Kinetic Study of the Decarboxylation of 5-Amino-1,3,4-oxadiazole-2-carboxylic Acid to 2-Amino-1,3,4-oxadiazole in Water as a Function of Proton Activity

By **Domenico Spinelli,*** Cattedra di Chimica Organica, Faculty of Pharmacy, University of Bologna, Bologna 40126, Italy
Renato Noto, Giovanni Consiglio, Giuseppe Werber, and **Francesco Buccheri,** Institute of Organic Chemistry, University of Palermo, Via Archirafi 20, Palermo 90123, Italy

The rate constants of the decarboxylation reaction of 5-amino-1,3,4-oxadiazole-2-carboxylic acid (I) have been measured in water, over a wide range of proton activities (from H_0 −0.95 to pH 4.77), at various temperatures, and the activation parameters have been determined. We present evidence for the occurrence of a decarboxyprotonation mechanism.

DECARBOXYLATION of aliphatic and aromatic (or heteroaromatic) acids are of interest because of their implications for laboratory syntheses [1] or biological processes.[2] These reactions have been extensively studied in the case of some aliphatic (β-oxobutyric [3] and amino- [4] or trihalogeno-acetic [5]) and aromatic (hydroxy-,[6] amino-,[7] or

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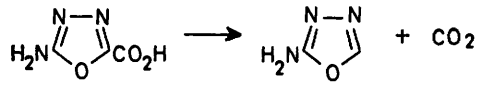
polynitro-benzoic [8]) acids. Decarboxylation reactions of some heteroaromatic carboxylic acids [9] have also been investigated. The experimental results obtained permit a choice to be made between the three postulated reaction mechanisms.

The first mechanism (carbon–hydrogen bond forming, often rate determining, followed by carbon–carbon bond breaking) has been observed in some aromatic hydroxy-[6] or amino-acids,[7] *i.e.*, in compounds susceptible to electrophilic attack. The second (concerted carbon–hydrogen bond forming and carbon–carbon bond breaking) is characteristic of acids [3a] such as β-oxo-acids * which can undergo cyclic intramolecular proton transfer. The third mechanism (rate-determining carbon–carbon bond breaking followed by carbon–hydrogen bond forming) usually occurs with acids which can yield stable carbanions such as trihalogenoacetate [5] or β-oxocarboxylate.[10]

The decarboxylation of the heteroaromatic acids studied seems to accord with the first (*e.g.* in the case of pyrrole-2-carboxylic acid) [9b] or the third mechanism (*e.g.* in the case of pyridine-2-carboxylic acid in water).[9c]

In order to gain information on the behaviour of other heteroaromatic carboxylic acids as a function of the nature of the heterocyclic ring and of the substituents present, we have studied the decarboxylation of 5-amino-1,3,4-oxadiazole-2-carboxylic acid (I) to 2-amino-1,3,4-oxadiazole (II) in water at various proton activities and at different temperatures. Compound (I) which



(I) (II)

contains an amino-group can behave in the same way as aminobenzoic acids [7] (first mechanism) or, because of the presence in the ring of two nitrogen atoms of the pyridine type which make the ring electron-deficient, can decarboxylate as to the pyridinecarboxylic acids [9c] (third mechanism).

Compound (I) is an aminocarboxylic acid, *i.e.*, a compound which in water furnishes different ionic and non-ionic species in equilibrium with oxonium ion. According to the usual convention,[11] we can represent aminocarboxylic acid as HA, its zwitterionic form as Z, its conjugate acid as H_2A^+, and its conjugate base as A^-, respectively. Taking into account that the ratio [Z] : [HA] is independent of proton activity, then the total ampholyte concentration can be treated as a single species [N] ([N] = [HA] + [Z]). Equilibria (1)—(4) occur in aqueous solution. If [C] is the total concentration of aminocarboxylic acid, the concentrations of the species H_2A^+, N, and A^- at any proton activity are

$$H_2A^+ \overset{K_1}{\rightleftharpoons} N + H^+ \quad (1)$$

$$K_1 = [N]\,[H^+]/[H_2A^+] \quad (2)$$

$$N \overset{K_2}{\rightleftharpoons} A^- + H^+ \quad (3)$$

$$K_2 = [A^-][H^+]/[N] \quad (4)$$

furnished by equations (5)—(7). Determining the ionization constants K_1 and K_2, related to equilibria (1)

$$[H_2A^+] = \frac{[C]}{K_1K_2/[H^+]^2 + 1 + K_1/[H^+]} \quad (5)$$

$$[N] = \frac{[C]}{[H^+]/K_1 + 1 + K_2/[H^+]} \quad (6)$$

$$[A^-] = \frac{[C]}{[H^+]^2/K_1K_2 + 1 + [H^+]/K_2} \quad (7)$$

and (3), it is clearly possible to calculate these concentrations. The K_1 and K_2 values determined were $K_1 = 1.36 \pm 0.05$ and $K_2 = (3.25 \pm 0.20) \times 10^{-2}$ mol l^{-1}.

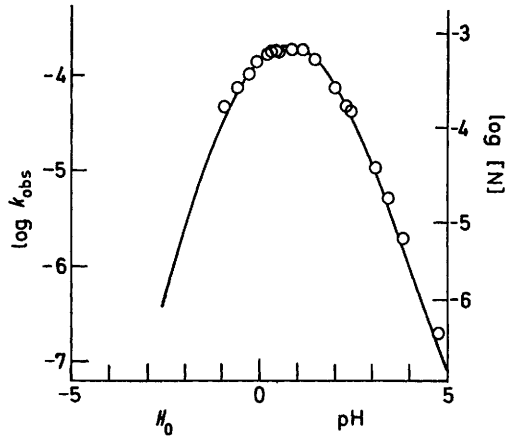


FIGURE 1 Open circles: plot of log k_{obs} for decarboxylation *versus* aciditiy functions. The curve is calculated for log [N] *versus* acidity functions [see text, equation (6)]

Kinetic Data.—The apparent first-order kinetic constants measured at each proton activity and the thermodynamic parameters are set forth in Table 1. As seen above, the concentrations of the species present (H_2A^+, N, and A^-) are much affected by proton activity as well as the rate constant values (see Figure 1). As a function of proton activity, the ampholyte concentrations and the rate constant values present a very similar pattern.

From this observation three hypotheses may be made.

* This kind of mechanism is still under discussion (K. J. Pedersen, *J. Phys. Chem.*, 1934, **38**, 559; K. R. Brower, B. Gay, and T. L. Koukol, *J. Amer. Chem. Soc.*, 1966, **88**, 1681; M. W. Logue, R. M. Pollack, and V. P. Vitullo, *ibid.*, 1975, **97**, 6868).

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TABLE 1

Apparent rate constants and activation parameters for the decarboxylation of 5-amino-1,3,4-oxadiazole-2-carboxylic acid (I) in water

Buffers [a]	pH (H_0)	10^4k/s^{-1} (t/°C) [b]	$\Delta H^{\ddagger}$ [c]/kcal mol^{-1}	$\Delta S^{\ddagger}$ [d]/cal mol^{-1} K^{-1}
A	(−0.95)	0.558 (40.2), 2.57 (51.4), 7.80 (60.0)	27.0	8.2
A	(−0.62)	0.758 (40.2), 3.64 (51.2), 10.3 (60.1)	26.7	7.7
A	(−0.30)	1.06 (40.2), 5.46 (51.3), 17.0 (60.1)	28.3	13.7
A	(−0.06)	1.44 (40.1), 7.23 (51.2), 21.5 (60.0)	27.7	12.2
B	0.21	1.75 (40.1), 8.66 (51.4), 25.2 (60.0)	27.3	11.3
B	0.29	0.394 (30.1), 1.78 (40.1), 9.04 (51.3)	28.3	14.8
B	0.37	0.380 (30.0), 1.78 (40.0), 7.16 (50.0)	27.9	13.4
B	0.50	0.391 (30.0), 1.79 (40.0), 7.37 (50.0)	27.9	13.5
B	0.85	0.415 (30.0), 1.83 (40.0), 8.27 (50.2)	28.4	15.0
B	1.10	0.420 (29.9), 1.84 (40.0), 8.03 (50.5)	27.4	11.8
C	1.45	0.329 (30.0), 1.53 (40.1), 7.36 (51.2)	28.0	13.5
C	1.98	0.757 (40.1), 3.60 (51.0), 11.1 (60.0)	27.3	9.9
C	2.28	0.484 (40.2), 2.57 (51.2), 7.98 (60.1)	28.7	13.2
C	2.41	0.420 (40.1), 1.93 (50.5), 6.21 (60.0)	27.5	9.1
C	3.04	0.112 (40.1), 0.520 (51.2), 1.77 (60.1)	27.9	8.0
C	3.42	0.0541 (40.2), 0.284 (51.4), 0.868 (60.0)	28.5	8.3
C	3.82	0.019 9 (40.2), 0.994 (51.3), 0.324 (60.1)	28.7	7.0
C	4.77	0.002 02 (40.0), 0.009 85 (51.5), 0.079 1 (67.0)	28.2	0.7

[a] Buffers: A, hydrochloric acid; B, hydrochloric acid–potassium chloride; C, hydrochloric acid–sodium citrate. [b] The rate constants are accurate to within ±3%. [c] At 40°, the maximum error is 0.5 kcal mol^{-1}. [d] At 40°.

(i) Compound (I) decarboxylates according to the first mechanism (protiodecarboxylation) with the anion as the species which is decarboxylated. In this case we have equation (8) which combined with (4) gives (9)

$$-\mathrm{d[C]}/\mathrm{d}t = k_{\mathrm{obs}}[\mathrm{C}] = k_{\mathrm{A}^-}[\mathrm{A}^-][\mathrm{H}^+] \quad (8)$$

$$k_{\mathrm{obs}}[\mathrm{C}] = k_{\mathrm{A}^-}K_2[\mathrm{N}] \quad (9)$$

where k_{A^-} represents the specific rate constant of decarboxylation of the anionic species. (ii) Compound (I) decarboxylates according to the third mechanism (decarboxyprotonation) with the ampholyte * as the species which is decarboxylated. In this case we have equation (10) where k_{N} represents the specific rate

$$-d[\mathrm{C}]/\mathrm{d}t = k_{\mathrm{obs}}[\mathrm{C}] = k_{\mathrm{N}}[\mathrm{N}] \quad (10)$$

constant of decarboxylation of the ampholyte. (iii) There is also the possibility of the simultaneous presence of the two mechanisms above, *i.e.*, in arithmetic terms, there is operating, at each proton activity, a linear combination of (9) and (10) [equation (11)] where a and

$$-d[\mathrm{C}]/\mathrm{d}t = k_{\mathrm{obs}}[\mathrm{C}] = (ak_{\mathrm{A}^-}K_2 + bk_{\mathrm{N}})[\mathrm{N}] \quad (11)$$

b indicate, respectively, numbers proportional to molar fractions (or other measures of concentration) of (I) that reacts *via* protiodecarboxylation and *via* decarboxyprotonation. The similar pattern of log k_{obs} and log [N] in relation to the proton activity (see Figure 1) allows us to write equation (12), whatever the mechanism implied [(9), (10), or (11)], where k^* is the specific rate constant of decarboxylation.

$$k_{\mathrm{obs}}[\mathrm{C}] = k^*[\mathrm{N}] \quad (12)$$

Substituting [N] for the value calculated through (6) and simplifying gives equation (13). Equation (13) in

$$k_{\mathrm{obs}} = k^* \frac{[\mathrm{H}^+]K_1}{[\mathrm{H}^+]^2 + [\mathrm{H}^+]K_1 + K_1K_2} \quad (13)$$

its logarithmic form (see Figure 2) allows the calculation of the specific rate constant (k^*) as the intercept. The values so obtained and the calculated activation parameters are collected in Table 2.

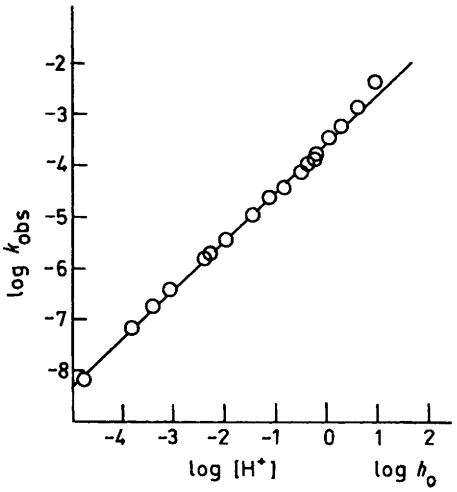

FIGURE 2 Logarithmic plot of k_{obs} according to equation (13) for decarboxylation at 40 °C (statistical data in Table 2)

TABLE 2

Calculated rate constants (k^*) and related activation parameters

10^3k^*/s^{-1} (t/°C) [a]	$\Delta H^{\ddagger}$ [b]/ kcal mol^{-1}	$\Delta S^{\ddagger}$ [b]/ cal mol^{-1} K^{-1}
0.280 [c] (40.0), 1.15 [d] (50.0), 4.26 [e] (60.0)	27.6	13.3

[a] Calculated using equation (13) in its logarithmic form (*e.g.*, see Figure 2). [b] At 40 °C. [c] Slope 0.963 ± 0.01, i (calculated intercept) ≡ log k^* −3.55 ± 0.02, r 0.999, n 18, t_s (t-test for slope) 86.6, t_i (t-test for intercept) 152.3, C.L. (confidence level) >99.9. [d] Slope 0.961 ± 0.01, i — log k^* −2.94 ± 0.02, r 0.999, n 18, t_s 98.2, t_i 143.2, C.L. >99.9. [e] Slope 0.956 ± 0.01, i — log k^* −2.39 ± 0.02, r 0.999, n 18, t_s 90.0, t_i 106.4, C.L. >99.9.

* Chemical considerations lead us to suppose that in this case the species more prone to decarboxylation should be the zwitterion.

Conclusions.—The kinetic data collected for the decarboxylation of (I) agree with two * of the three possible reaction mechanisms already observed in other heterocyclic acids or their linear combination (see above), but some chemical considerations induce us to prefer decarboxyprotonation.

In fact, protiodecarboxylation requires as a first step an electrophilic attack on the ring by a proton, *i.e.*, a reaction not very probable in a heterocyclic ring which is known [12] to be resistant to electrophilic attack because of the presence of two nitrogen atoms of the pyridine type. Moreover, acids which give this type of reaction mechanism, (*e.g.*, anthranilic and pyrrole-2-carboxylic acids) have a reactivity lower than that observed by us, in contrast with the known observation that a pyrrole ring (an electron rich ring) easily undergoes electrophilic substitution unlike 1,3,4-oxadiazole (an electron deficient ring).[13] Thus, it is hard to accept that protiodecarboxylation can operate as a unique mechanism, taking into account also that it should operate at a pH at which the proton activity is much lower than that of (I).

Moreover, the fact that kinetic experimental data fit equation (13) linearly in its logarithmic form allows us to exclude the possibility of the simultaneous presence of protiodecarboxylation and decarboxyprotonation because in this case equation (11) requires the constancy of a and b at any proton activity and the above mentioned chemical considerations make this constancy improbable owing to the fact that, in this case, the contribution of the protiodecarboxylation mechanism should remain constant at high pH (see above). On the other hand the presence of the two nitrogen atoms (of the pyridine type) seem to favour decarboxyprotonation, especially of the zwitterionic species. In fact the protonated electron deficient ring can easily display an incipient negative charge deriving from carbon–carbon bond breaking. Then the new formed zwitterion easily takes up a proton, giving protonated 2-amino-1,3,4-oxadiazole.

* A cyclic mechanism for decarboxylation involving as the basic centre 3-N of the oxadiazole ring (actually the less basic one) seems less probable because of the low probability of this type of mechanism in polar solvents at variance with the results for apolar solvents.

† If the mechanism operating is decarboxyprotonatio then value of the activation entropy calculated from the values of k_N (*i.e.*, in this case we have $k_N = k^*$) is lower than the true value or equal to it. In fact because the species which decarboxylates is presumably only Z, the true kinetic constant is k_Z which is higher or equal to k_N, to which it is linked by the relation $k_Z = k_N(1 + K_Z)$, where K_Z is the constant for the equilibrium $Z \rightleftharpoons HA$. If the equilibrium is shifted towards Z, K_Z tends to zero and k_Z tends to k_N.

Moreover, the calculated value of activation entropy † (large and positive, see Table 2) also favours the decarboxyprotonation mechanism. The high value of the activation enthalpy agrees with both the proposed mechanisms: in fact, it can be linked to the carbon–carbon breaking step as well as to the electrophilic protonation process followed by the partial loss of aromatic character of the 1,3,4-oxadiazole ring.

EXPERIMENTAL

Materials.—The acid (I) and the amine (II) were prepared and purified as described in the literature.[14]

Buffer Solutions.—Buffer solutions were prepared as suggested by Batts [15] using citrate in the pH region 2—4.77, and hydrochloric acid for pH < 2. Each buffer was adjusted to ionic strength 1.0 with potassium chloride. The pH measurements were made with Radiometer PHM63 digital pH meter with combined Radiometer GK 2301C electrode in cells thermostatted to 20.0 ± 0.1 °C. The concentrations of solutions of hydrochloric acid > 1M have been titrated with standard sodium hydroxide using phenolphthalein as indicator. The H_0 values used (at 20 °C) for these solutions are those of Gel'bshein *et al.*[16]

pK_a *Determinations.*—Ionization constants were determined at 20 °C by a spectrophotometric method. The method of computation for the determination of the ionization constants described by Dunn [17] was used. Absorbance measurements were made at 250 nm where the absorbance *versus* pH curve shows a maximum for the acid form. K_2 were determined at ionic strength 1.0; for K_1 this is not possible.

Kinetic Measurements.—The kinetics of the decarboxylation reactions were followed spectrophotometrically by measuring the disappearance of (I) at the wavelength of its absorption maximum (250 nm). The concentration employed was 10^{-3}M and the withdrawn samples were quenched in an excess of aqueous sodium hydroxide. Ionic strength of the buffered solutions was kept constant at the value of 1.0 through addition of KCl.

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