

Studies on Decarboxylation Reactions. Part 5 [1].
Micellar Catalysis and Mixed Solvents Effects on the
Decarboxylation of Some *N*-Alkyl- or
N-Aryl-substituted 5-Amino-1,3,4-oxadiazole-2-carboxylic Acids

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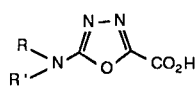
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The effect of micelles and mixed solvents on the decarboxylation of some *N*-alkyl- or *N*-aryl-substituted 5-amino-1,3,4-oxadiazole-2-carboxylic acids has been studied. The data support the unimolecular decarboxylation mechanism proposed by us. Moreover, they show that mixed solvents and micelles have different effects on reactivity of the amino acids under study.

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The rates of decarboxylation reactions of aminocarboxylic acids containing five-membered rings such as 1,3,4-oxa- and 1,3,4-thiadiazoles are affected [1,2] by the structure of the acid and by the experimental conditions of the reaction (solvents used and the presence of additives such as micelles or salts). The data we have collected are well interpreted on the basis of our hypothesis that the unimolecular decarboxylation reaction proceeds through a zwitterionic species. In order to provide information about the effects of the solvation on the decarboxylation rate, we now report data on the reactivity of acids **1a-d** in some mixed solvents (DMSO/water and dioxane/water) and of



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- a, R = R' = H
b, R = R' = Me
c, R = H, R' = *n*-Bu
d, R = R' = Ph

1a-d and **1c-d** in water in the presence of cationic micelles (CTAB) and nonionic micelles (Triton X-100), respectively. We have chosen the series of aminocarboxylic acids **1a-d** containing different substituents at the exocyclic nitrogen atom to test the behaviour of a series of substrates having different hydrophobic character. Considering that the substituents *n*-BuNH- and PhNH- have very similar π -values [3] one can suppose that the substituent Ph₂N- is more hydrophobic than *n*-BuNH-.

The apparent first-order kinetic constants in the presence of micelles have been measured in the acid concentration range 0.1-0.5 *M* (Tables I and II). In the case of acids **1a-c** this range corresponds [1,2a] to the range where the reactivity is at a maximum and is scarcely affected by the acid concentration. Therefore, although there is a different influence of the reaction medium on

the reactivity, a comparison of the results should be possible. For acid **1d** the situation is quite different: in this instance [1] the maximum of reactivity is at a higher acid concentration (1*M* hydrochloric acid) and therefore in the range which we have studied, the reactivity is not constant. This fact can indicate a different medium effect on dissociation equilibria and as a consequence it prevents a valid comparison with the other acids studied. On the other hand, the use of a different acidity range would also render heterogeneous the data collected.

Both cationic and nonionic micelles increase the reactivity of the substrates studied and different kinetic effects have been observed. In the studied range of micellar concentrations (0.1-8.0 × 10⁻² *M*), the typical plateau of unimolecular reactions [4] has been observed only with **1d**; of course, according to the hydrophobic character expected on the basis of π -values (see before), **1d** shows a binding constant higher than for **1a-c**.

In the presence of cationic micelles the observed increase of reactivity (measured by the ratios k_{ψ}/k_0 , see Table I) shows the sequence **1c** > **1d** > **1b** > **1a**, which does not parallel fully the variation of the hydrophobic character of the amino groups. In fact, if this were the only operating factor, an inversion between the reactivities of **1c** and **1d** would be expected. Indeed, some other factors can influence the catalytic effect, e.g., a different influence of micelles on the equilibria [5] involving the aminocarboxylic acids **1a-d** and the volume of molecules **1a-d**. Bearing in mind that the proton activity affects only slightly the micellar catalysis, one can exclude a great influence of cationic micelles on acid-base equilibria of substrates **1a-d**. On the other hand, these data do not give any information about the influence of micelles on the equilibria between the possible ampholytes.

Table I

Observed Rate Constants ($k_{obs} \times 10^4, s^{-1}$) [a] for the Decarboxylation of Acids **1a-d** in the Presence of CTAB and Different Hydrochloric Acid Concentrations at 313.0 ± 0.1 K

10^2 [CTAB]	k_{obs} at [HCl] = 0.5 M				k_{obs} at [HCl] = 0.2 M				k_{obs} at [HCl] = 0.1 M			
	1a	1b	1c	1d	1a	1b	1c	1d	1a	1b	1c	1d
	1.76	1.03	1.20	10.4	1.97	1.25	1.71	10.1	2.02	1.31	1.74	7.93
0.1				43.3				34.0				9.08
0.2				54.9				38.4				11.4
0.4				62.4				44.4				13.9
0.8	1.94	1.31		58.9	2.19	1.53		48.1	2.17	1.63		25.3
1.0	1.98	1.41	3.91	61.9	2.21	1.61	4.11	51.0	2.19	1.73	5.15	26.4
2.0	2.28	1.68	7.11	68.6	2.53	1.99	6.56	49.9	2.46	2.00	6.85	27.3
4.0	2.52	2.04	11.6	69.6	2.85	2.54	10.0	52.7	2.75	2.67	10.4	29.0
6.0	2.91	2.65	14.8		3.19	3.17	11.5		3.05	3.18	12.6	
8.0	3.13	3.15	17.7	63.8	3.83	3.37	13.6	51.8	3.19	3.46	14.7	31.0
k_{ψ}/k_0	1.8	3.1	14.8	6.1	1.7	2.7	8.0	5.1	1.6	2.6	8.5	3.9

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

Table II

Observed Rate Constants ($k_{obs} \times 10^4, s^{-1}$) [a] for the Decarboxylation of Acids **1c-d** in the Presence of Triton X-100 and Different Hydrochloric Acid Concentrations

10^2 [Triton]	k_{obs} at [HCl] = 0.5 M		k_{obs} at [HCl] = 0.2 M		k_{obs} at [HCl] = 0.1 M	
	1c [b]	1d [c]	1c [b]	1d [c]	1c [b]	1d [c]
		1.20		1.71		1.74
0.8		2.12		3.10		8.50
1.0		2.66		3.68		8.80
2.0		4.45		4.92		10.0
4.0		8.05		7.80		11.3
6.0		10.6		12.9		13.0
8.0		12.8		14.9		14.3
k_{ψ}/k_0		10.7		8.7		13.0
						8.7
						13.7

[a] The rate constants are accurate to within $\pm 3\%$. [b] At 313.0 ± 0.1 K. [c] At 293.0 ± 0.1 K.

In the presence of nonionic micelles the catalytic effect is higher with **1d** than with **1c**. This inversion of the kinetic effect which agrees with the hydrophobic character of the two substituted amino groups (see Table II) seems to depend on an increase of the catalytic effect on the decarboxylation of **1d** (at the same micellar concentration and at 0.5 M hydrochloric acid the k_{ψ}/k_0 ratios increase from 6 to 12 on going from CTAB to Triton X-100), whereas the effect on **1c** remains nearly constant. We have not studied the reactivity of acids **1a-b** with nonionic micelles because the solutions of Triton X-100 absorb strongly in the same wavelength range as the acids.

The general picture of the catalysis by the two micellar systems used is quite similar and the relevant kinetic effects measured can be compared with those observed in some other micelle-catalysed decarboxylation reactions. So one can remark that micellar catalysis on **1a** is lower than that calculated for the unimolecular decarboxylation of salts of both 2-cyanophenylacetic [6] and 6-nitrobenz-

isoxazole-3-carboxylic acids [7].

The structures of initial and transition states in the two cases (zwitterionic in our case, anionic in those previously studied) can account for the different behaviour; moreover, the nature of the anionic center and the different hydrophobic character of the various starting materials can affect the micellar catalysis.

Considering that in part micellar kinetic effects can be determined by structural and physical modifications of the solvent brought out by the surfactants and that similar modifications of the water solvent can be caused by adding another solvent, we have studied the decarboxylation reaction of acid **1c** in various water-dioxane mixtures at 0.1, 0.2, and 0.5 M hydrochloric acid and water-dimethyl sulphoxide mixtures at 0.2 M hydrochloric acid (Table III). A plot of kinetic constants vs. molar fractions of DMSO or dioxane at 0.2 M hydrochloric acid (Figure) shows clearly a break point in the solvent effect at ca. 0.18 and 0.06: in both DMSO and dioxane there is a low and a high catalytic effect at low and high organic solvent concentration, respectively.

Table III

Observed Rate Constants ($k_{obs} \times 10^4, s^{-1}$) [a] for the Decarboxylation of Acids **1c** in Mixed Solvents at 303.0 ± 0.1 K

W/Dioxane (v:v) Dioxane %	k_{obs} at [HCl] = 0.5 M	k_{obs} at [HCl] = 0.2 M	k_{obs} at [HCl] = 0.1 M
	0.400	0.600	0.600
5	0.386	0.454	0.480
10	0.475	0.606	0.643
20	1.04	1.25	1.37
30		3.38	
40		6.56	
50	8.70	10.3	11.6
60		21.2	
70		40.2	

W/DMSO (v:v) DMSO %	k_{obs} at [HCl] = 0.2 M
—	0.600
10	0.540
30	1.54
40	2.74
45	3.82
50	5.52
55	7.38
60	12.1
65	16.6
70	21.2

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

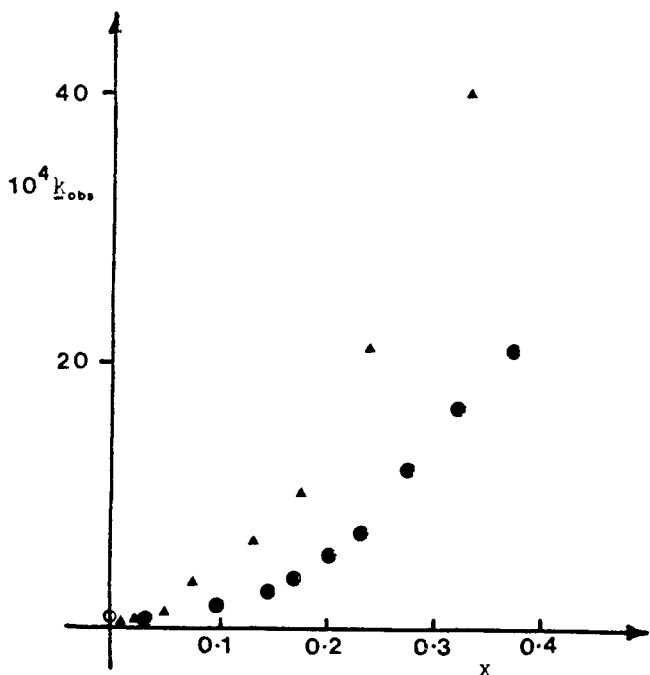


Figure. Plot of the observed decarboxylation rate constants of acid **1c** vs. the molar fraction of dioxane (▲) or DMSO (●) in the presence of 0.2 M hydrochloric acid.

For the corresponding study of acids **1a**, **b**, and **d** (Table IV), we have chosen only one high concentration of dioxane and DMSO (50% and 70%, respectively). Similar-

ly as for micellar catalysis, the increase of reactivity determined by the solvent added is lower than in decarboxylation reactions of salts of 2-cyanophenylacetic [8] and 6-nitrobenzisoxazole-3-carboxylic [9] acids.

Table IV

Observed Rate Constants ($k_{obs} \times 10^4, s^{-1}$) [a] for the Decarboxylation of Acids **1a-d** in Mixed Solvents at 303.0 ± 0.1 K

HCl	k_{obs} in W/Dioxane (50:50 v:v)			
	1a	1b	1c	1d
0.5	5.70	6.35	8.70	36.0
0.2	7.00	8.04	10.3	33.0
0.1	7.90	8.75	11.6	31.8

HCl	k_{obs} in W/DMSO (30:70 v:v)			
	1a	1b	1c	1d
0.2	23.5	18.9	21.2	42.0

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

The data in mixed solvents point out two facts: the effect of the organic solvents used (dioxane and DMSO) is higher than that of anionic and nonionic micelles; moreover, taking into account that many physico-chemical properties of water/organic solvent mixtures are not linearly correlated with the organic solvent concentration and that they usually present a break point, the non-linear relation between the reactivity and any function of organic solvent concentration as well as the break points at different sol-

vent concentrations clearly show the role of the structure of the solvent in determining the catalytic kinetic effect.

Therefore both the data on micellar catalysis and those on mixed solvents effects strongly support the unimolecular decarboxylation mechanism proposed by us. Other things being equal, both the micelles and the organic solvents added cause a desolvation effect of the reagents larger than that of the transition states and the resultant lower stability of reagents with respect to the transition states leads to lower activation energies than in pure water.

As expected, mixed solvents and micelles show different effects on the reactivity of amino acids **1a-d**. Mixed solvents show kinetic effect depending on the structure of the acids and the effectiveness of the organic solvent increases with increasing the hydrophobic character of the side chain. In conclusion, it appears that many interlocking effects of the side chain structure can operate: polar effects seem predominant in water, whereas the hydrophobic effect and the size of the amino acids can give a different balance in mixed solvents and micelles. Micelles are more or less effective catalysts as a function of the micelle-substrate interactions which depend not only on the hydrophobic character of the side chain but, for the same micelle, also on the effective size of the amino acid.

EXPERIMENTAL

Synthesis and Purification of Compounds.

Amino acids **1a**, **b** and **d** [10] and **1c** [1] were prepared according to the literature. Dioxane, dimethyl sulphoxide (reagent grade, Carlo Erba),

commercial CTAB (Merck, pro analysis), and Triton X-100 (J. Baker) were used without further purification.

Kinetic Measurements.

The kinetics of decarboxylation were followed spectrophotometrically as previously described [2a] by measuring the disappearance of amino acids **1a-d** at 250, 260, 264 and 290 nm, respectively. In the presence of nonionic micelles the kinetics were followed at 300 nm.

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