Studies on Decarboxylation Reactions. Part 4.[1a] Kinetic Study of the Decarboxylation of Some *N*-Alkyl- or *N*-Phenyl-substituted 5-Amino-1,3,4-oxadiazole-2-carboxylic Acids

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The rate constants of the decarboxylation reaction of compounds (Ib—f) have been measured in water over a range of proton activities, at various temperatures. The results obtained strongly support the unimolecular decarboxyprotonation mechanism.

BOTH the mechanism and rate of decarboxylation of aminocarboxylic acids in water are largely affected by the structure of the starting acid. The different reaction pathways, and the equilibria between the various species involved, are shown in the Scheme. The relevant apparent kinetic constants can be calculated by equation (1) where equations (2) and (3) apply.

$$k_{obs.} = k_N K_1[H^+]/A + (k_{A^-}K_1K_2)/A + k_{H_2A}[H^+]^2K_1B/A + k_{HA}K_1K_2[H^+]B/A \quad (1)$$

$$A = K_1K_2 + K_1[H^+] + [H^+]^2 \quad (2)$$

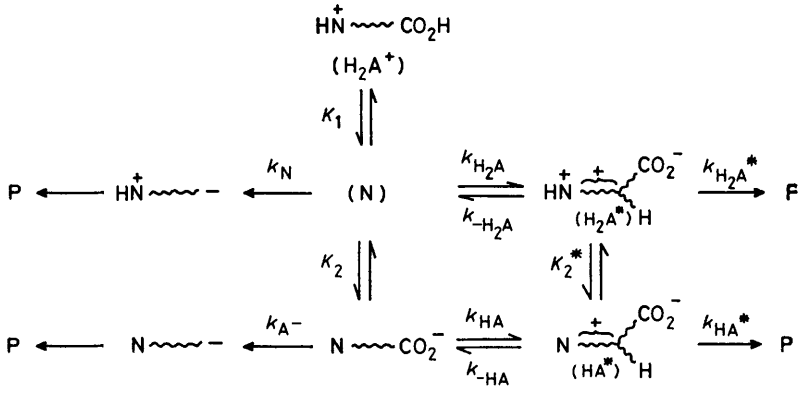
$$B = \frac{k_{H_2A^*}[H^+] + k_{HA^*}K_2^*}{(k_{-H_2A} + k_{H_2A^*}[H^+]) + (k_{-HA} + k_{HA^*})K_2^*} \quad (3)$$

The shape of the curve obtained by plotting log $k_{obs.}$ *versus* the proton activity is affected by the kinetic constants pertaining to the single steps (k_N, k_{A^-}, k_{H_2A}, k_{-H_2A}, k_{HA}, k_{-HA}, $k_{H_2A^*}$, k_{HA^*}) as well as by the equilibrium constants (K_1, K_2, K_2^*). However, taking into account the electronic effects of the nitrogen atom, we have $k_N > k_{A^-}$ and $k_{HA} > k_{H_2A}$. Thus, in general, equation (1) can be simplified for certain values of K_1, K_2, and $[H^+]$.

The kinetic data reported in the literature have been interpreted on the basis of two different reaction mechanisms: the protiodecarboxylation mechanism is characteristic of pyrrole-2-carboxylic acids [2] and of 2-X-4-amino-[3] or 4-X-2-amino-benzoic [4] acids (*i.e.* of acids derived from an aromatic substrate prone to S_EAr reactions); on the other hand, a decarboxyprotonation mechanism has been proposed in the case of pyrimidine-[5] or pyridine-2-carboxylic [6] acids (*i.e.* with acids derived from aromatic substrates of low reactivity towards electrophiles).

An interesting situation has been observed with 3-aminopyridine-2-carboxylic acid [6b] where the simultaneous presence of two nitrogen atoms (the amino-group activating and the aza-group deactivating S_EAr reactions) makes both mechanisms operate.

We have recently studied the decarboxylation of acid (Ia): [1b,†] here, the heterocyclic ring (1,3,4-oxadiazole), which is strongly deactivated with respect to S_EAr, largely counterbalances the effect of the amino-group and, as we have pointed out, the decarboxyprotonation mechanism occurs.



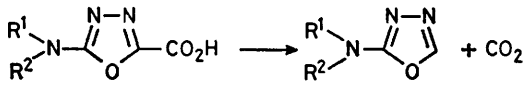
SCHEME

Our hypothesis is supported by comparison, *e.g.*, between the rate coefficients measured for (Ia) and those obtained for other aminocarboxylic acids which follow the protiodecarboxylation mechanism. If protiodecarboxylation also operates in our reactions, the inequality $k_{obs.} \leqslant k_{H_2A}[H^+] + K_2k_{HA}$ should be observed.

† Similar results have been obtained for the decarboxylation of 5-amino-1,3,4-thiadiazole-2-carboxylic acid.[1c]

At $[H^+]$ 0.1M (where we measured the highest $k_{obs.}$) and using K_2 calculated by us,[1b] k_{H_2A}, and k_{HA} at 80 °C for anthranilic acid,[4b] we can calculate $k_{obs.} \leqslant 5.7 \times 10^{-4} \times 0.1\ s^{-1} + 3.25 \times 10^{-2} \times 9.6 \times 10^{-2}\ s^{-1}$, *i.e.* $k_{obs.} \leqslant 3.2 \times 10^{-3}\ s^{-1}$. This value is at least one order of magnitude lower than that calculated from the apparent activation parameters for the decarboxylation of (I) ($k_{obs.}$ 3.2×10^{-2} s^{-1}). As a matter of fact, because protiodecarboxylation requires electrophilic attack, as a first step, the k_{H_2A} and k_{HA} values should be much lower for an aminocarboxylic acid derived from 1,3,4-oxadiazole than from benzene.

As expected, the discrepancy increases if we use the values at 150 °C of 3-aminopyridine-2-carboxylic acid,[6b] a compound which because of its structure can be compared with acid (I). The value obtained in this



(I) (II)

a; $R^1 = R^2 = H$

b; $R^1 = R^2 = Me$

c; $R^1 = Me, R^2 = H$

d; $R^1 = Bu^n, R^2 = H$

e; $R^1 = Ph, R^2 = H$

f; $R^1 = R^2 = Ph$

case ($k_{obs.} \leqslant 3.3 \times 10^{-5}\ s^{-1}$) is at least six orders of magnitude lower than that calculated as above for the decarboxylation of (I) at 150 °C ($k_{obs.} \simeq 40\ s^{-1}$), furnishing convincing evidence against the occurrence of a protiodecarboxylation mechanism.

In order to provide further support for this conclusion we now report the results obtained studying the behaviour of some *N*-alkyl- (Ib—d) or *N*-aryl- (Ie—f) substituted 2-amino-1,3,4-oxadiazolecarboxylic acids. Indeed, the two decarboxylation mechanisms predict opposite effects for nitrogen substituents.

Kinetic Data.—The apparent first-order kinetic constants at 40 °C and the thermodynamic parameters are set forth respectively in Tables 1 and 2. In order to stress the differences in behaviour of compounds (Ia—f) and to make the comparison of reactivities easier we present the curves obtained by plotting log $k_{obs.}$ for decarboxylation *versus* the acidity function (Figure).

TABLE 1

Apparent rate constants (s^{-1})[a] for the decarboxylation of acids (Ib—f) in water at 40 °C

Compound									
(Ib)		(Ic)		(Id)		(Ie)		(If)	
$pH(H_0)$	$10^4 k_{obs.}$	$pH(H_0)$	$10^4 k_{obs.}$	$pH(H_0)$	$10^4 k_{obs.}$	$pH(H_0)$	$10^4 k_{obs.}$	$pH(H_0)$	$10^4 k_{obs.}$
(−1.24)	0.111	(−1.24)	0.186	(−1.00)	0.215	(−1.12)	5.85	(−1.36)	3.34
(−1.00)	0.224	(−1.00)	0.249	(−0.74)	0.331	(−0.93)	7.14	(−1.08)	4.96
(−0.74)	0.337	(−0.74)	0.476	(−0.50)	0.523	(−0.50)	9.79	(−0.92)	5.89
(−0.21)	0.713	(−0.50)	0.685	(−0.21)	0.653	(−0.12)	10.8	(−0.74)	8.17
0.44	0.902	(−0.21)	0.988	0.43	1.12	0.40	9.77	(−0.12)	9.30
0.72	0.972	0.20	1.23	0.72	1.16	0.72	8.45	0.22	9.65
1.00	1.04	0.44	1.34	1.01	1.16	1.00	6.64	0.30	9.10
1.32	0.862	0.72	1.49	1.30	1.13	1.44	3.94	0.40	9.09
1.63	0.755	1.00	1.44	1.70	0.849	1.75	2.39	0.70	7.50
2.03	0.512	1.32	1.31	2.00	0.595	2.00	1.18	1.00	5.76
2.33	0.340	1.63	1.11	2.30	0.374	2.33	0.597	1.30	3.99
2.78	0.139	1.84	0.892	2.70	0.201	2.67	0.243	2.03	1.05
		2.03	0.662	3.05	0.044			2.67	0.246
		2.33	0.429						
		2.75	0.184						
		3.04	0.126						

[a] The rate constants are accurate to within ±3%. Wavelengths in nm (log ε) used for kinetic measurements: (Ib) 270 (3.72), (Ic) 260 (3.79), (Id) 264 (3.86), (Ie) 340 (3.84), (If) 290 (3.90).

TABLE 2

Apparent activation parameters [a] for the decarboxylation of acids (Ia—f)

Compound	$\Delta H^{\ddagger}$ [b]/kcal mol^{-1}	$\Delta S^{\ddagger}$ [c]/cal mol^{-1} K^{-1}	
(Ib)	27.9	12.1	(HCl 0.2M)
(Ic)	26.8	9.5	(HCl 0.2M)
(Id)	27.8	12.0	(HCl 0.2M)
(Ia) [d]	27.6	13.3	
(Ie)	25.1	8.1	(HCl 1M)
(If)	25.0	7.2	(HCl 1M)

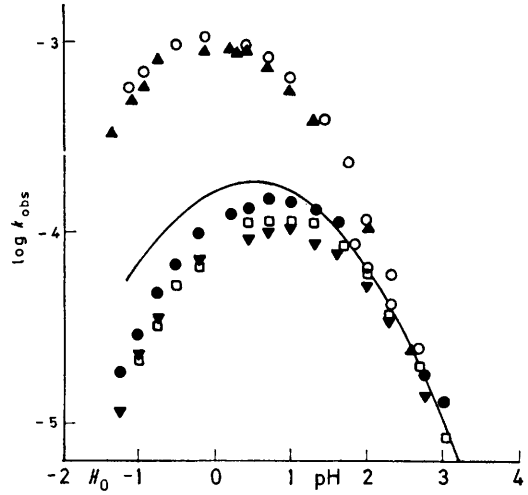
[a] Calculated from kinetic constants measured at three temperatures (40—60 °C). [b] At 40 °C, the maximum error is 0.6 kcal mol^{-1}. [c] At 40 °C. [d] Data from ref. 1b.

An examination of the Figure shows the different effects exerted on the height of the curve by alkyl (reduction of reactivity) and by aryl (increase of reactivity) substituents * present on the exocyclic amine nitrogen. Moreover the presence of alkyl groups has little influence on the position of the maximum whereas

* The reactivity trend parallels the electronic effects of the groups linked to amine nitrogen atom apart from (Ie and f) for which $(k_{obs.})_{(Ie)} > (k_{obs.})_{(If)}$ indicating that steric effects prevent the two phenyl groups from exerting their complete electronic effects. The higher reactivities of (Ie and f) compared with (Ia—d) are linked to lower activation enthalpy values not completely counterbalanced by activation entropy variations.

aryl substituents shift the maximum *ca.* 1 unit towards higher acidity.

Because the pH at the maximum of the curve corresponds to the isoelectric point [pH = $1/2(pK_1 + pK_2)$] and the observed shape of the curve is nearly



Plot of log $k_{obs.}$ for decarboxylation of acids (Ib—f) at 40.0 ± 0.1 °C *versus* acidity function: ▼ (Ib); ● (Ic); □ (Id); ○ (Ie); and ▲ (If). The solid line refers to (Ic) [1b]

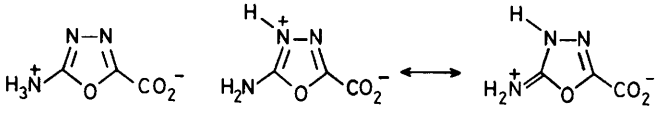
the same in every case, we can assume that alkyl groups cause no or little variation of the dissociation constants whereas aryl groups cause a significant increase. At this point, expression (4), which links the reactivity to proton activities, kinetic constants of the ampholyte N,* and

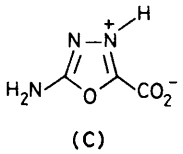
$$k_{obs.} = k_N \frac{K_1[H^+]}{[H^+]^2 + K_1K_2 + K_1[H^+]} \quad (4)$$

$$k_{obs.} = k_N[2(K_2/K_1)^{\frac{1}{2}} + 1] \quad (5)$$

equilibrium constants is simplified to (5) where the value of the fraction ranges between 1/3 and 1. As a consequence, a variation in reactivity lower than a factor of 3 *can* depend only on variations of the equilibrium constants; on the other hand variations higher than a factor of 3 *must* be related to variations in both equilibrium constants and k_N.

* In the case of 5-amino-1,3,4-oxadiazole-2-carboxylic acid the ampholyte N represents the isoprotonic species, *i.e.* the undissociated acid (Ia) and the zwitterionic forms (A)—(C).





Thus, we can safely say that the variation in reactivity observed in *N*-arylamino-acids [$(k_{obs.})_{(Ie-f)}/(k_{obs.})_{(Ia)} \simeq 6$] depends essentially on structural (steric or electronic) effects which affect even the kinetic constants, whereas the small variation observed with *N*-alkylamino-acids [$(k_{obs.})_{(Ib-d)}/(k_{obs.})_{(Ia)} \simeq 0.6$] can depend on variations in equilibrium and/or kinetic constants.

At low proton activities (pH $\geqslant$ *ca.* 2.8) all the amino-acids considered are decarboxylated at the same rate, *i.e.* K_2/k_N = constant. We can obtain the same result by simplifying (4): at low hydrogen ion concentrations (in the range where $[H^+] \ll K_1$) (4) turns into (6)

$$k_{obs.} = k_N \frac{[H^+]}{[H^+] + K_2} \quad (6)$$

$$1/k_{obs.} = 1/k_N + K_2/k_N[H^+] \quad (7)$$

and equation (7) is then obtained. On plotting $1/k_{obs.}$ *versus* $[H^+]$ the K_2/k_N value (see Table 3) can be calculated for each amino-acid. The similar values (90 ± 10 mol l^{-1} s) observed clearly indicate that structural variations on the amine nitrogen cause parallel variations both on decarboxylation kinetic constants (k_N) and on second equilibrium constants (K_2), *i.e.* each factor (steric or electronic), which destabilizes the

TABLE 3

K_2/k_N Values [a] for the decarboxylation of acids (Ia—f) in water at 40 °C

Compound	K_2/k_N	t [b]	C.l. [c]	r [d]	n [e]
(Ib)	100 ± 3	38.0	>99.9	0.9998	4
(Ic)	98.5 ± 3	38.1	>99.9	0.9994	5
(Id)	84 ± 4	21.4	>99.9	0.998	4
(Ia) [f]	85.9 ± 0.4	255	>99.9	0.999 95	7
(Ie)	81.5 ± 1	89.2	>99.9	0.9999	6
(If)	79 ± 1	62.0	>99.9	0.9999	4

[a] Calculated from equation (5) (see text). [b] *t* test. [c] Confidence level. [d] Correlation coefficient. [e] Number of points. [f] Data from ref. 1*b*.

ampholyte (N) with respect to the anionic form (A^-), at the same time favours the decarboxylation of the ampholyte.

The results allow the following conclusions to be drawn. (1) The amino-acids (Ia—f) decarboxylate by the same mechanism, as indicated also by the small variations in the activation parameters, which are clearly related to structural changes (see below). (2) The constancy of the K_2/k_N values agrees with a unimolecular mechanism (decarboxyprotonation). (3) The effects of substituents also agree with a unimolecular mechanism.

Let us consider the last point more extensively. If the protiodecarboxylation mechanism were operating, on the basis of the known electronic effects exerted by NMe_2, NHMe, $NHBu^n$, NH_2, NHPh, and NPh_2 (*e.g.* see literature values [7] for σ_p or σ_p^+), the substitution of amine hydrogen atoms by alkyl groups should increase the reactivity towards decarboxylation, and substitution by aryl groups should decrease the reactivity. On the contrary in the decarboxyprotonation mechanism the opposite effects should be and are observed. Therefore

we can definitely exclude the protiodecarboxylation mechanism and state that the decarboxyprotonation mechanism is strongly indicated.

It is necessary to emphasize that in spite of the presence of strong electron-repelling substituents in the ring which should favour the protiodecarboxylation mechanism, the mechanism which operates is unimolecular and this happens because of the presence of two nitrogen atoms (pyridine-like) in the ring which prevents the proton electrophilic attack from being the first stage of the reaction.

EXPERIMENTAL

Materials.—The acids (Ib—c and e—f) and the amines (IIb—c and e—f) were prepared and purified as described in the literature.[8]

5-n-Butylamino-1,3,4-oxadiazole-2-carboxylic Acid (Id) *and 2-n-Butylamino-1,3,4-oxadiazole* (IId).—Compounds (Id) and (IId) were prepared and purified according to general methods [8] and gave satisfactory analytical data. Compound (Id) melted at 73 °C with decarboxylation giving (IId) which had m.p. 48—49 °C, $\delta(CDCl_3)$ 0.80—1.85 (7 H, m, Bu^n), 3.4 (2 H, m, Bu^n), 6.42 (1 H, s, NH), and 7.84 (1 H, s, 5-H).

Kinetic Measurements.—The kinetics of decarboxylation were followed spectrophotometrically as previously described [1b] by measuring the disappearance of amino-acids at a convenient wavelength (see Table 1). The pH measurements were made as previously described.

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