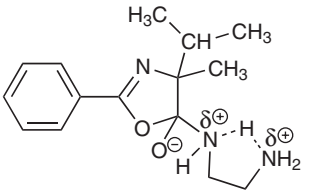


**Figure 11.** Intramolecular general base catalysis in aminolysis of **1a**

Further, we studied the aminolysis of **1a** in ethylenediamine buffers, where the aminolysis product **4a** is formed along with the hydrolysis product **2a**. Figure 10 presents the dependences of the observed rate constant measured in ethylenediamine buffers, $k_{obs}$ ($s^{-1}$), for derivative **1a** on concentration of ethylenediamine buffer, $c_{Buffer}$ ($mol\,l^{-1}$), at various pH values.

In contrast to propylamine buffers, the dependence of $k_{Buffer}$ on molar fraction $\alpha$ of amine in buffer is linear, and the acidic buffer component is kinetically inactive (Fig. 10, inset). In this case, the linear dependence can be interpreted by the decomposition of $\mathbf{In}^{\pm}$ being assisted by intramolecular acid–base catalysis with participation of the amino group of the ethylenediamine moiety of $\mathbf{In}^{\pm}$ in an analogous way to that described[15] for benzylpenicillin. It can be presumed that the intramolecular acid–base catalysis will accelerate the decomposition of the intermediate to such an extent that in this case also the rate-limiting step of reaction will consists in the formation of $\mathbf{In}^{\pm}$. The effective molarity (Fig. 11) of the terminal group of the ethylenediamine moiety and/or its conjugated acid is very high.[20,21] The observed rate constant ($k_{obs}$) obeys Eqn (10), and $^{a}k_1 = 0.39 \pm 0.01\,l\,mol^{-1}\,s^{-1}$.

## CONCLUSION

In the acid-catalysed hydrolysis of 4-alkyl-4-methyl-2-aryl-4,5-dihydro-1,3-oxazol-5-ones (**1a**–**m**), the steric bulkiness of the alkyl group at the 4-position gradually more and more favours the attack of the C-2 carbon atom by a water molecule. In the case of the 4-*tert*-butyl derivatives, the proportions of the hydrolyses taking place at the C-5 and C-2 carbon atoms are about 70 and 30%, respectively. The aminolysis using propylamine with 4-isopropyl-4-methyl-2-phenyl-1,3-oxazol-5(4*H*)-one (**1a**) and 4-isopropyl-2-(4-metoxyphenyl)-4-methyl-1,3-oxazol-5(4*H*)-one (**1b**), giving the respective amides **3a** and **3b**, takes place in such a way that the rate-limiting step is the decomposition of the intermediate $\mathbf{In}^{\pm}$, which is catalysed by both buffer components. The base-catalysed decomposition is four times faster than the acid-catalysed decomposition in both cases (**1a** and **1b**). The nitro group at the 4-position of the benzene ring of **1f** causes an overall acceleration of aminolysis compared with that of **1a** and **1b** and a change in the rate-limiting step. Intramolecular acid-base catalysis is operating in the case of aminolysis of **1a** by etylenediamine giving *N*-(1-{[(2-aminoethyl)amino]carbonyl}-1,2-dimethylpropyl) benzamide (**3a**).

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