Kinetics of Racemization and Hydrolysis of Oxazol-5(4*H*)-ones

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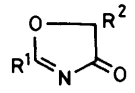
The kinetics of hydrolysis and ionization of three substrates, 4-benzyl-2-phenyl-, 4-methyl-2-phenyl- and 4-benzyl-2-methyl-oxazol-5(4*H*)-one have been investigated. Under neutral and basic conditions both reactions are buffer and hydroxide ion catalysed. In aqueous solution, ionization, leading to racemization of the optically active oxazolones, and ring opening occur competitively with similar rate constants. In solvents with lower dielectric constants, ionization becomes much faster than ring opening. An intermediate corresponding to a minor reaction pathway has been detected; it results probably from the addition of water to the C–N double bond.

The oxazol-5(4*H*)-ones have long been known to be relatively acidic substrates responsible in most cases for the racemization observed during peptide synthesis.[1] The kinetics and mechanism of their hydrolysis have been studied by two groups [2,3] but although the formation of the enolate resulting from ionization was detected as a side-equilibrium under basic conditions, no attempt was made to measure its rate of formation and ascertain its effect on the kinetics of hydrolysis.

As a part of a project designed to produce optically active acyl-amino-acids by hydrolysis of oxazolones in the presence of chiral catalysts,[4] we have undertaken a full kinetic study of the ionization and hydrolysis of substrates (1)—(3). The information obtained, together with some data on the alcoholysis reaction, show that the rate of ionization is frequently comparable to that of ring opening. Furthermore, the detection of an intermediate indicates that the mechanism of the hydrolysis might be more complex than previously thought.



(1) R^1 = Ph, R^2 = CH_2Ph
(2) R^1 = Ph, R^2 = Me
(3) R^1 = Me, R^2 = CH_2Ph

Experimental

Materials.—The oxazolones (1)—(3) were prepared as described previously.[4] The organic solvents, salts, and buffers were analytical reagents used without further purification except the dioxan which had to be freed from peroxides by a conventional method.[5]

Methods.—The kinetics of deprotonation and hydrolysis were measured by following the appearance and disappearance of the enolates of the oxazolones at 350 nm for the 2-phenyl-oxazolones and at 256 nm for 2-methyl-4-benzyloxazolone. The fast reaction (absorbance increase) was measured on a Durrum stopped flow spectrophotometer and the slow reaction on a Cary 16 or a Unicam 1800 spectrophotometer. The hydrolysis reactions were run in distilled water at an ionic strength of 0.1 in the presence of 1% acetonitrile.

The percentage of enolate at high pH was measured by pH jump experiments as explained in the Results section. The results were further checked by one pH jump determination in which the percentage of enolate is obtained from the ratio in the change in absorbance during the hydrolysis in acetate buffer at pH 5 between a solution incubated for 5 s at pH 12, then acidified, and a solution in which the substrate is injected directly at pH 5. The two methods agree within 1—2%.

The general mathematical treatment of the kinetics corresponding to Scheme 1 (see Results section) is based on standard methods.[6]

The enolate concentration will vary with time according to equation (1) where equation (2) holds, λ_1 and λ_2 being the

$$[En^-] = \frac{k_1 [OX]_0}{\lambda_1 - \lambda_2} (e^{-\lambda_1 t} - e^{-\lambda_2 t}) \quad (1)$$

$$\lambda_{1,2} = \frac{(k_1 + k_{-1} + k_2) \pm \sqrt{(k_1 + k_{-1} + k_2)^2 - 4k_{-1}k_2}}{2} \quad (2)$$

apparent rate constants of the fast and slow steps, respectively.

The individual rate constants k_1, k_{-1}, and k_2 are obtained from equations (3) or (4). In equation (3), $[En^-]_{extrap.}$

$$k_1 = \frac{[En^-]_{extrap.}}{[OX]_0} \times (\lambda_1 - \lambda_2) \quad (3)$$

$$k_1 = \frac{[En^-]_{max.}}{[OX]_0} \times \frac{(\lambda_1 - \lambda_2)}{(e^{-\lambda_1 t_{max.}} - e^{-\lambda_2 t_{max.}})} \quad (4)$$

is the enolate concentration obtained by extrapolation to t = 0 of the absorbance change of the slow step divided by the extinction coefficient; in equation (4), the value at the time of maximum enolate accumulation is used. k_{-1} and k_2 are derived from equations (5) and (6) leading to (7). The attribution

$$\lambda_1 + \lambda_2 - k_1 = k_{-1} + k_2 \quad (5)$$

$$\lambda_1\lambda_2 = k_{-1}k_2 \quad (6)$$

$$k_{-1,2} = \frac{(\lambda_1 + \lambda_2 - k_1) \pm \sqrt{(\lambda_1 + \lambda_2 - k_1)^2 - 4\lambda_1\lambda_2}}{2} \quad (7)$$

of the k_+ and k_- value to k_{-1} or k_2 is done on the basis of the extra-kinetic criterion of constant pK_a [equations (8) or (9)].

$$\frac{k_1}{k_{-1}} = \frac{(k_{1 \cdot OH}[OH^-] + k_{1 \cdot B}[B] + k_{1 \cdot H_2O})}{(k_{-1 \cdot H_2O} + k_{-1 \cdot BH^+}[BH^+] + k_{-1 \cdot H^+}[H^+])} = \frac{K_a}{[H^+]} \quad (8)$$

$$k_{-1} = k_1 [H^+]/K_a \quad (9)$$

Accordingly, the value of k_+ or k_- closest to that calculated by this formula is attributed to k_{-1}. The constants obtained in this way are then plotted as a function of the buffer concentration and extrapolated, yielding equations (10)—(12).

$$k_{1\ extrap.} = k_{1 \cdot H_2O} + k_{1 \cdot OH}[OH^-] \quad (10)$$

$$k_{-1\ extrap.} = k_{-1 \cdot H^+}[H^+] + k_{-1 \cdot H_2O} \quad (11)$$

$$k_{2\ extrap.} = k_{2 \cdot H_2O} + k_{2 \cdot OH}[OH^-] \quad (12)$$

The values of $k_{1 \cdot H_2O}$, $k_{1 \cdot OH}$, $k_{-1 \cdot H^+}$, and $k_{-1 \cdot H_2O}$ are calculated together by a curve fitting method minimizing the sum of the squares of the percentage of error in which the condition

$$\frac{k_{1 \cdot OH}[OH^-]}{k_{-1}} = \frac{k_{1 \cdot H_2O}}{k_{-1 \cdot H^+}[H^+]} \quad (13)$$

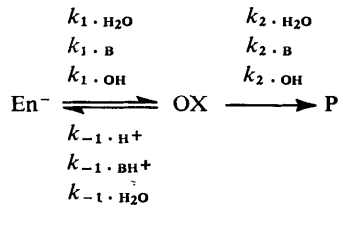
(13) required by the principle of microscopic reversibility was imposed. The values of $k_{2 \cdot OH}$ and $k_{2 \cdot H_2O}$ were obtained from plots of $k_{2\ extrap.}$ *versus* $[OH^-]$ and $k_{2\ extrap.}/[OH^-]$ *versus* $[H^+]$, respectively (to minimize the effect on $k_{2 \cdot H_2O}$ from a small intercept with a large slope).

Detection of the Intermediate with Hydroxylamine.—The solution to be analysed (1 ml) containing the oxazolone was added to a 1.33M-NH_2OH·HCl–2M-NaOH solution (1 ml). After 5 min, 20% $FeCl_3 \cdot 6H_2O$ in 4M-HCl (1 ml) was added. After 10 min, the absorbance at 540 nm was read against a blank. For 4-benzyl-2-phenyloxazolone, the extinction coefficient is 5.8×10^2 l mol^{-1} cm^{-1}; under the same conditions, *N*-benzoyl-L-phenylalanine methyl ester gives a value of $(5.4 \pm 0.3) \times 10^2$ l mol^{-1} cm^{-1}.

Benzoylalanyl O-(4-Methyl-2-phenyloxazolinyl) Ester.—the enol ester ' dimer ' of the oxazolone is formed by adding the corresponding oxazolone dissolved in acetonitrile to water at pH 7.8 so that its concentration remains above 10^{-3}M. The ' dimer ' precipitates as a solid, m.p. 234—236 °C, *m/e* 350 (M^+); $\nu_{max.}$ (KBr disk) 3 260, 1 785, 1 745, 1 680, 1 620, 1 575, and 1 535 cm^{-1}; δ($CDCl_3$) 7.86—7.26 (10 H, Ph), 1.57—1.70 and 1.76 (6 H, d + s, 2 CH_3), 5.0, 5.12, 5.23, 5.35, (1 H, q, CH), and 6.66 (1 H, NH).

Results

Scheme 1 for the hydrolysis in neutral or basic conditions



Scheme 1

applies to all the oxazolones where OX, En$^-$, and P stand for the neutral oxazolone, the corresponding enolate, and the product. For the deprotonation and ring-opening reaction, there are three possible pathways: a water reaction, a buffer catalysed, and a hydroxide ion catalysed pathway.

The final product of reactions run at pH 7.8 or 11.0 has been identified by i.r. spectroscopy and t.l.c. as the corresponding acyl-amino-acid.

The kinetics of hydrolysis have been measured on three substrates, 4-benzyl-2-phenyl- (1), 4-methyl-2-phenyl- (2), and the 4-benzyl-2-methyl-oxazolone (3). The first has been investigated most thoroughly.

Determination of the Ratio of the Rates of Deprotonation versus *Ring Opening at High pH and of the Extinction Coefficient of the Enolate.*—A full kinetic analysis of the hydrolysis of the oxazolones under neutral and basic conditions where they can ionize requires a determination of whether or not the acid–base reaction is a fast equilibrium as assumed in previous investigations.[2,3]

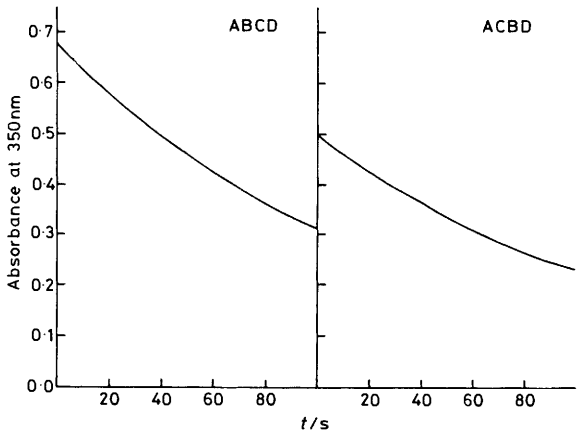


Figure 1. Enolate absorbance measured in pH jump experiments with the 4-benzyl-2-phenyloxazolone. Reagents: A, NaOH (2.7 ml, 10^{-2}M); B, acetic acid (30 µl, 1M); C, oxazolone (20 µl, 7.9×10^{-3}M) in acetonitrile; D, NaOH (250 µl, 1M). In the first experiment, the oxazolone (C) is added to the acetate buffer and after 8 s brought to pH 12: $k_{obs} = 9.7 \times 10^{-3}$ s^{-1}, $(D_0 - D_\infty)_{extrap.} = 0.675$; after correction for 8 s at pH 5, $D_0 = 0.677$. In the second experiment, the oxazolone is added to NaOH at pH 12, neutralized after 8 s, and brought back to pH 12 after 8 s: $k_{obs} = 9.8 \times 10^{-3}$ s^{-1}, $(D_0 - D_\infty)_{extrap.} = 0.460$; after correction for percentage hydrolysed at pH 12 and 5, $D_0 = 0.497$

If the rate of deprotonation is not much faster than the rate of ring opening, the oxazolone will never yield 100% enolate even at a pH much higher than the pK_a ($k_1 \gg k_{-1}$). Instead, at high pH, it will quickly be transformed into a mixture of enolate and product in the ratio k_1/k_2. Then the enolate will decompose slowly with a rate constant given by equation (14).

$$k_{slow} = k_{-1}k_2/(k_1 + k_2) \quad (14)$$

That this is indeed the case is shown by pH jump experiments and by working with an optically active oxazolone.

In the pH jump (Figure 1), two experiments are compared. In the first, the oxazolone stock solution is injected into a buffer at pH 5.0 and after 8 s brought to pH 12; the enolate concentration is then followed as a function of time. In the second experiment, the oxazolone is injected into NaOH at pH 12, neutralized after 8 s, and brought back to pH 12. Clearly, the yield of anion detected in the second experiment is significantly lower. The amount of oxazolone that has irreversibly disappeared during the 8 s at pH 12 is much larger than calculated from the rate of enolate disappearance at that pH. The data are consistent with the partitioning of the oxazolone into 28% product and 72% enolate (after correction for the amount hydrolysed before neutralization).

If an optically active oxazolone is hydrolysed at pH 11 in the pH-stat, there is a residual optical activity in the product corresponding to an enantiomeric excess of 27.3% for the 4-benzyl-2-phenyloxazolone (by comparison with an optically pure sample of *N*-benzoyl-L-phenylalanine). This corresponds to an enolate yield of 72.7%.

The percentage of enolate is determined by analogous experiments for the three oxazolones. From these and the absorbance extrapolated to zero time of a solution of known concentration at high pH, the true extinction coefficients of

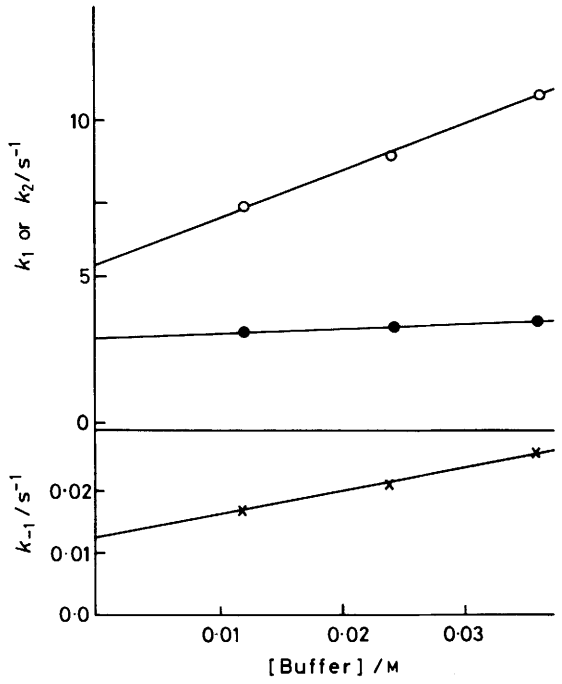


Figure 2. Effect of the buffer on the rates of deprotonation k_1 (○), reprotonation (×), and ring opening (●) of the 4-benzyl-2-phenyloxazolone, in carbonate buffer at pH 10.38 and 25 °C

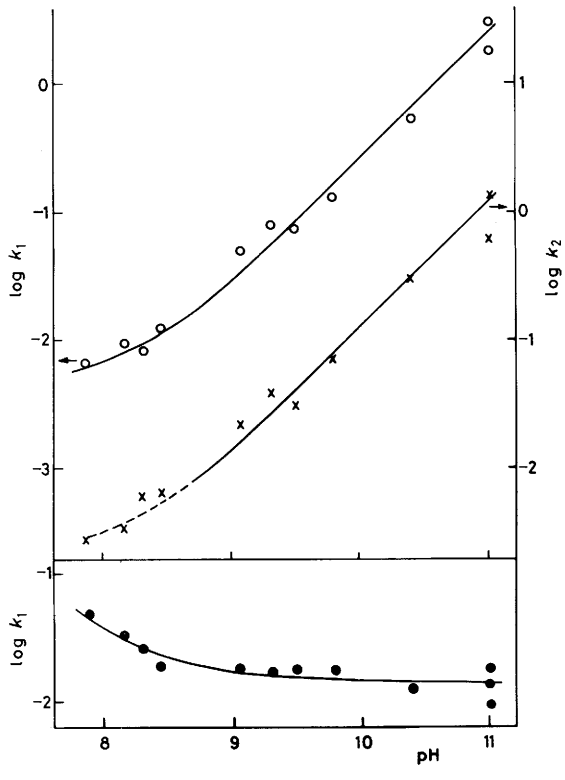


Figure 3. pH Dependence of the rate constants of protonation, deprotonation, and ring opening of 4-benzyl-2-phenyloxazolone at 25 °C

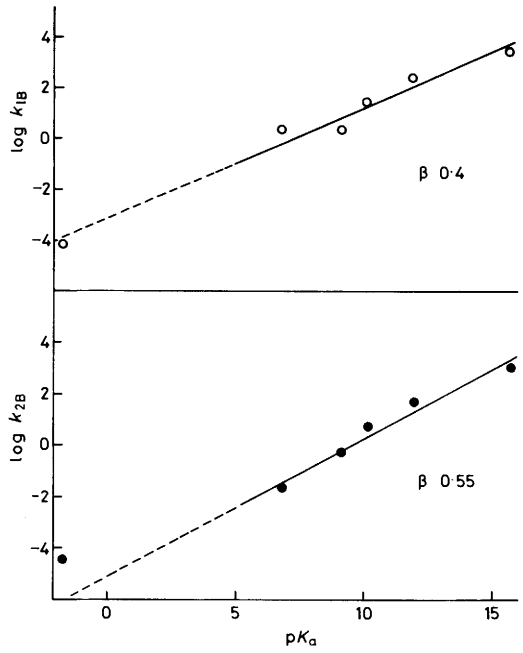


Figure 4. Brönsted plots for the rate constants of deprotonation and ring opening of the 4-benzyl-2-phenyloxazolone. The β values calculated by excluding the water points are 0.4 ± 0.06 for ionization (○) and 0.55 ± 0.05 for ring opening (●)

Table 1. Maximum enolate yields at high pH in water and extinction coefficient of the enolates

Oxazolone	Anion (%)	$\lambda_{max.}$/ nm	$\Delta\varepsilon_{app.}$/ l mol^{-1} cm^{-1}	$\Delta\varepsilon$/ l mol^{-1} cm^{-1}
(1)	71.8 [a]	350	12 890	17 950
(2)	67.0 [a]	350	10 500	15 560
(3)	57.3 [b]	256	3 835	6 690

[a] At pH 11.0. [b] At pH 12.0.

the enolates are easily determined. These data are collected in Table 1.

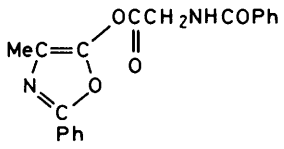
Rate Constants of the Acid–Base and Ring-opening Reaction in Water.—The individual rate constants k_1, k_{-1}, and k_2 obtained from λ_1 and λ_2 and the maximum enolate concentration are plotted as a function of the buffer concentration (Figure 2). The slopes are then plotted as a function of the fraction of the basic form of the buffer to give k_B and k_{BH^+}; from the pH dependence of the intercept (Figure 3) the values of $k_1 \cdot_{H_2O}$, $k_1 \cdot_{OH}$, $k_{-1} \cdot_{H^+}$, $k_{-1} \cdot_{H_2O}$, $k_2 \cdot_{H_2O}$, and $k_2 \cdot_{OH}$ are obtained (Table 2). These rate constants are then used to construct the Brönsted plots (Figure 4). The values of k_{-1} and pK_a in the Tables have been statistically corrected (divided by 2 or decreased by 0.3) to take into account the fact that there is one way of deprotonating the substrate but two ways of protonating the enolate (to give the L- or D-oxazolone). This is a peculiarity of racemic carbon acids. This correction is introduced to facilitate the comparisons with the data obtained with chiral catalysts (see following paper).

Solvent Effect on the Ratio of the Rates of Deprotonation versus *Ring Opening.*—The oxazolones have generally been thought to racemize faster than they react with nucleophiles. That this is indeed so in solvents of lower dielectric constant was checked by determining the enolate yield in 10^{-2}M-lyate

Table 2. pK_a Values and catalytic rate constants of deprotonation, reprotonation, and ring opening of the oxazolones in water at 25 °C

Oxazolone	pK_a [a]	Catalyst	$k_1 \cdot_B$/l mol^{-1} s^{-1}	$k_{-1} \cdot_{BH^+}$ [a]/l mol^{-1} s^{-1}	$k_2 \cdot_B$/l mol^{-1} s^{-1}
(1)	8.72 ± 0.08	H_3O^+–H_2O [b]	(4.3 ± 0.3) × 10^{-3}	(2.28 ± 0.16) × 10^6	(1.97 ± 0.32) × 10^{-3}
		Phosphate $H_2PO_4^-$ — HPO_4^{2-}	2.03 ± 0.18	79.2 ± 4.7	0.025 ± 0.003
		Borate	1.76 ± 0.22	0.243 ± 0.026	0.520 ± 0.057
		Carbonate	21.8 ± 1.74	1.05 ± 0.09	4.54 ± 0.34
		Phosphate HPO_4^{2-} — PO_4^{3-}	165 ± 13	1.01 ± 0.13	43.2 ± 3.7
		H_2O–OH^- [b]	(2.65 ± 0.15) × 10^3	(1.41 ± 0.08) × 10^{-2}	(1.29 ± 0.16) × 10^3
(2)	8.94 ± 0.1	H_2O–OH^- [b]	(2.57 ± 0.7) × 10^3	(2.27 ± 0.6) × 10^{-2}	(1.26 ± 0.3) × 10^3
(3)	10.34 ± 0.1	H_2O–OH^- [b]	(1.26 ± 0.1) × 10^3	0.274 ± 0.02	(7.55 ± 0.92) × 10^2

[a] Statistically corrected. [b] The k_{H_2O} values are in s^{-1}.



(4)

in methanol, propan-2-ol, t-butyl alcohol, and 80% dioxan–water. The following values were found: 57, 98, 99, and 98%, respectively. The result obtained in 80% dioxan shows that the change in the k_1/k_2 ratio is not due solely to steric hindrance. It may be worth mentioning that if the dioxan is not peroxide free (even an analytical reagent) the enolate yield is much lower.

Even a relatively small percentage of organic solvent can affect the k_1/k_2 ratio which changes from 2.6 in 0.5% CH_3CN to 4.0 in 10% CH_3CN for 4-benzyl-2-phenyloxazolone.

Detection of an Intermediate.—The reaction scheme developed so far does not yet account for the full complexity of the reaction. An intermediate that accumulates in the medium can be detected after complete disappearance of the oxazolone in the far-u.v. region at 260 nm for the 2-phenyloxazolones. The absorbance change corresponding to its disappearance increases from 0.05 at pH 7.86 in phosphate buffer to 0.16 at pH 12 (NaOH), for 4-methyl-2-phenyloxazolone (5.5 × 10^{-5}M). The rate of disappearance of that species has been measured from pH 9.2 to 12.8; the data fit the equation $k_{obs} = k_{lim}[OH^-]/(K_b + [OH^-])$ with k_{lim} 2.8 × 10^{-3} s^{-1} and $K_b = 3.0 \times 10^{-3}$ mol l^{-1}. An analogous reaction is observed with the other oxazolones. This intermediate can also be detected by a reaction with the hydroxylamine. Like esters,[7] the oxazolones give an hydroxamic acid detectable by its complex with iron(III) chloride. When samples of a hydrolysing oxazolone solution at pH 7.8 are added to a hydroxylamine solution, the hydroxamic acid yield decreases in a biphasic curve. The initial phase whose rate is identical with the rate of disappearance of the substrate corresponds to a loss of 85% of the initial value. The remaining 15% of hydroxylamine-positive material corresponding to the intermediate, and present after complete disappearance of the substrate, disappear then slowly. It is no longer possible to form any enolate at high pH from a solution containing the intermediate; its formation thus appears to be irreversible. Analogous results are obtained with 4-benzyl-2-methyloxazolone except that at pH 7.86 30% intermediate is detected. The rate of disappearance at pH 7.8 is 3.8 × 10^{-5} s^{-1}.

Because of the low yield of intermediate, we have been unable to isolate and characterize it fully; however, an i.r. spectrum of the reaction mixture lyophilized immediately after the hydrolysis of the oxazolone shows a weak peak at 1 740 cm^{-1} besides the peaks characteristic of the final product.

When the hydrolysis of the oxazolone is run at higher concentration (above 2 × 10^{-3}M for 4-methyl-2-phenyloxazolone) a new product precipitates from the reaction mixture whose properties are consistent with the structure of the enol ester (4). At pH 12, this compound regenerates 50% of enolate, whose rate of disappearance is as expected.

Discussion

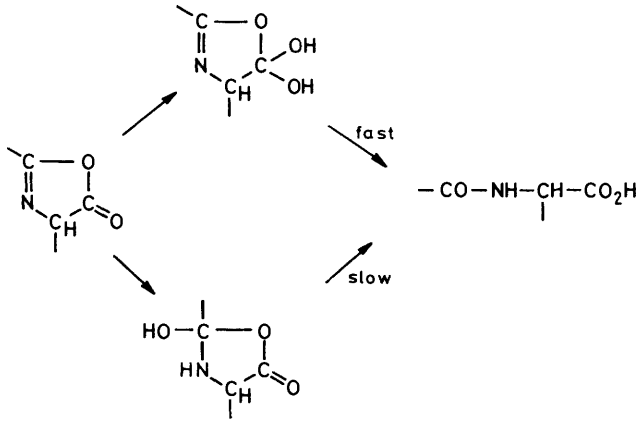
There is a substantial amount of information in the literature on rate equilibria correlations for carbon acids.[8,9] From these and the approximate pK_a values of the oxazolones derived from kinetic analyses in which the ionization is assumed to be a fast equilibrium, the rate of the ionization reaction would be predicted to be at least ten times larger than that of ring opening. The data reported here indicate that they occur at approximately the same rate; this necessitates a more complex kinetic analysis.

While acetylacetone, an acid of approximately the same pK_a as the 2-phenyloxazolones, is deprotonated by OH^- with a rate constant of 4 × 10^4 l mol^{-1} s^{-1}, the oxazolones are ionized nearly 20 times more slowly. This comparatively slow rate results from the need for a more extensive electronic rearrangement to form the pseudoaromatic cyclic enolate than in the diketone system.

Previous work on the reaction of optically active oxazolones with a variety of nucleophiles showed that, except with the most reactive among them like hydrazine or other α-effect nucleophiles, a very substantial racemization was observed. Our data with the alcohols or dioxan–water mixture show that in solvents of lower dielectric constant, the ratio deprotonation *versus* ring opening increases. This is a consequence of the fact that the deprotonation forms a highly delocalized anion while the ring opening involves localized charges. This difference remains even if the main pathway for the ring-opening reaction is concerted as proposed recently [3] and does not include a tetrahedral intermediate.

The limited data presented here indicate that the Brönsted coefficient of the ionization reaction falls in the expected range. The slope of the plot for the ring-opening reaction (excluding the water point) is somewhat larger than for the deprotonation: the k_1/k_2 ratio increases with a decrease in the pK_a of the catalyst. For the initial purpose of this study, to hydrolyse the oxazolones in the presence of chiral catalysts and obtain an optically active product, it is necessary to have a relatively large k_1/k_2 ratio; this can be achieved by working in the presence of a buffer of lower pK_a, like the phosphate buffer. Lowering the polarity of the medium is also effective.

The mechanism of the ring opening may be more complex than previously thought. An intermediate is detected after the complete disappearance of the substrate, but there is a discrepancy between the calculated and the observed concentration of that intermediate. The disappearance of the substrate being irreversible, the concentration of the intermediate can be



Scheme 2.

calculated from the rate constants of disappearance of the oxazolone and of the intermediate by application of the kinetic equations for consecutive reactions;[6] at pH 7.8, it reaches 92 and 85% for 4-benzyl-2-phenyl- and 4-benzyl-2-methyl-oxazolone, respectively, when the substrate concentration is reduced to 1%. These values are much larger than what is actually found.

These results suggest that the substrate disappears by two competing pathways; the main pathway would be the generally accepted C=O addition mechanism, with no accumulation of intermediate; the minor one would result from C=N addition (Scheme 2).

Although the evidence in favour of the structure of the intermediate is very limited because it could not be isolated, several arguments show that it is reasonable. (1) The presence of a peak at 1 740 cm^{-1} in the i.r. spectrum and the detectability with the hydroxylamine are consistent with a lactone structure. (2) An oxazolone structure is about equivalent to an anhydride; from the thermodynamic point of view, the equilibrium constant of water addition to acetic anhydride is predicted to be close to 1.0.[10] (3) Although isotopic labelling techniques have shown that C=O addition is probably the only pathway for the hydrolysis of the 2-phenyl-4-unsubstituted oxazolone,[3] the ratio of C=O to C=N addition is known to be very much dependent on the structure of the nucleophile and substrate, with the increase in steric hindrance in position 4 favouring C=N addition.[11] Furthermore, the replacement of a phenyl by a methyl group in position 2 should increase the percentage of C=N reaction as observed. (4) This intermediate should have a pK_a of *ca.* 11 ± 1 as calculated from linear free energy relationships;[4,12] the pH dependence of its decomposition is consistent with this.

The only property which is somewhat unexpected for this structure is the rate of its decomposition, which appears to be very slow for the expulsion of a carboxylate from a tetrahedral intermediate, even taking into account that the reaction is not favoured by stereoelectronic effects [13] and that the leaving group remains in the molecule.

Acknowledgements

V. D. is grateful to the Belgian Institute for Scientific Research in Industry and Agriculture (IRSIA) for a fellowship. J. F. is a Research Associate of the Belgian National Fund for Scientific Research.

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Received 2nd July 1982; *Paper* 2/1110