  Bull. Chem. Soc. Jpn., 56, 2469—2472 (1983)

Effect of Multiple Field Assistance with Reversed Micelles on the Decarboxylation of 6-Nitro-1,2-benzisoxazole-3-carboxylate

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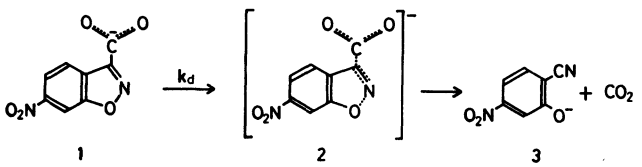
(Received January 22, 1983)

Decarboxylation reaction of 6-nitro-1,2-benzisoxazole-3-carboxylate (**1**) in cationic and anionic reversed micelles has been investigated with particular attention to the microenvironmental effect, such as microviscosity, micropolarity, and microactivity, in the specific and restricted reaction field as provided by reversed micelles. In 0.20 M CTAC/0.32 M $H_2O/CHCl_3$ reversed micelles, the reaction was accelerated about 1300-fold compared with that in bulk aqueous solution. Of various surfactant aggregate systems such as aqueous micelle, bilayer, and reversed micelle, the cationic reversed micelle could provide the most effective reaction field for the present decarboxylation reaction. This reaction is never accelerated in an anionic aqueous micelle. However, in the anionic AOT reversed micelle, the reaction was apparently accelerated by both lowering the micropolarity and increasing the microviscosity around the substrate. The unique rate enhancement for the decarboxylation reaction of **1** provided by reversed micelles was interpreted in terms of the "multiple field assistance."

The specific reaction field of the enzyme active site provides multiply and simultaneously different effects such as a proximity, an electronic or a structural strain, an orbital steering, an anchoring effect, and so forth. Hence, enzymes can specifically control chemical equilibria and reaction pathways or rates by *simultaneously* adjusting pH, polarity, viscosity, and activity in the microenvironment. This specific effect has been called "multiple field assistance."[1] We ourselves have presented many examples so far that reversed micelles can mimic the enzyme active site and provide a specific reaction field to afford the "multiple field assistance" for various organic[2-5] and inorganic reactions.[6-9] Because, the state and nature of water in the interior core of micelles are known to be less polar,[10,11] highly viscous,[5,10,12-14] and more active,[2,7,15-18] largely different from those of bulk water.

In the present study, as an extension of a series of our studies, the effect of the specific microenvironment, the multiple field assistance, of the water pool provided by several ionic reversed micelles on the unimolecular decarboxylation of 6-nitro-1,2-benzisoxazole-3-carboxylate (**1**) was investigated. Unimolecular reaction seems most convenient to inspect the microenvironmental effect, especially the effect of restricting the mobility of substrates on the reaction rate or path.[5,19] In addition, the decarboxylation of **1** is very insensitive to an acid-base catalysis, while extremely sensitive to solvent polarity.[20-23]



1 2 3

Scheme 1.

Experimental

Materials. 6-Nitro-1,2-benzisoxazole-3-carboxylic acid was prepared according to the method described previously.[24,25] The white and needle crystals, after drying *in vacuo* over P_2O_5 at 110 °C, showed mp 167—169 °C [lit,[25] 167—169 (monohydrate)]. Preparations and purifications of hexadecyltrimethylammonium bromide (CTAB),[9] hexadecyltrimethylammonium chloride (CTAC),[9] and sodium 1,2-bis(2-ethylhexyloxycarbonyl)ethanesulfonate (AOT)[3] were described elsewhere. Solvents employed were carefully purified, dried, and stored under prevention against moisture over molecular sieves Linde 4A.

Miscellaneous Measurements. When the *R*-value (=$[H_2O]$/[surfactant]) was changed, the water content in reversed micelles was carefully determined on a Karl-Fischer moisture automatic titration apparatus, Kyoto Electronics MFG, Model MK-AIII.

In order to examine the microscopic polarity and viscosity in the core of micelles, fluorescence spectra and steady-state fluorescence polarizations of trisodium 8-methoxy-1,3,6-pyrenetrisulfonate (Py–OMe)[10] cosolubilized in micelles were measured on a Hitachi 650-10S fluorospectrophotometer and a Union Giken FS-501S fluorescence polarization spectrophotometer using a sharp cut-off filter Y-46 (Hoya Glass Works, Tokyo).

An aqueous stock solution of the substrate **1** was freshly prepared just before the use. Reaction rates were followed by monitoring an increase in the absorbance at around 415 nm based on the release of 2-cyano-5-nitrophenolate (**3**) using a Hitachi Model 200-10 spectrophotometer equipped with a thermoregulated cell compartment. The first-order rate constants, k_d, for the decarboxylation were obtained by the Guggenheim treatment[26,27] and the correlation coefficients were always larger than 0.999. Chloroform was used as the bulk organic solvent for CTAB and CTAC micelles, while heptane was employed for AOT micelles. Surfactant concentrations were kept at 0.20 M through all the runs, while the substrate concentration was 7.2×10^{-5} M (M=mol dm^{-3}) unless otherwise stated. The reaction was initiated by injecting an aliquot (15 μl) from the stock solution of **1** into the cell containing a given amount of micellar solution (3.0 ml) with an appropriate amount of aqueous sodium hydroxide solution.

Results and Discussion

Rate constants of the decarboxylation of **1** at 30 °C in reversed micelles are summarized in Table 1 along with those in pure solvents and in a surfactant bilayer system. Clearly from Table 1, of the surfactant-aggregate systems the CTAC reversed micelle provided the most effective reaction field for the decarboxylation of **1** to be accelerated. For the decarboxylation of **1**, the dehydration

TABLE 1. RATE CONSTANTS (k_d) OF THE DECARBOXYLATION OF 6-NITRO-1,2-BENZISOXAZOLE-3-CARBOXYLATE (**1**) AT 30 °C AND FLUORESCENCE CHARACTERISTICS OF *o*-METHYLPYRANINE (Py–OMe) IN VARIOUS REACTION FIELDS

Environment	$k_d/10^{-6}$ s^{-1}	Emission maximum / nm	p[d]
Water	7.3[a]	430	0.01
MeOH	250[a]	410	0.03
EtOH	1 000[a]	407	0.04
CH_3CN	2 900 000[a]	404	0.03
Me_2CO	24 000 000[a]	401	0.03
0.2 M CTAC/H_2O/$CHCl_3$ (R=1.6)	9 600	411	0.10
0.2 M CTAB/H_2O/$CHCl_3$ (R=1.4)	6 700	415	—
0.2 M AOT/H_2O/heptane (R=1.7)	41	420	0.19
CTAB aq micelle	350[b]	410	—
$2C_{12}N^+2C_1$[c] bilayer	3 000[b]	—	—

a) From Ref. 22. b) From Ref. 35. c) Didodecyldimethylammonium bromide. d) Fluorescence depolarization (see text).

(desolvation) of the substrate is one of essential factors for the rate enhancement.[20-23] In fact, a linear relationship between log k_d and the wave number of the absorption maximum of Methyl Orange has been previously presented by Kunitake and his coworkers for the polysoap-catalyzed decarboxylation of **1**.[27] First of all, hence, we must consider the effect of micropolarity (desolvation) around the substrate on the large rate acceleration in cationic reversed micelles. Even in the reversed micellar system, the decarboxylation of **1** must proceed in an aqueous environment. Nevertheless, the decarboxylation rate in the cationic CTAC micelle was enhanced about 1300-fold compared with that in bulk water (Table 1). However, this rate enhancement seems to involve the effect of the lowered micropolarity in the reversed micellar core. Table 1 gives also the fluorescence maxima of Py–OMe to assess the micropolarity of the reaction field.[10] Py–OMe is definitely localized only in the water pool of reversed micelles owing to its highly ionic character and is considered to be a convenient probe to know the microenvironment around a water soluble substrate.[10] Results of Table 1 suggest that the micropolarity of the cationic aqueous and reversed micelles as the reaction field is almost comparable to that of methanol. Nevertheless, the reaction rate in the CTAC reversed micelle is still 40-times higher than that in methanol. As is already known, the decarboxylation of **1** is effectively accelerated by cationic aqueous micelles,[28-30] cationic polymers with a hydrophobic side chain (polysoap),[27,31,32] polymeric crown ethers complexable with cations, K^+ or Na^+,[33,34] and synthetic bilayer membranes with a positive surface charge.[35] These catalytic effects are ascribed to the stabilization of the anionic transition state (**2**) with an electrostatic assistance by the positive surface charge of these molecular assemblies. Certainly, the anionic SDS aqueous micelle can not promote this reaction.[28,29] Also in the interior core of the cationic reversed micelles, hence, the additional rate acceleration may be ascribed to the electrostatic assistance by lowering the transition state energy upon interaction of the activated complex with the cationic surface in the micellar core.

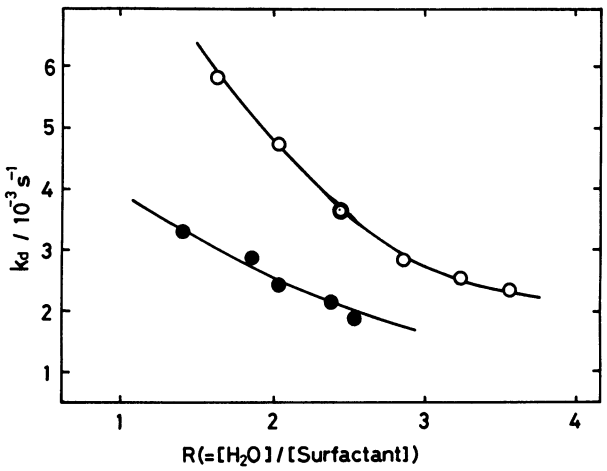


Fig. 1. The decarboxylation rates, k_d, as a function of R-value in 0.20 M CTAC/7.4×10^{-5} M aq NaOH/$CHCl_3$ (—○—) and 0.20 M CTAB/7.4×10^{-5} M aq NaOH/$CHCl_3$ (—●—) reversed micelles containing 7.2×10^{-5} M substrate **1** at 25.0 °C.

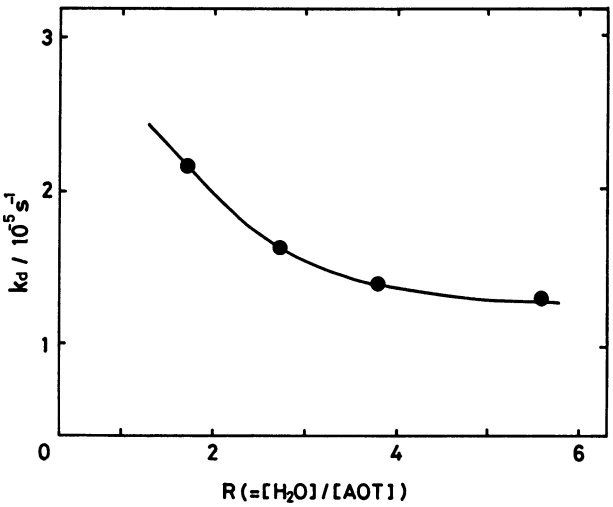


Fig. 2. The decarboxylation rate of **1** (7.2×10^{-5} M) in 0.20 M AOT/7.4×10^{-5} M aq NaOH/heptane reversed micelle as a function of R-value at 25.0 °C.

TABLE 2. THERMODYAMIC PARAMETERS OF ACTIVATION FOR THE DECARBOXYLATION OF 1 IN DIFFERENT REVERSED MICELLAR SYSTEMS AT 25.0 °C

System	R	E_a / kcal mol^{-1} b)	ΔH^* / kcal mol^{-1} b)	ΔS^* / e.u.	ΔG^* / kcal mol^{-1} b)
CTAC/$CHCl_3$ reversed micelle	1.6	23.4	22.8	7.7	20.5
	2.4	23.8	23.2	8.3	20.8
	3.2	25.1	24.6	12.0	21.0
CTAB/$CHCl_3$ reversed micelle	1.4	22.7	21.1	4.4	19.8
	2.0	24.7	24.1	10.3	21.0
	2.5	24.7	24.1	10.0	21.2
AOT/heptane reversed micelle	1.9	25.2	24.6	2.6	23.8
Water[a)]	—	32.6	32.0	25.4	24.4

a) From Ref. 22. b) 1 cal=4.184 J.

The CTAB reversed micelle showed lower catalytic efficiency than the CTAC one (Table 1 and Fig. 1). One reason is the slightly higher microscopic polarity in the interior core of the CTAB micelle compared with the case of CTAC micelle as suggested by the fluorescence maximum of Py–OMe (Table 1). As is well known, the hydration number for bromide ion is smaller than that for chloride ion. This means that more free water may exist in the interior core of the CTAB micelle than in the CTAC one when compared at an identical R-value, thus the former providing a more polar microenvironment. Another reason is the difference in the aggregation number between both surfactants. It has been found that for cationic reversed micelles the aggregation number decreases with an increase in the radius of the counter anion of the surfactant.[36] Assuming that one molecule of the substrate is encapsulated in a micelle, the larger aggregates (the higher aggregation number) will provide the more effective electrostatic assistance, leading to a larger rate enhancement.

Nevertheless an anionic aqueous micelle cannot accelerate this reaction,[28,29] the anionic reversed micelle shows a small, but discernible catalytic activity for the reaction. In the interior core of the AOT reversed micelle, the micropolarity is just middle between water and methanol, while the microviscosity is higher than that of the cationic reversed micelle (Table 1). Most probably, opening the benzisoxazole ring will relax the intramolecular strain upon the decarboxylation, of which effect will be more amplified in a highly viscous environment. Therefore, it appears that the release of the internal strain as well as the decreased micropolarity counteract the large destabilization of the anionic transition state with the negative surface charge of the micellar core.

Figures 1 and 2 show the rate deceleration with an increase in the R-value, or the water content, of the cationic and anionic reversed micelles, respectively. In reversed micellar systems the effect of water content on the reaction was drastic, though the rate is hardly affected by a minute amount of water in a simple organic solvent.[27] In general, an increase in the R-value leads to an increase in the micropolarity and a decrease in the microviscosity of the water pool.[11,14,18] We also observed similar phenomena for the present system employing the fluorescent probe, Py–OMe.[10] This means that in reversed micelles one can control the polarity, viscosity, and activity of the reaction field and consequently the reaction rate by changing the water content of micelles. In any event, both an increase in the micropolarity and a decrease in the microviscosity act as negative effect on the present decaboxylation (Figs. 1 and 2).

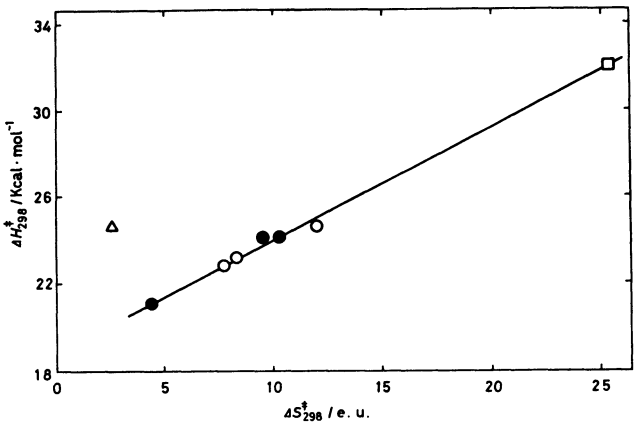


Fig. 3. Isokinetic relationship for the decarboxylation of 1 in various microenvironments, water (□), CTAC reversed micelles (○), CTAB reversed micelles (●), and AOT reversed micelle (△).

In Table 2, thermodynamic parameters of activation for the decarboxylation of 1 in reversed micelles are listed along with those in bulk aqueous solution previously reported by Kemp and Paul.[22] Its isokinetic relationship is given in Fig. 3. Except for the AOT reversed micelle, a good linear relation was obtained with the isokinetic temperature β=517 K. This means that under the reaction conditions adopted (at 298 K) the reaction is controlled enthalpically. Figure 3 supports the above argument that the low catalytic efficiency of the AOT reversed micelle in this reaction may be derived from the destabilization of the anionic transition state with the electrostatic repulsion brought about by the negative surface charge of the micellar core (ΔH^*-control). This negative effect might exceed the rate acceleration effects by the decreased polarity (ΔH^*-control) and the increased internal strain of the substrate molecule in the highly restricted reaction field (ΔS^*-

control). In any event, it is clear that in the specific and restricted reaction field as provided by reversed micelles the reaction rate is controlled simultaneously by plural factors.

Authors are grateful to Professors Toyoki Kunitake (Kyushu University) and Seiji Shinkai (Nagasaki University) for their fruitful discussion. We also thank Mr. Ichiro Miwa for his measurement of the fluorescence depolarization. This work was supported by Grants-in-Aid (No. 447068 and 56550594) for Scientific Research from the Ministry of Education, Science and Culture.

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