Intramolecular Cyclization of the Pyridoxal-Histidine Schiff Base Controlled in Reversed Micelles

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A reversed micelle is an aggregate of surfactant formed in a nonpolar organic solvent with ionic or polar heads of surfactant inside. The equilibrium, rate, and pathway of several reactions are dramatically controlled in the interior of such micelles, which mimic an enzyme active site.[1,2] We have undertaken a systematic investigation of organic and inorganic reactions in reversed micelles to understand the origin and extent of such an effect.[3-14]

The present article concerns the intramolecular cyclization of the Schiff base formed from histidine and pyridoxal (1), which does not decarboxylate readily.[15-17] The reaction occurs in two distinct stages (Scheme I),[18] , the first of which involves rapid formation of the Schiff base 2 with an equilibrium constant K, while the second stage involves a slow unimolecular cyclization with a rate constant k_c. Thus we can look at the effect of reversed micelles simultaneously on both the equilbrium (bimolecular) and rate (unimolecular) processes. For this purpose, both cationic CTACl (hexadecyltrimethylammonium chloride)/H_2O/$CHCl_3$ and the anionic AOT (sodium 1,2-bis-[[(2-ethylhexyl)oxy]carbonyl]ethanesulfonate)/H_2O/C_7H_{16} reversed micelles were employed. Decreasing the water content [a decrease in the R value (=[H_2O]/[surfactant])] leads to restricted mobility of the reacting species[13,14] as well as to a decrease in the micropolarity of the reaciton field.[14] These effects provide a means for controlling the intramolecular cyclization of the Schiff base. As expected, we were able to effectively depress the cyclization reaction in the restricted reaction field of reversed micelles in a manner analogous to that in enzymatic systems.

Results and Discussion

The rate of formation of Schiff bases from pyridoxal and amino acids is considerably enhanced in reversed micelles,[8] because of local concentration effects on the bimolecular reaction. The equilibrium constant K decreases with an increase in the R value of the micelles (Table I). This seems reasonable considering that water is a product of the reaction, and the two reactants are diluted upon the expansion of the pool size.

In the reversed micelles studied, the reaction of histidine with pyridoxal showed a two-step spectral change: an initial rapid increase in the absorption at 419 nm corre-

Scheme I

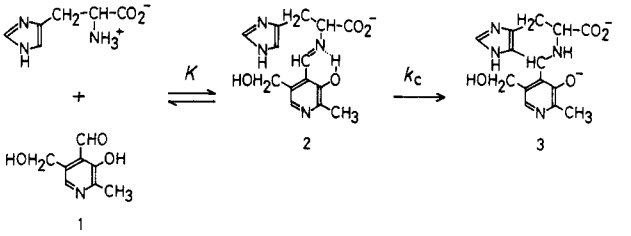

Table I. Equilibrium Constants for the Formation of Pyridoxal Schiff Base of Alanine in 0.10 M AOT/1.5 mM Aqueous NaOH/C_7H_{16} Micelles at 25.0 °C

R value	K, M^{-1}	R value	K, M^{-1}
2.9	9.8×10^3	4.9	5.9×10^3
3.9	6.9×10^3	∞ [a]	1.45×10

[a] In water.[19]

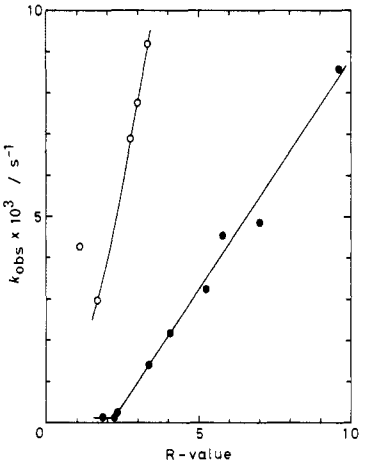

Figure 1. Pseudo-first-order rate constant for the cyclization of the pyridoxal-histidine Schiff base in reversed micelles as a function of R value at 25.0 °C: [pyridoxal] = 1.0×10^{-4} M; [histidine] = 5.0×10^{-4} M; ○, 0.10 M CTACl/1.5 mM aqueous NaOH/$CHCl_3$; ●, 0.10 M AOT/1.5 mM aqueous NaOH/C_7H_{16}.

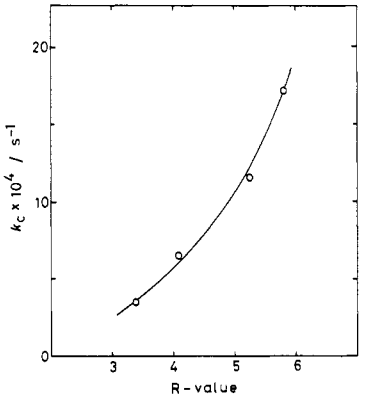

Figure 2. Specific rate constant for the cyclization of the pyridoxal-histidine Schiff base (see text) as a function of R value in 0.10 M AOT/1.5 mM aqueous NaOH/C_7H_{16} at 25.0 °C.

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sponding to Schiff base formation, followed by a much slower decay of this band concomitant with a new absorption maximum at 290 nm. This spectral change is identical with those observed in water[20] or methanol,[21] confirming that cyclization takes place. The reaction product was spectroscopically identical with an authentic sample of the tetrahydropyrido[3,4-*d*]imidazole (**3**).[22] It has been shown by Mackay and Shepherd that the cyclization product is an inhibitor of histidine decarboxylase.[17] In reversed micelles, the rate of cyclization was also appreciably affected by the water content (Figure 1). The apparent pseudo-first-order rate constant k_{obsd} consists of the formation constant for the Schiff base, K, and the specific rate constant for the cyclization, k_c (eq 1). The K value of Schiff base formation between pyridoxal and histidine cannot be determined accurately because of the subsequent rapid cyclization. However, since the K value for Schiff base formation is not appreciably affected by the structure of the amino acid in the reversed micelle,[8] the specific rate constant of the cyclization k_c could be evaluated by adopting the K value obtained for Schiff base formation between pyridoxal and alanine. As shown in Figure 2, the k_c value so obtained diminished with decrease in the R value. This means that the cyclization can be effectively retarded by a decrease in the pool size of the reversed micelle. In addition, the cyclization rate constant in the reversed micelle is much smaller than that observed in bulk water ($k_c = 2.8 \times 10^{-2}$ s^{-1}). This is attributable to the altered micropolarity and/or the restriction effect on the mobility of the substrate in the restricted reaction field provided by the micelle. As the core size expands, the micropolarity in the interior core approaches that of bulk water,[14] which should be unfavorable for Schiff base formation but not for cyclization.

$$k_{obsd} = k_c \frac{K[\text{histidine}]}{K[\text{histidine}] + 1} \quad (1)$$

Since the cyclization reaction is subject to base catalysis,[23] the effect of hydroxide ion concentration on the reaction rate was studied in the reversed micelles as well as in methanol. The variation of k_{obsd} as a function of hydroxide ion concentration was linear, and the specific second-order rate constants for the base catalysis are 154 and 0.023 M^{-1} s^{-1} in the 0.10 M AOT/0.77 M H_2O/heptane reversed micelle and in methanol, respectively. Thus the effect of hydroxide ion is accentuated above 6700 times in the micelle. The local high concentration of hydroxide ion in the micellar core is no doubt responsible in part for the large rate increase. However, even if this local concentration effect (72-fold) is taken into account, the hydroxide ion is still 93 times more effective as a catalyst in the micelle. The hydroxide ion in the anionic reversed micellar core is in part free from both the interaction with the head group of the anionic surfactant and from hydration due to a lack of sufficient water molecules, both effects leading to an increase in the activity of hydroxide ion.

Matsushima has reported that copper(II) or zinc(II) effectively inhibits the cyclization of the histidine–pyridoxal Schiff base.[24] Unlike these transition-metal ions,[24] magnesium(II) ion was a poor inhibitor of the cyclization in bulk water because of extensive hydration and/or its lesser ability to coordinate with a common ligand. In reversed micelles, however, even magnesium(II) ion was effective in suppressing the cyclization by chelation with the Schiff base. The addition of 1.0×10^{-4} M magnesium(II) ion (equimolar to pyridoxal) to the 0.10 M CTACl/0.17 M H_2O/1.5 mM NaOH/chloroform reversed micelle shifts the absorption maximum of the Schiff base from 419 to 380 nm because of complexation.[12] Under these conditions, the cyclization was inhibited by a factor of 2.4. The inhibitory effect is presumably due to the "naked" character of the metal ion in the reversed micelles.[3,5]

In summary, the bimolecular pyridoxal–histidine Schiff base formation was remarkably enhanced, while the subsquent unimolecular cyclization was effectively retarded, in reversed micelles with a decrease in the R value. This reaction control is attributed to "multiple field assistance",[11] where the microscopic polarity, the local concentration (proximity), and/or the mobility of substrates (microviscosity) are simultaneously altered. In addition, the respective effects of hydroxide or magnesium(II) ion in promoting or inhibiting cyclization of the Schiff base originates from the less hydrated character of these ions in the specific reaction field provided by reversed micelles.

Experimental Section

Materials. Pyridoxal hydrochloride was obtained from Wako Pure Chemicals Co., Ltd., Tokyo. 4-[3-Hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl]-4,5,6,7-tetrahydropyrido[3,4-*d*]imidazole-6-carboxylic acid (**3**) was prepared according to the literature.[22] Purifications of AOT [sodium 1,2-bis[[(2-ethylhexyl)oxy]carbonyl]-1-ethanesulfonate][3] and CTACl (hexadecyltrimethylammonium chloride)[10] have been described.

Methods. Formation of the Schiff base from pyridoxal and amino acids was monitored spectrophotometrically on a Hitachi 124 or 200–10 spectrophotometer at 25.0 °C.[8] Rates of cyclization of the histidine Schiff base were determined by following the disappearance of the Schiff base absorption at 419 nm, and the apparent first-order constants were calculated by the Guggenheim method.[22]

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A Mild Two-Step Method for the Hydrolysis/Methanolysis of Secondary Amides and Lactams

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During the course of another investigation we required a mild method for the hydrolysis of lactams into their corresponding acyclic ω-amino acid derivatives. As will be detailed below, the method also proved to be equally effective for the hydrolysis of secondary amides. While many classical methods exist for the hydrolysis of primary and tertiary amides,[1,2] the efficient hydrolysis of secondary

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