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KINETICS OF THE ACID-CATALYSED RING-OPENING REACTION OF 2-PHENYL-4,4-DIMETHYL-2-OXAZOLIN-5-ONE WITH THE ETHYL ESTER OF DL-ALANINE

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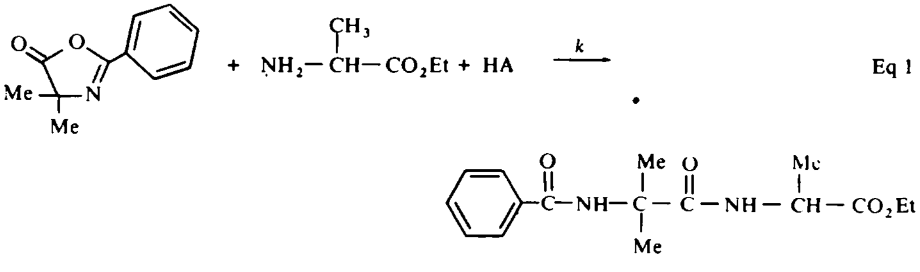
Abstract—The kinetic behaviour of the acetic acid catalysed reaction of 2-phenyl-4,4-dimethyl-2-oxazolin-5-one (**1**) with the ethyl ester of DL-alanine (**2**) in CCl_4, to give the ethyl ester of N-(N'-benzoyl-α-aminoisobutyryl)-DL-alanine (**3**) is investigated. Within the range of concentrations employed, the reaction follows the rate equation $v = \{k_0 + k[\text{monomer}]\}\,[\text{oxa}]\,[\text{ester}]$, where k_0 is the specific rate constant of the uncatalysed reaction, and k' is that of the catalysed reaction.

The influence of the variation of **1**, **2** and acetic acid on the specific rate constant is studied. It is shown that only if the acetic acid monomer is regarded as the catalyst can the system be adequately described quantitatively. The participation of other acid species as catalysts is discussed.

OXAZOLINONES are known to react with amines, ring opening to give amides,[1] [2] and it has been reported that these reactions are catalysed by the amine hydrochlorides.[3] Similarly, oxazolinones react with aminoacid esters to give peptide esters,[4–6] and these reactions have been the object of some quantitative mechanistic studies.[7–9]

In order to investigate the mechanism of the reaction between 2-phenyl-4,4-dimethyl-2-oxazolin-5-one (1) and the ethyl ester of DL-alanine (2) to give the ethyl ester of N-(N'-benzoyl-α-aminoisobutyryl)-DL-alanine (3) we have determined its kinetics in CCl_4 at 20°.



Eq 1

Our first attempts to measure the rate of the reaction showed it to be very slow and that it did not follow a simple kinetic course. It is known that aminoacid esters can autocondense, giving rise to piperazinediones or peptides,[10,11] and recently the mechanisms of these reactions have been investigated.[12] It could be expected that if the ring-opening reaction was too slow, the ester might autocondense in addition to reacting with the oxazolinone, thereby complicating the mechanism.

Following the observations of Carter *et al.*,[3] we had noted in some preliminary experiments that the reaction was catalysed by acids, and we studied it using acetic acid.

RESULTS AND DISCUSSION

In the experiments performed the concentration of each component was varied independently. Within the range of concentrations employed for 1 and 2, the reaction was first order with respect to each reactant. Fig 1* is the plot obtained when Eq. 2 was applied to one run, and it shows good agreement of the results.

$$k = \frac{2{\cdot}303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)} \qquad \text{Eq 2}$$

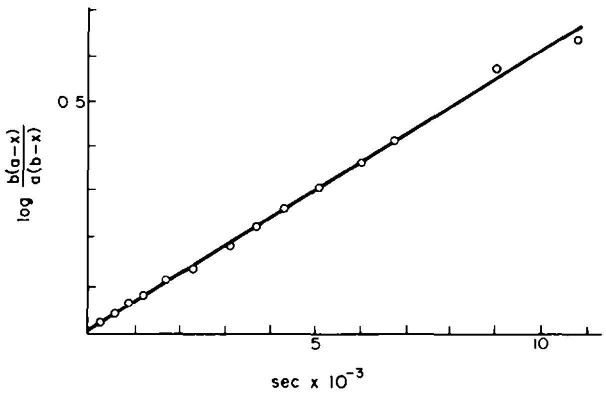


FIG 1. Plot of log $\frac{b(a-x)}{a(b-x)}$ *vs t* [sec] for one run in which [oxa] = 99·60 × 10^{-4} M; [ester] = 222·06 × 10^{-4} M; [AcOH] = 16·85 × 10^{-4} M. k = 11·51 × 10^{-3} M^{-1} sec^{-1}; i = 0·0025; and r = 0·999

Variation of the concentration of **1**. Table 1 shows that, when the initial concentrations of **2** and acetic acid were kept constant, while that of **1** was varied, the values of k remained constant, with an average of 13·66 × 10^{-3} M^{-1} sec^{-1}.

Variation of the concentration of **2**. When the initial concentrations of **1** and acetic acid were kept constant, while that of **2** was varied, the values of k no longer remained constant. Table 2 shows that, as the concentration of **2** was increased, the values of k decreased.

TABLE 1. INFLUENCE OF THE VARIATION OF THE CONCENTRATION OF 1 ON k WHEN [ESTER] = 150·75 × 10^{-4} M AND [AcOH] = 16·85 + 10^{-4} M

[oxa] M × 10^4	$k \times 10^3$ M^{-1} sec^{-1}
21·50	13·93
42·40	12·58
52·30	14·45
63·80	13·64
104·25	13·71

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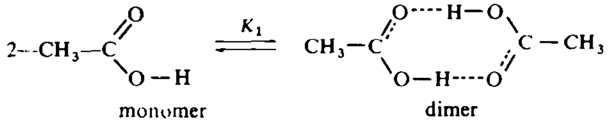
[*] The following abbreviated expressions shall be used subsequently to denote, respectively, the concentrations of the oxazolinone **1**, the ester **2**, total acetic acid, acetic acid monomer, acetic acid dimer (**4**) and ion pair **5**: [oxa], [ester], [AcOH], [monomer], [dimer] and [IP]

TABLE 2. INFLUENCE OF THE VARIATION OF [ESTER] WHEN [OXA] = $100{\cdot}50 \times 10^{-4}$ M AND [AcOH] = $16{\cdot}85 \times 10^{-4}$ M

[ester] M × 10^4	[monomer] M × 10^4	[dimer] M × 10^4	[IP] M × 10^4	$k \times 10^3$ $M^{-1}sec^{-1}$	k' $M^{-2}sec^{-1}$
33·58	4·51	4·58	3·13	24·87	54·01
61·45	4·09	3·76	5·24	20·94	49·95
146·34	3·02	2·06	9·43	14·81	47·35
167·95	2·86	1·84	10·28	13·61	45·80
181·10	2·75	1·71	10·69	13·23	46·25
222·06	2·44	1·34	11·70	11·65	45·66
294·05	2·03	0·93	13·01	10·04	46·95
307·86	1·97	0·87	13·19	9·33	44·77

Qualitatively, this fact may be accounted for by considering that, for each concentration of 2, except the two lowest ones, the concentration of the catalytic species remains constant, but it decreases when the concentration of 2 increases.

However, in order to explain this observation quantitatively, it can be assumed that acetic acid takes part in the following preliminary equilibria:



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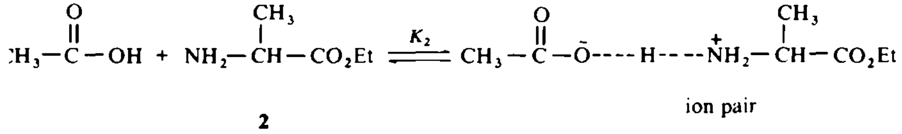
Eq 3



$$CH_3-\overset{O}{\overset{\|}{C}}-OH + NH_2-\overset{CH_3}{\overset{|}{C}H}-CO_2Et \overset{K_2}{\rightleftharpoons} CH_3-\overset{O}{\overset{\|}{C}}-\bar{O}\cdots H\cdots\overset{+}{N}H_2-\overset{CH_3}{\overset{|}{C}H}-CO_2Et$$

2 5

Eq 4

According to this scheme, the catalyst could be any one of the acid species, which we shall denote by HA, present in the system, or a combination of them. To determine which of the species HA is the one that actually takes part in the reaction it is necessary to know the values of K_1 and K_2 of Eqs 3 and 4, respectively.

The dimerization of acetic acid in CCl_4 has been investigated quantitatively by Harris and Hobbs,[13] who reported values for K_1 that vary from 3225 to 5555, with an average of 4000, and by Barrow and Yerger,[14] whose values fluctuate between 1000 and 2650, with an average of 2000. In view of the discrepancy in the reported values and the dispersion of the data, we chose to use the results obtained by Offermanns,[15] who, using the method of Harris and Hobbs,[13] found a value of 2252 at 20°, with a correlation of 0·98 for the range of concentrations employed in this work.

Barrow and Yerger[16] have also studied quantitatively the interaction of acetic acid and amines in CCl_4, and they report the existence of equilibria of the kind represented by Eq 4, in addition to others that occur at higher concentrations than the ones we used. Offermanns[15] has determined K_2 for the interaction depicted by Eq 4, obtaining a value of 228 ± 45 at 20°.

In the presence of HA, **1** reacts with **2** to give **3** as shown in Eq 1. The rate equation for this reaction would be

$$v = k\,[\text{oxa}][\text{ester}] \qquad \text{Eq 5}$$

with

$$k = k_0 + k'\,[\text{HA}] \qquad \text{Eq 6}$$

where k_0 is the specific rate constant for the uncatalysed reaction and k' is that for the catalysed reaction.

As had already been pointed out, an increase in the concentration of **2** caused a decrease in the rate constant k, so that the ion pair (**5**) can be rejected as an efficient catalytic species, not only because its concentration increases together with that of **2**, but also because its steric configuration is unfavourable.

On the other hand, the concentrations of both monomeric acetic acid and its dimer (**4**) decrease when that of **2** increases, but it can be reasonably assumed that the catalytic capacity of the monomer is greater than that of the dimer. Therefore, the active catalytic species, HA, would be the monomer, whose concentration can be obtained from the following relations:

$$[\text{AcOH}] = 2[\text{dimer}] + [\text{IP}] + [\text{monomer}] \qquad \text{Eq 7}$$

from Eq 3:

$$[\text{dimer}] = K_1[\text{monomer}]^2 \qquad \text{Eq 8}$$

from Eq 4:

$$[\text{IP}] = K_2\frac{[\text{monomer}]\,[\text{ester}]}{1 + K_2[\text{monomer}]} \qquad \text{Eq 9}$$

therefore

$$[\text{monomer}]^3 + \frac{2K_1 + K_2}{2K_1K_2}[\text{monomer}]^2 + \frac{K_2[\text{ester}] - K_2[\text{AcOH}] + 1}{2K_1K_2}[\text{monomer}] - \frac{[\text{AcOH}]}{2K_1K_2} = 0 \qquad \text{Eq 10}$$

In addition to the initial concentrations of **2**, Table 2 shows the concentrations of monomer, dimer **4** and ion pair **5** calculated from Eqs 10, 8 and 9, respectively; and the values of k and k'. The values of k' are seen to be constant, and for this to happen the ratio of $k - k_0$ to [HA] must also be constant, a condition that is not fulfilled if dimer **4** is regarded as species HA, but is satisfied if the monomer is considered to be HA, thus confirming the assumption that the monomer is the most important catalyst. The fact that the first two values of k' are too high can be explained because, at low concentrations of **2**, the concentration of HA does not remain constant, and the reaction does not follow strictly a second order relation.

Variation of the concentration of acetic acid. Table 3 shows the variation of the values of k when the initial concentration of acetic acid is varied. The values of k calculated from Eq 6 are also included, showing their good agreement with the observed values, and providing further support for the assumption that the monomer is the catalyst.

TABLE 3. INFLUENCE OF THE VARIATION OF [AcOH] WHEN [OXA] = 85·54 × 10^{-4} M

[ester] M × 10^4	[AcOH] M × 10^4	[monomer] M × 10^4	[IP] M × 10^4	$k \times 10^3$ $M^{-1} sec^{-1}$	$k_{calc} \times 10^3$ $M^{-1} sec^{-1}$
115·58	3·37	0·85	2·20	5·14	4·56
114·52	6·74	1·59	4·01	8·64	8·08
113·29	10·11	2·26	5·55	11·43	11·27
116·23	13·48	2·78	6·93	15·07	13·74
113·63	16·85	3·41	8·20	16·99	16·74
116·67	20·22	3·89	9·50	19·69	19·02
118·14	30·33	5·26	12·65	27·63	25·54

When k is plotted *vs* [monomer], a straight line is obtained with a slope that corresponds to k' and an intercept corresponding to k_0, with a correlation of 0·99. The value of k_0 is 0·51 × 10^{-3} M^{-1} sec^{-1}, and that of k' is 50·42 M^{-2} sec^{-1}, in good agreement with the average value of k' obtained from Table 2, which is 47·59 M^{-2} sec^{-1}.

When acetic acid was added to a solution of **1** in CCl_4, the concentration of the dimer (**4**) and, to a larger extent, that of the monomer decreased, as evidenced by the absorptions of their CO groups in the IR;[14] however, no change could be detected in the absorption of the CO group of **1**. Since acetic acid must participate in some kind of interaction with **1**, but this does not occur to a measurable extent with the latter's CO group, the most probable sites would be the N and O atoms of the ring. In both cases, the catalytic effect would be transmitted through the delocalized electron system, but the N would be favoured due to its greater basicity.

It can be concluded that the catalytic species in the system is monomeric acetic acid, the catalysed reaction being about 10^5 times faster than the uncatalysed one. When the reactants are present in large excess with respect to the catalyst, the reaction follows second order kinetics.

EXPERIMENTAL

IR spectra and kinetic measurements were obtained on a Leitz model IIIG spectrophotometer. M.ps. were determined on a Leitz microscope hot stage and are uncorrected. Elemental analyses were performed by Mr. Juan García in this Faculty.

Materials. AcOH and CCl_4 (E. Merck, Darmstadt, reagent grade) were kept over silica gel and were used without further purification.

2-*Phenyl-4,4-dimethyl-2-oxazolin-5-one* (**1**), was prepared from **6** by Mohr's method as described,[17] and was purified by recrystallisation from light petroleum or by distillation under reduced pressure, m.p. 46–47° (lit.[18] 34°); IR (KBr): 1825 (C=O) and 1647 cm^{-1} (C=N). (Found: C, 70·1; H, 5·9; N, 7·3%; $C_{11}H_{11}O_2N$ requires: C, 69·82; H, 5·86; N, 7·40%).

N-*Benzoyl-α-aminoisobutyric acid* (**6**) was prepared from benzoyl chloride and α-aminoisobutyric acid. The final product was contaminated with benzoic acid that could only be removed by sublimation at 121°/3 mm. When impure **6** was treated with Ac_2O to give **1**, benzoic acid was converted into benzoic anhydride, that forms a eutectic mixture with **1**, from which it cannot be separated by crystallisation or by fractional distillation, a fact that would account for the low m.p. reported for **1** in the lit.[18]

Ethyl ester of DL-*alanine* (**2**). DL-Alanine was converted into its ethyl ester hydrochloride, from which the free ester (**2**) was obtained by the method described;[9] b.p. 32–34°/4 mm (lit.[19] 48°/11 mm); n_D^{20} 1·4186.

N-(N'-*Benzoyl-α-aminoisobutyryl*)-DL-*alanine ethyl ester* (**3**). Equimolar solns of **1** and **2** (25 ml; 1·55 × 10^{-3} moles of each) in CCl_4, to which had been added AcOH (4·2 × 10^{-5} moles), was allowed to stand, with occasional shaking, for 3 days at 20°. The crystalline ppt was filtered off, the solvent evaporated at 30°, and the residue combined with the first crop of crystals to yield 0·465 g (97·8%) of crude **3**. Recrystallisation from toluene yielded colorless, silky needles of pure **3**, m.p. 122–123°: IR (KBr): 3311 and 3268 (NH), 1733 (ester C═O), 1655 and 1640 (amide I), 1543 and 1504 (amide II), and 720 and 695 cm^{-1} (monosubstituted benzene ring). (Found: C, 62·8; H, 7·3; N, 9·0%; $C_{16}H_{22}O_4N_2$ requires: C, 62·73; H, 7·24; N, 9·14%).

Kinetics. The kinetics of the ring-opening reaction was followed as described,[9] measuring the disappearance of the CO stretching absorption band of **1** in the IR at 1825 cm^{-1}; matched 1 mm NaCl cells were used, and the solvent and all the solns were kept in a constant temp bath at 20 ±0·02°. Readings were taken (8–15) until the reaction reached about 80% completion, the absorbance being determined by the base line method.[20,21] The stability of the solns of **1**, **2** and AcOH in CCl_4 had been established previously by recording their complete IR spectra every 12 hr during 4 days, without noting any appreciable variations.

The concentration of **1** at zero time was obtained by extrapolation of a plot of rate *vs* time, and concentrations at time *t* by interpolation in a plot of absorbance *vs* concentration.

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