Studies on Decarboxylation Reactions. Part 7.[1] Kinetic Study of the Decarboxylation of 2-Amino- and 2-Phenylamino-thiazole-5-carboxylic Acids

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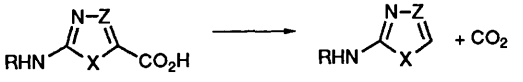
The rate constants of the decarboxylation reaction of 2-amino- and 2-phenylamino-thiazole-5-carboxylic acid (**3a–b**), and, for comparison, of 5-phenylamino-1,3,4-thiadiazole-2-carboxylic acid (**2b**) have been measured in water over a range of proton activities. The results obtained suggest: (i) compound **2b** decarboxylates, in the whole range of proton activity studied, through a unimolecular decarboxyprotonation mechanism characteristic of 1,3,4-oxa- and 1,3,4-thiadiazole derivatives; (ii) in contrast, **3a–b** decarboxylate *via* either a unimolecular decarboxyprotonation or a bimolecular protiodecarboxylation mechanism as a function of proton activity.

The 5-amino-1,3,4-oxadiazole-2-carboxylic acids **1** give, on heating, the corresponding 2-amino-1,3,4-oxadiazoles (Scheme 1). The data obtained suggest that in acidic solution the



1a; X = O, Z = N, R = H
1b; X = O, Z = N, R = Ph
2a; X = S, Z = N, R = H
2b; X = S, Z = N, R = Ph
3a; X = S, Z = CH, R = H
3b; X = S, Z = CH, R = Ph

Scheme 1

decarboxylation proceeds through a slow carbon–carbon bond cleavage followed by a fast carbon–hydrogen bond formation in the intermediate carbanion, *i.e.* a unimolecular decarboxyprotonation mechanism.[2] The rate of decarboxylation of **1** is affected by many factors, such as the experimental conditions (proton activity,[2] solvent,[3] added surfactant,[3] *etc.*), or the structure of the amino acid (*e.g.*, the nature of the substituents on the exocyclic nitrogen).[4]

The comparison between the reactivity of 5-amino-1,3,4-oxadiazole (**1a**) and 5-amino-1,3,4-thiadiazole-2-carboxylic acid (**2a**) clearly shows how the endocyclic group VI heteroatom (O *vs.* S) can influence the reaction rate (which is lower in the latter case[5]) without affecting the nature (decarboxyprotonation) of the mechanism. In order to gain information on the influence of the two endocyclic nitrogen atoms on the decarboxylation reaction, 2-aminothiazole-5-carboxylic acid **3a** was synthesized, and its apparent first-order decarboxylation rate constant measured in various acidic aqueous solutions. One can expect that the strong electron withdrawing effect of pyridine-like nitrogen atoms should favour the unimolecular decarboxyprotonation mechanism, by stabilizing the negative charge in the intermediate carbanion. The effect of the substitution on the exocyclic nitrogen atom was also investigated by synthesizing the *N*-phenyl derivatives **2b** and **3b** and measuring the apparent rate constants of the relevant decarboxylations.

Results and Discussion

The apparent first-order rate constants for the decarboxylation of compounds **2** and **3**, as a function of pH or H_0 are reported in Table 1. It can be observed that compounds **2** are 20–40 times more reactive than the corresponding derivatives **3**. Moreover

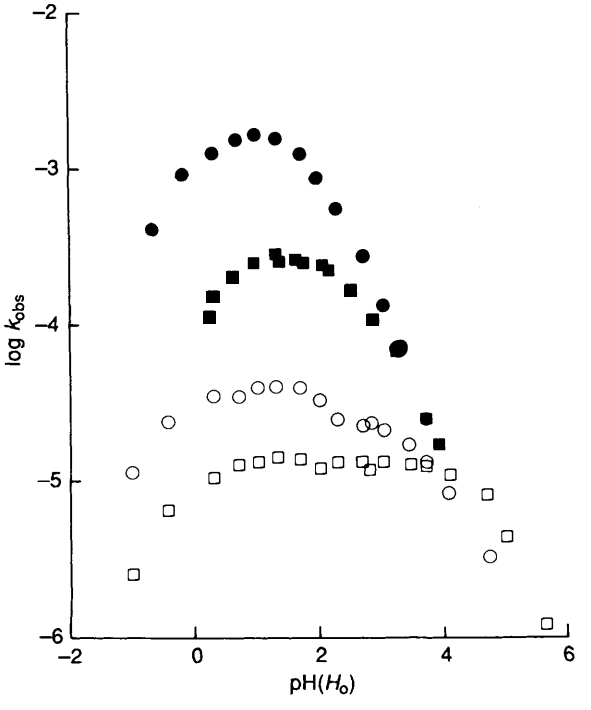


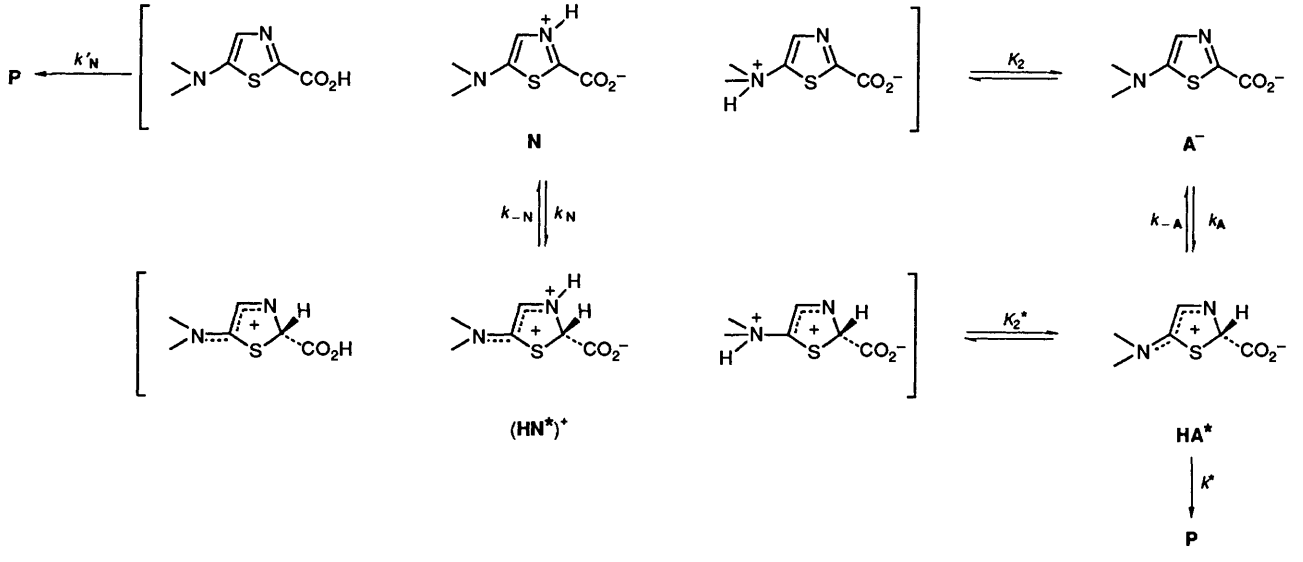
Fig. 1 Plot of log k_{obs} for decarboxylation of acids **2a** (■), **2b** (●), **3a** (□) and **3b** (○) *vs.* acidity functions (H_0 or pH) at 60.0 ± 0.1 °C

the *N*-phenyl substitution provides a small reactivity increase [$(k_{obs})_{2b}/(k_{obs})_{2a}$ = 5.8 and $(k_{obs})_{3b}/(k_{obs})_{3a}$ = 2.8, at the reactivity maxima], coupled with a shift of the reactivity maximum towards higher acidity, as previously observed in the corresponding oxadiazole derivatives. These results seem to agree with the previously proposed[2–5] unimolecular decarboxyprotonation mechanism. In fact, the thiadiazole ring can stabilize the negative charge of the intermediate anion better than the thiazole ring. Moreover, we reported that the *N*-phenyl substitution increases the rate of decarboxylation in the case of 5-amino-1,3,4-oxadiazole-5-carboxylic acids (**1b** being more reactive than **1a** by a factor of *ca.* six at the reactivity maximum).[4] However, a plot of the kinetic constants against pH or H_0 (see Fig. 1) shows also a qualitative difference between the data for thiadiazoles and thiazoles, *i.e.* a flattening of the curve for the latter. As a consequence the rate of decarboxylation of **3a** is nearly constant in a range of three pH units (0.7–3.7). If a unimolecular decarboxyprotonation

Table 1 Apparent rate constants/s^{-1} [a] for the decarboxylation of acids **2a**, **2b**, **3a** and **3b** in water at 60 °C and I_c = 1 mol dm^{-3}

2a [b]		**2b**		**3a**		**3b**	
pH(H_0)	$k_{obs}/10^{-5}$ s^{-1}	pH(H_0)	$k_{obs}/10^{-5}$ s^{-1}	pH(H_0)	$k_{obs}/10^{-5}$ s^{-1}	pH(H_0)	$k_{obs}/10^{-5}$ s^{-1}
0.25	11.8	(−0.65)	41.2	(−1.00)	0.251	(−1.00)	1.14
0.32	15.0	(−0.18)	90.6	(−0.42)	0.647	(−0.42)	2.40
0.61	20.6	0.30	122	0.30	1.03	0.32	3.43
1.00	24.7	0.70	152	0.71	1.26	0.71	3.39
1.32	27.5	1.00	160	1.02	1.29	1.02	3.90
1.36	25.7	1.30	156	1.34	1.40	1.30	3.92
1.61	26.2	1.70	124	1.70	1.37	1.71	3.92
1.76	25.2	2.00	86.5	2.02	1.20	2.02	3.30
2.03	24.0	2.30	55.4	2.31	1.28	2.30	2.46
2.16	22.3	2.70	28.5	2.70	1.29	2.72	2.21
2.52	16.8	3.00	12.8	2.82	1.32	2.84	2.32
2.88	11.2	3.30	7.17	3.05	1.29	3.05	2.10
3.23	6.57			3.46	1.26	3.45	1.69
3.73	2.46			3.71	1.22	3.71	1.28
3.91	1.69			4.11	1.09	4.10	0.841
				4.70	0.817	4.71	0.325
				5.01	0.434		
				5.67	0.121		

[a] The rate constants are accurate to within ±3%. [b] Data from ref. 5.



Scheme 2

mechanism were operating, k_{obs} would be proportional to the concentration of the ampholyte species and the experimental log k_{obs} *vs.* pH curve could be used to estimate the constants for the equilibrium (1).

$$H_2A^+ \overset{K_1}{\rightleftharpoons} N \overset{K_2}{\rightleftharpoons} A^- \qquad (1)$$

In fact the K_1 value thus obtained (*ca.* 1) is larger than that for the corresponding thiadiazole (K_1 0.39)[5], a result which does not agree with the nature of the two heterocyclic rings. Moreover, a value of K_1 (0.011) for **3a** (T = 20 °C; I_c = 1.0 mol dm^{-3}) was spectrophotometrically determined, the difference with the estimated value being too large to be ascribed to the experimental uncertainty. Thus, the replacement in the ring of a nitrogen atom with a methyne group most likely affects the mechanism of the decarboxylation. The flattening of the log k_{obs} *vs.* pH or H_0 plots might be a consequence of this, and a few hypotheses can be advanced in order to explain such behaviour. (i) A reaction between two species involved in the equilibrium (1) could occur. In this case, though, apparent second-order kinetics would be observed and this does not appear. (ii) Both the ampholyte (**N**) and the protonated acid (H_2A^+) could be active species of comparable reactivity in the unimolecular decarboxylation reaction. The decrease of the rate at high proton concentration could be then justified by an increasing amount of the twice protonated, inactive acid H_3A^{2+} [eqn. (2)].

$$H_2A^+ + H^+ \rightleftharpoons H_3A^{2+} \qquad (2)$$

However we were not able to measure this equilibrium constant spectrophotometrically, because the UV spectrum of **3a** is practically unchanged in the 0.5–5 mol dm^{-3} [HCl] range, whereas if the present hypothesis were correct the experimental curve would display comparable concentrations of H_2A^+ and H_3A^{2+}. (iii) Two different mechanisms of decarboxylation could operate, *i.e.* a unimolecular decarboxyprotonation of the ampholyte at low acidities, overwhelmed at higher acidities by a bimolecular protiodecarboxylation.† Scheme 2 illustrates the pattern suggested, where the **HA*** and **HN*** species are Wheland intermediates.

† The protiodecarboxylation mechanism proceeds through a slow proton attack followed by a fast carbon–carbon bond cleavage.

The fit to the behaviour observed requires that the HN* species be inactive in the decarboxylation reaction. In fact, if the HA* $\rightleftharpoons$ HN* equilibrium leans to the right, the decarboxylation of HN* (which contains the poor CO_2H leaving group) would likely occur *via* HA*, taking advantage of its ionized carboxylic function.

Applying the steady-state approximation to ([HA*] + [HN*]) the expression for the dependence of the apparent first-order constant on acidity can be obtained [eqn. (3)]. Eqn. (3) is

$$k_{obs} = \{k^*(k_A K_2 + k_N[H^+])/(k_{-A} + k^* + k_{-N}[H^+]/K^*_2) + k'_N\} \cdot K_1[H^+]/([H^+]^2 + K_1[H^+] + K_1K_2) \quad (3)$$

a linear combination of the two simpler eqns. (4) and (5), and

$$A = k^*(k_A K_2 + k_N[H^+])/(k_{-A} + k^* + k_{-N}[H^+]/K^*_2) \cdot K_1[H^+]/([H^+]^2 + K_1[H^+] + K_1K_2) \quad (4)$$

$$B = k'_N K_1[H^+]/([H^+]^2 + K_1[H^+] + K_1K_2) \quad (5)$$

eqn. (5) pertains to a unimolecular decarboxyprotonation mechanism which is similar to that which allowed us to explain the decarboxylation kinetic data for **2a**. In contrast, eqn. (4) has been suggested by Dunn[6] to explain the decarboxylation of 3-hydroxy- and 3-amino-pyridine-2-carboxylic acid: it also fits a bell-shaped curve, but its maximum value generally does not correspond to the isoelectric point, unless the condition given in eqn. (6) is verified. Moreover, when $[H^+] \ll K_2$ eqn. (3)

$$K_2^*/K_2 = k_A k_{-N}/[k_N(k_{-A} + k^*)] \quad (6)$$

becomes eqn. (7) *i.e.* that of a simple anion protiodecarboxyl-

$$k_{obs} = k^* k_A[H^+]/(k_{-A} + k^*) \quad (7)$$

ation and the trend at higher acidities is still consistent with experimental data.

Thus, the results herein seem to show, interestingly, that the replacement of an endocyclic nitrogen atom with a methyne group 'activates' a decarboxylation mechanism alterntive to that observed for 1,3,4-thiadiazole derivatives; the increase of π-electron density on going from the thiadiazole to the thiazole system enables the attack of a proton onto a carbon atom of the heterocycle, making protiodecarboxylation a viable pathway which takes over in highly acidic conditions.

The same mechanistic conclusions can be achieved by considering the data on the decarboxylation of 2-phenylaminothiazole-5-carboxylic acid (**3b**). A comparison between the reactivities of **3a** and **3b** shows that the latter decarboxylates faster in the range −1.0 (H_0) to 3.5 (pH), but the ratio of the rate constants is lower than that observed for the corresponding thiadiazole derivatives (2.8 and 5.8 at the reactivity maximum, respectively, considering only the range where the decarboxyprotonation mechanism is operating for the four compounds). It can be remarked that this behaviour clearly matches that already observed for a series of *N*-substituted 5-amino-1,3,4-oxadiazole-2-carboxylic acids,[4] which decarboxylate through the same mechanism.

Experimental

Synthesis and Purification of Compounds.—All m.p.s are uncorrected. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer (Nujol dispersion). ^{1}H NMR spectra were determined on a Varian EM 360 (60 MHz; internal standard tetramethyl silane). Mass spectra were recorded on a JEOL JMS-01-SG-2 mass spectrometer. Starting materials are Fluka or Carlo Erba products.

5-Phenylamino-1,3,4-thiadiazole-2-carboxylic acid (**2b**) (as the sodium salt),[7] 2-phenylamino-1,3,4-thiadiazole,[8] 2-aminothiazole[9] and 2-phenylaminothiazole[10] were prepared according to the literature. In order to obtain a very pure amino acid, suitable for kinetic studies, a slight modification of reported procedures[11] was employed for the synthesis of **3a**.

Methyl 2-Aminothiazole-5-carboxylate.—Thiourea (3.0 g, 39 mmol) was added to a mixture of methyl 2-chloro-3-oxopropanoate[12] (5.5 g, 40 mmol) and water (3 cm^3) and smoothly warmed. The solution was neutralized with cold aqueous ammonia. The yellow solid formed was then collected (3.0 g, 49%) m.p. 191–193 °C (Found: C, 38.1; H, 3.9; N, 17.6. $C_5H_6N_2O_2S$ requires C, 37.96; H, 3.82; N, 17.71%); ν_{max}(Nujol)/cm^{-1} 3340 (N–H) and 1680 (C=O); δ_H([$^2H_6$]-DMSO) 7.80 (2 H, br s, NH_2), 7.65 (1 H, s, Het-H) and 3.68 (3 H, s, Me); *m/z* 158 (M^+, 100), 127 (20), 99 (35), 73 (25), 58 (30), 57 (35) and 44 (36).

2-Aminothiazole-5-carboxylic Acid (**3a**).—Methyl 2-aminothiazole-5-carboxylate (320 mg, 2.0 mmol) was added to sodium hydroxide (80 cm^3; 0.1 mol dm^{-3}), stirring at r.t. being continued until complete dissolution of the ester. The solution was then acidified with glacial acetic acid, and the precipitation of the amino acid (210 mg, 74%) was induced by scratching. The collected solid was purified by dissolution in sodium hydroxide (0.1 mol dm^{-3}) followed by reprecipitation with glacial acetic acid, m.p. 185 °C (phase transformation) (Found: C, 33.1; H, 2.9; N, 19.50. $C_4H_4N_2O_2S$: requires C, 33.33; H, 2.80; N, 19.44%); δ_H([$^2H_6$]DMSO) 8.5 (1 H, br s, CO_2H), 7.60 (2 H, br s, NH_2) and 7.52 (1 H, s, Het-H); *m/z* 144 (M^+, 100), 126 (14), 99 (21), 73 (35), 58 (34) and 44 (22).

Methyl 2-Phenylaminothiazole-5-carboxylate.—Methyl 2-chloro-3-oxopropanoate[12] (1.0 g, 7.3 mmol) and 1.0 g (6.6 mmol) of *N*-phenylthiourea in ethanol were refluxed for 1 h. The cooled solution was slightly basified with dilute aqueous NH_3. The crude product (570 mg, 38%), was purified by recrystallization from water–ethanol; m.p. 178–180 °C; (Found: C, 56.2; H, 4.2; N, 12.1. $C_{11}H_{10}N_2O_2S$ requires C, 56.39; H, 4.30; N, 11.96%); ν_{max}(Nujol)/cm^{-1} 1710 (C=O); δ_H([$^2H_6$]acetone) 9.70 (1 H, br s, NH), 7.80 (1 H, s, Het-H), 7.4 (5 H, m, Ph) and 3.73 (3 H, s, Me); *m/z* 234 (M^+, 100), 233 (29), 203 (19), 175 (37), 174 (55), 91 (19), 77 (39), 57 (36) and 44 (36).

2-Phenylaminothiazole-5-carboxylic Acid (**3b**).—Methyl 2-phenylaminothiazole-5-carboxylate (330 mg, 1.4 mmol) was added to sodium hydroxide (20 cm^3; 0.2 mol dm^{-3}), stirring at r.t. to almost complete dissolution. The filtered solution was acidified with glacial acetic acid. Crude compound **3b** was purified by dissolution in sodium hydroxide (0.2 mol dm^{-3}) followed by reprecipitation with glacial acetic acid; yield 180 mg (52%), m.p. 180 °C (phase transformation) (Found: C, 54.65; H, 3.75; N, 12.7. $C_{10}H_8N_2O_2S$ requires C, 54.53; H, 3.66; N, 12.72%); δ_H([$^2H_6$]DMSO) 8.5 (1 H, br s, CO_2H), 7.5 (6 H, m, Ph + NH) and 7.76 (1 H, s, Het-H); *m/z* 220 (M^+, 100), 202 (15), 175 (30), 174 (39), 91 (20), 77 (41), 57 (38) and 45 (29).

pK *Determinations.*—Ionization constants were determined at 20 °C and at I_c = 1 mol dm^{-3} by a spectrophotometric method, according to a reported computational procedure.[13] For the determination of pK_2 of **3a** the absorbance measurements were made at λ = 272 nm, while for pK_2 of **2b** the wavelength of λ = 310 nm was used, where the two curves show a maximum. The following values have been calculated: for **2b**, pK_2 3.20; for **3a**, pK_1 1.95 and pK_2 3.96.

Kinetic Measurements.—The kinetics of decarboxylation were followed spectroscopically as previously described[2] by

measuring the disappearance of the amino acids **3a**, **3b** and **2b** (as potassium salts) at λ = 285, 317 and 358 nm, respectively. The pH measurements were made as previously described.

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