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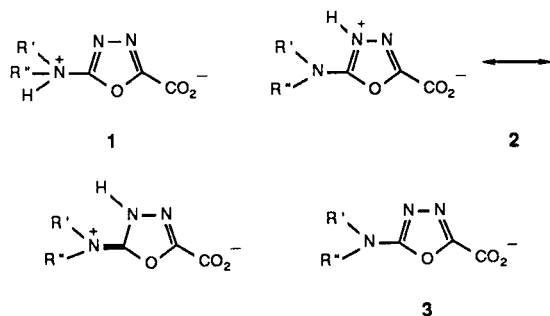
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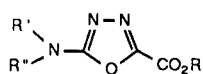
The dissociation constants (K_1) of both acids **4a-c** and esters **5a-c** and the rate constants of the decarboxylation reaction of acids **4a-c** have been measured at various high concentrations of hydrochloric acid (0.5-8.0 M range). The results obtained have enabled us to suggest the probable structure of the zwitterion which undergoes decarboxylation.

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The rates of the decarboxylation reaction of some 5-amino-1,3,4-oxa(thia)diazole-2-carboxylic acids are affected by many factors. The data obtained [1,2] at various proton activities by studying the effects of surfactants, of the substituents present on the exocyclic nitrogen, and of the solvents used allowed us to suggest unimolecular decomposition mechanism of one of the possible zwitterions [**1-3**, $R' = R'' = H$]. In order to gain information on the



composition of the ampholyte mixture and possibly on the structure of the zwitterion which decomposes, we have measured both the dissociation constants (K_1) related to equilibrium 1 at 298 K and the decomposition rates of acids **4a-c** at high concentration of hydrochloric acid (0.5-8.0 M) at 313 K. Also the dissociation constants of the conjugated acids of esters **5a-c** have been measured.



4, $R = H$; **5**, $R = Me$

a, $R' = R'' = H$
b, $R' = H, R'' = Ph$
c, $R' = R'' = Ph$

Kinetic and equilibrium data are collected in Tables I-III. In the range studied the decarboxylation rates decrease with increasing acid concentration, indicating either that the H_2A^+ species is not able at all to decarboxylate or that its decarboxylation rate is much lower than that of the zwitterionic species.

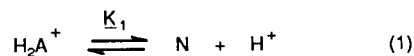
Table I

Observed Rate Constants [a] for the Decarboxylation of Acids **4a-c**
at Various Hydrochloric Acid Concentrations at 313.0 ± 0.1 K

[HCl]	4a $k_{obs} \times 10^4, s^{-1}$	[HCl]	4b $k_{obs} \times 10^4, s^{-1}$	[HCl]	4c $k_{obs} \times 10^4, s^{-1}$
0.50	1.76	1.00	10.8	1.86	10.2
1.00	1.42	1.80	9.79	2.36	8.66
1.25	1.28	2.40	8.50	2.40	8.17
1.48	1.06	3.00	7.14	3.00	5.89
2.00	0.767	3.60	5.85	3.45	4.96
2.22	0.758	5.10	2.60	4.40	3.34
3.00	0.558	6.00	1.66	6.00	1.37
		8.00	0.458	8.00	0.542

[a] The rate constants are accurate to within $\pm 3\%$.

In the range of proton activities studied, the following scheme for the decarboxylation reaction is operational where H_2A^+ , N, and P represent the conjugate acids of



aminocarboxylic acids, the ampholytes [3], and the reaction products, respectively. Equations 1-2 recall the

Table II

Values of Dissociation Constants (K_1) Related to Equilibrium (1) for Compounds **4a-c** and **5a-c** Measured in Hydrochloric Acid Solution at 298.0 ± 0.1 K

Substrate	m [a] \pm s _m [b]	K_1 [a] \pm s [b]	λ [c]
5a	1.02 \pm 0.01	-0.13 \pm 0.01	275 nm
5b	1.00 \pm 0.06	-1.01 \pm 0.07	291 nm
5c	1.05 \pm 0.11	-1.15 \pm 0.13	293 nm
	($\phi \cdot 1$) [d] \pm s [b]		
5a	-0.95 \pm 0.04	-0.12 \pm 0.02 [d]	275 nm
5b	-1.11 \pm 0.16	-1.03 \pm 0.09 [d]	291 nm
5c	-1.10 \pm 0.18	-1.21 \pm 0.12 [d]	293 nm
4a		-0.43 \pm 0.03 [e] (-0.13) [f]	234 nm
4b		-0.88 \pm 0.17 [e]	270 nm
4c		-1.44 \pm 0.15 [e]	225 nm

[a] Slopes and intercepts obtained through least squares analysis of $\log I$ vs. $-H_o$. [b] Standard deviations. [c] Wavelengths used for the determination of the dissociation constants. [d] Slopes and intercepts obtained through least squares analysis of $(\log I - \log [H^+])$ vs $(H_o + \log [H^+])$. [e] In the case of acids **1a-c** the K_1 values have been calculated using the equation $1/K + D_o/[h_o(D_{BH^+} - D)] = D/[h_o(D_{BH^+} - D)]$ suggested by Hammett [see L. A. Flexser, L. P. Hammett and A. Dingwall, *J. Am. Chem. Soc.*, **57**, 2103 (1935)]. [f] Data from ref [2a].

Table III

Parameters Used for the Application of Equations 7 and 9 to Kinetic Data of Table I

Substrate	Equation [a]	a [b]	$\phi \pm s_\phi$ [c]	b \pm s _b [c]
4a	7	100	1.15 \pm 0.06	3.85 \pm 0.02
4b	7	750	0.21 \pm 0.01	1.89 \pm 0.01
4c	7	200	0.52 \pm 0.02	2.42 \pm 0.02
			($\phi \cdot \phi_\neq$) \pm s [c] $\log k_N$	
4a	9		3.02 \pm 0.11	-3.76 \pm 0.04
4b	9		1.84 \pm 0.07	-2.48 \pm 0.07
4c	9		1.92 \pm 0.03	-2.37 \pm 0.02

[a] H_o -values from M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

[b] The a-values are those which give the best straight lines. [c] Standard deviations.

scheme of acid-catalysed reactions [4] and, although in our case the active species is the unprotonated one, we think that useful information can be obtained from studies of the decarboxylation reaction at high proton activities by applying the method employed in the studies of acid-catalysed reactions.

Using the steady state treatment for equations 1-2, the following relation between the observed rate constants and true kinetic and equilibrium constants can be obtained.

$$k_{obs} = \{ (k_N K_1 / [K_1 + h_o(f_N f_{BH^+} / f_{H_2A^+} f_B)]) \} f_N / f_\neq \quad (6)$$

Following the Bunnett-Olsen hypothesis [5], *i.e.*, considering

$$f_N f_{BH^+} / f_{H_2A^+} f_B = (f_{BH^+} / f_B f_{H^+}) \phi$$

and also putting $f_N / f_\neq = 1$ [6], equation (6) can be rearranged to

$$\log (1 / k_{obs} - a) + H_o = \phi (H_o + \log [H^+]) - b \quad (7)$$

where $a = 1 / k_N$ and $b = \log K_1 k_N$.

According to the suggestion of Modena, Scorrano, *et al.* [7] the Bunnett-Olsen hypothesis can be also applied to the ratio f_N / f_\neq and one can write

$$\log f_N / f_\neq = (\phi - \phi_\neq) (H_o + \log [H^+]) \quad (8)$$

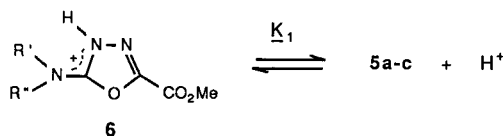
thus, (6) becomes

$$\log k_{obs} - \log [N] / ([N] + [H_2A^+]) = \log k_N + (\phi - \phi_\neq) (H_o + \log [H^+]) \quad (9)$$

Obviously it is possible from the K_1 values to calculate the ratio $[N] / \{ [N] + [H_2A^+] \}$ at any proton activity.

The results obtained by applying equations (7) and (9) to kinetic and thermodynamic experimental data have been collected in Table III; together with the equilibrium data (see Table II) they can provide useful information [8].

If one looks at the protonation data, it can be said that the values of ϕ and m for esters **5a-c** are very close showing that these compounds are bases of the same structural type [5]. This allows us to exclude protonation on the exocyclic nitrogen [**5a**, **5b** and **5c** are a primary, secondary and tertiary heteroaromatic amine, respectively, and these three classes of amines usually show different ϕ and m values for each class]. Therefore the site of protonation would be an endocyclic nitrogen, presumably the nitrogen-4, because of the electronic effects of the amino and carbomethoxy groups. This conclusion is also supported by a comparison of the pK_A values. The variation range (*ca.* 1.3 units) is too small if referred to as a change from a primary to a secondary and to a tertiary aromatic amine (there is a change of *ca.* 9.6 units, on going from aniline to diphenylamine and to triphenylamine). The variations of pK_A measured by us well agree with the electronic effects [10] exerted by the various exocyclic amino substituents on the basicity of nitrogen-4. Considering the pK_A , ϕ , and m values observed, we are inclined to exclude steric effects by exocyclic amino substituents on the basicities of nitrogen-4. Therefore the protonation reaction would be well depicted by the following equilibrium. Moreover, looking at the uv spectra obtained one can observe that at high proton activity both the species H_2A^+ deriving from



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the acid and from the corresponding ester show absorption maxima at about the same wavelength (λ max *ca.* 240 nm) and the spectra are practically superimposable.

For the acids **4a-c** we observe a trend of pK_A values similar to that seen for esters **5a-c** which allows us to assume that also in the acids the protonation site is nitrogen-4. On the other hand, this result agrees with the assumptions based on the similar electronic effects exerted by carboxylic and carbomethoxy substituents, (e.g., compare the σ_m -values [10] +0.37 for both $-\text{CO}_2\text{H}$ and $-\text{CO}_2\text{Me}$ substituents).

Let us now consider the information coming from kinetic data: the first consideration is that positive values for $(\phi - \phi_{\neq})$ indicate [7] a solvation of the initial state higher than that of the transition state, thus confirming the data obtained in the studies of the effects of surfactants and of mixed solvents. On the other hand the ϕ and $(\phi - \phi_{\neq})$ values calculated agree with two different possibilities: 1) the decarboxylating species are different in the protonation site for the acid **4a** and for the acids **4b** and **4c**; 2) the decarboxylating species is in any case the zwitterion protonated on the exocyclic nitrogen. As seen before, different situations have to be expected because of the different nature of the amino group (primary, secondary, or tertiary).

We favor the first hypothesis. In fact, we think that even if the ampholyte exists essentially as an undissociated acid, the most important zwitterionic species should be **2**, protonated at nitrogen-4. Let us consider the reactivity in the unsubstituted aminocarboxylic acid **4a**: a comparison between **1** and **2** allows one to foresee a higher ability to decarboxylate of **1** with respect to **2**, because in **1** the positive charge is localized on the *p*-substituent whereas in **2** it is delocalized in the two stabilized resonance structures. In contrast, when the exocyclic nitrogen is substituted with one or two phenyl groups, because of steric and electronic effects, the protonation at exocyclic nitrogen becomes unlikely and the favoured and reactive structure is **2** with a positive charge localized on nitrogen-4, because the ability of the exocyclic nitrogen to conjugate is strongly lowered by the electronic effect of phenyl groups.

EXPERIMENTAL

Synthesis and Purification of Compounds.

The acids **4a-c** and the esters **5a-c** were prepared and purified as described in the literature [11]. Reagent-grade hydrochloric acid (Carlo Erba) was used.

K_1 Determinations.

Ionization constants were determined in hydrochloric acid at 293 K by a spectrophotometric method. The methods of computation for the determination of the ionization constants and wavelengths used are reported in Table II.

Kinetic Measurements.

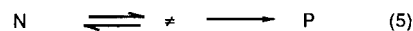
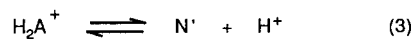
The kinetics of decarboxylation was followed spectrophotometrically as previously described [2a] by measuring the disappearance of amino acids **4a-c** at 250, 340 and 290 nm, respectively.

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- [3] The ampholytes are isoprotic species, i.e. the undissociated acids or the various possible zwitterions **1-3**. As a consequence, the reaction scheme would include another equilibrium as indicated below, where N'



and N would represent all the possible ampholytes and the active ampholyte which decomposes, respectively. For the discussion of data it is equivalent to consider equations 1-2 or 3-5.

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[6] This equality implies that transition and initial states are bases of the same family [5].

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[8] It must be remarked that there is a mutual agreement among the values calculated for a , b , K_1 and $\log k_N$. Considering the various values of $\log k_N$ one must remember that, if one uses equations 3-5, a direct comparison of k_N values can be misleading, because the k_N values are also a function of K_1 .

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