Iodination Reactions of Ketones in the Reversed Micellar Systems of Dodecylammonium Propionate in Hexane

Manabu Senō, Koji Araki, and Shinsaku Shiraishi

Institute of Industrial Science, The University of Tokyo, Roppongi 7-22, Minato-ku, Tokyo 106

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The iodination reactions of ketones in the reversed micellar systems of dodecylammonium propionate (DAP) in hexane were studied at 25.0 °C in relation to the enzymatic function of aldolase or enolase. The reaction rate in the DAP reversed micellar system is 10^6—10^7 times greater than that in the system without DAP, 100 times greater even in comparison with that in DAP aqueous system at pH 6.8. As in the ammonium ion catalyzed reaction in aqueous media, the reaction in the presence of DAP proceeds *via* ketimine formation between ammonium groups of DAP and acetone and subsequent enolization of ketimine to enamine, which reacts very rapidly with iodine. The catalytic effect of DAP reversed micellar system in each reaction step was discussed. Further, this reversed micellar system shows a marked selectivity for acetone as compared with higher analogs.

Recently, Fendler *et al.* reported that the reversed micellar systems in nonpolar solvents catalyze several reactions and provide a favorable model for active sites of enzymes, and that the catalytic effect of these systems is related to the reaction field furnished with water pool in cores of reversed micelles, the polarity of which is lower than that of bulk water.[1,2] We also observed that the reversed micellar system of dodecylammonium propionate (DAP) in hexane shows an enzyme-like behavior in the hydrolysis of adenosine 5′-triphosphate (ATP).[3] We have studied the fundamental properties of this reversed micellar system, and shown that the catalytic effect is closely related to the properties of the water solubilized in the cores of reversed micelles.[4]

The functional groups of enzymes usually show their catalytic activities and specificities through some chemical interaction with substrates. It is of interest to demonstrate the reaction in which the functional groups of surfactant participate through the bond formation with substrate in the reversed micellar system, in order to clarify the enzymatic function.

In this paper, results of the studies on the iodination reaction of ketones in DAP reversed micellar system are given. The reaction is catalyzed by the conjugate acids of primary and secondary amines in aqueous media, proceeding *via* the formation of ketimine intermediate.[5] It has been proposed that at the active sites of aldolase and enolase their amine or ammonium groups participate in the reaction through the ketimine formation with carbonyl groups of a substrate. The ammonium group of DAP is expected to play a similar role in the iodination of ketones.

Experimental

Materials. Preparation and purification of DAP were described previously;[3] mp 55—56 °C (lit, 54—56 °C)[6]; Found (Calcd), C, 70.04 (69.44), H, 12.80 (12.82), N, 5.57 (5.40)%. Acetone was purified by the usual method. The other ketones were of reagent grade.

Iodination Rates of Ketones. A given amount of aqueous solution of iodine, containing a large excess of potassium iodide to suppress the formation of *N*-iodo derivatives,[5] was solubilized in hexane by DAP, the temperature of this reversed micellar solution being maintained at 25.0 °C. After the attainment of thermal equilibrium, the reaction was started by addition of ketone or a ketone/hexane solution in the UV cell of 10 or 2 mm in path length, and the decrease in absorption of triiodide ion at 363 nm was recorded with a Union stopped-flow spectrophotometer model RA-1100 with an RA-108s digital-memory unit. For slow reactions, a Hitachi 124 spectrophotometer was employed.

In DAP aqueous systems, the absorption band due to triiodide ion appears at 353 nm. The reaction in hexane in the absence of DAP, where the solution contains no potassium iodide, was traced by measuring the decrease in absorbance of iodine at 520 nm.

Ketimine Formation Reactions. The UV spectra of mixed solutions of DAP and acetone in hexane were recorded with a Union SM-401 spectrophotometer with an SM-4012 data-analyzer at 25.0 °C, at least half an hour after preparation of the sample solution in order to ensure the attainment of equilibrium. The absorption band of the ketimine intermediate was constructed from the spectra. The rates of ketimine formation were traced by recording the increase in absorption band of ketimine at 250 nm by the stopped-flow method.

Results

Mechanism of Iodination Reaction of Acetone in DAP Reversed Micellar Systems. The iodination reactions of acetone in DAP reversed micellar system were carried out under conditions where acetone concentration was

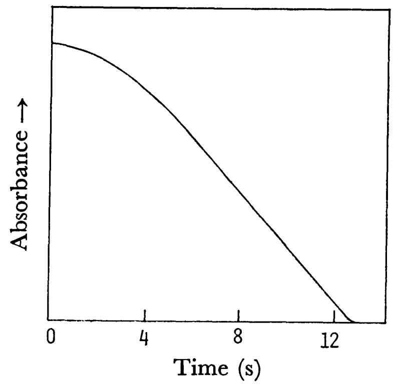


Fig. 1. The decrease in absorbance of triiodide ion at 363 nm. The typical instance of the initial stage and the subsequent steady state of the iodination reaction of acetone in the DAP reversed micellar system at 25.0 °C, where DAP, acetone, iodine and water concentrations are 1×10^{-1}, 5×10^{-4}, 1×10^{-4}, and 1.11×10^{-1} M, respectively.

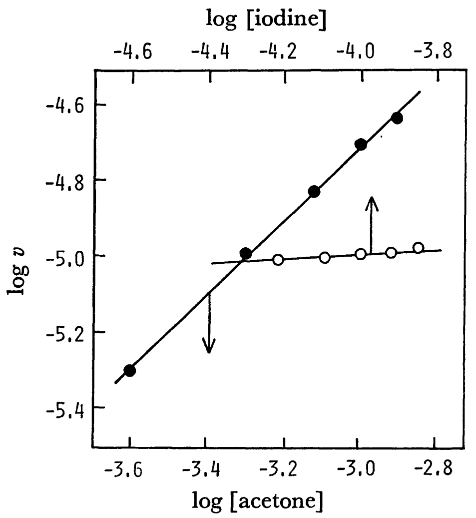


Fig. 2. Dependences of iodination rate of acetone (v) on concentrations of acetone (iodine concentration is 1×10^{-4} M) and iodine (acetone concentration is 5×10^{-4} M) in the DAP reversed micellar system at 25.0 °C, where DAP and water concentrations are 1×10^{-1} and 8.33×10^{-2} M, respectively.

much smaller than DAP concentration so that the reaction caused no large effect on micellar properties. A short induction period was observed, after which the reaction attained a steady reaction rate (Fig. 1). The dependence of the rates of the steady reaction, v, on the concentrations of various components was examined. The rate was proportional to acetone concentration and almost independent of iodine concentration (Fig. 2). A similar behavior was observed in the aqueous system.7) The results indicate that the iodination step is very fast and the preceding steps, especially the enolization step of substrate, are slow and rate-determining. On the other hand, the dependence of v on DAP and water concentrations is complicated (Figs. 3 and 4). These results suggest that the effect of the reaction field in the reversed micellar system is not as simple as that in the aqueous ammonium ion catalyzed reaction, where the rate is proportional to the ammonium ion concentration together with the acetone concentration.5)

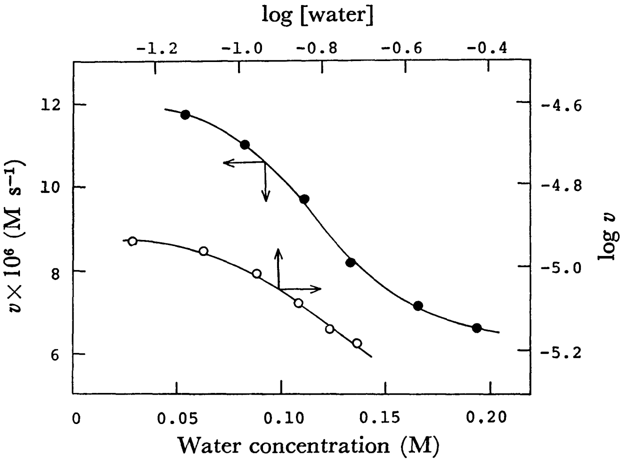


Fig. 3. Dependence of iodination rate of acetone (v) on water concentration in the DAP reversed micellar system at 25.0 °C, where DAP, acetone and iodine concentrations are 1×10^{-1}, 5×10^{-4}, and 1×10^{-4} M, respectively.

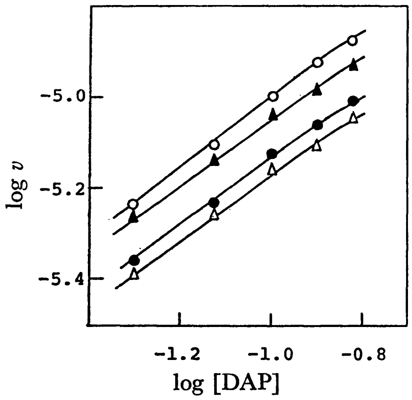


Fig. 4. Dependence of iodination rate of acetone (v) on DAP concentration at various [DAP]/[water] ratios; (○): 1.20, (▲): 0.901, (●): 0.719, and (△): 0.599, where acetone and iodine concentrations are 5×10^{-4} and 1×10^{-4} M, respectively.

The above results suggest also the existence of a reaction intermediate. For the sake of confirmation, the UV spectra of the DAP reversed micellar solution were measured in the presence of acetone. The result is shown in Fig. 5. Addition of acetone causes a broad

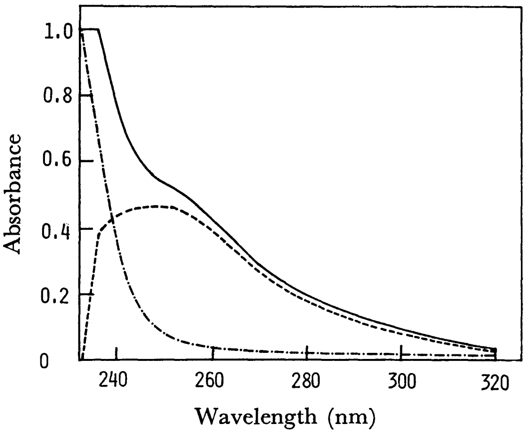


Fig. 5. UV spectra of the DAP reversed micellar solutions at 25.0 °C; (-·-·-): DAP (1.5×10^{-1} M) in the absence of acetone, (——): DAP (1.5×10^{-1} M) in the presence of acetone (7.5×10^{-3} M) and (------): the difference spectra of above two spectra.

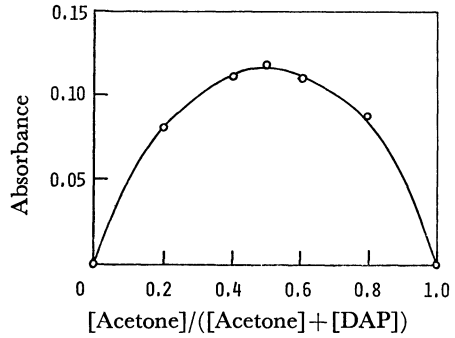


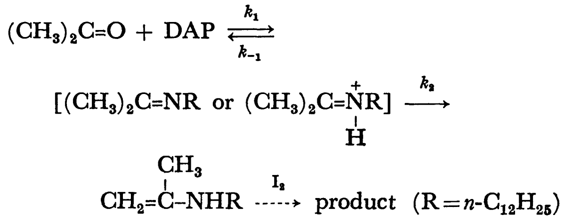
Fig. 6. Continuous variation method applied to the absorption band of the intermediate at 250 nm at 25.0 °C. Total concentration of acetone and DAP is kept constant at 2×10^{-2} M.

absorption band at 240—260 nm ($\lambda_{max}=250$ nm) as a shoulder of the DAP absorption band. The continuous variation method applied to this absorption band revealed that it should be ascribed to a 1 : 1 adduct of DAP and acetone (Fig. 6). The equilibrium constants of the formation of this intermediate, K_i, and its molar extinction coefficient, ε, were obtained by means of the equation

$$\frac{[A]_0}{d} = \frac{1}{\varepsilon K_i}\cdot\frac{1}{[D]_0} + \frac{1}{\varepsilon} \qquad ([D]_0 \gg [A]_0) \qquad (1)$$

where d is the absorbance of the intermediate at 250 nm, and $[D]_0$ and $[A]_0$ are the initial concentrations of DAP and acetone, respectively. The analysis reveals that the reaction intermediate has an absorption maximum at 250 nm ($\varepsilon=127$), and this spectrum is not so different from that of *N*-isopropylidenebutylamine in cyclohexane ($\lambda_{max}=246$ nm, $\varepsilon=140$).[8]

These results, together with a comparison of the results on the aqueous ammonium ion catalyzed reaction, lead us to conclude that the iodination of acetone in DAP reversed micellar system in hexane proceeds *via* the formation of ketimine and subsequent enolization of ketimine, as proposed for the ammonium ion catalyzed reaction in aqueous media. The reaction mechanism can be written as follows.



$$(CH_3)_2C{=}O + DAP \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}}$$
$$[(CH_3)_2C{=}NR \text{ or } (CH_3)_2C{=}\underset{\underset{H}{|}}{\overset{+}{N}}R] \xrightarrow{k_2}$$
$$CH_2{=}\overset{\overset{CH_3}{|}}{C}{-}NHR \xrightarrow{I_2} \text{product} \quad (R{=}n\text{-}C_{12}H_{25}) \qquad (2)$$

where k_1, k_{-1}, and k_2 are the rate constants of formation, decomposition and enolization, respectively, of ketimine. The step of formation of carbinolamine caused by addition of ammonium ion to acetone and the step of dehydration of carbinolamine to form ketimine could not be discriminated from each other. A combined step is given in terms of k_1 and k_{-1} in scheme (2). There is a possibility of direct enolization of acetone catalyzed by DAP. However, this pathway could be neglected, since the reaction rate during the induction period is much smaller than the steady rate. According to the above mechanism, the initial rate, v, and the apparent second-order rate constant, k_{app}, at the steady state are given under the conditions $[D]_0 \gg [A]_0$ as follows:

$$v = k_{app}[D]_0[A]_0 = \frac{k_2[D]_0[A]_0}{K_m+[D]_0} \qquad (3)$$

where $K_m=(k_{-1}+k_2)/k_1$.

Kinetic Analyses of Iodination Reaction of Acetone. The first-order rate constants, $k°$, and the second-order rate constants, k_{app}, in various reaction systems are given in Table 1. The values of K_m and k_2 could be estimated

Table 1. Iodination rate constants of acetone in various systems at 25.0 °C

Solvent	DAP(M)	Water(M)	$k°(s^{-1})$[e]	$k_{app}(M^{-1}\ s^{-1})$
Hexane[a]	1×10^{-1}	8.33×10^{-2}	2.02×10^{-2}	2.02×10^{-1}
Hexane[a]	1×10^{-1}	1.11×10^{-1}	1.75×10^{-2}	1.75×10^{-1}
Hexane[a]	1×10^{-1}	1.39×10^{-1}	1.50×10^{-2}	1.50×10^{-1}
Hexane[a]	1×10^{-1}	1.67×10^{-1}	1.38×10^{-2}	1.38×10^{-1}
Hexane[b]	0	0	5.2×10^{-9}	—
Water[c] (pH 6.8)	4×10^{-2}	—	7.6×10^{-5}	1.9×10^{-3}
Water[d] (pH 6.8)	0	—	2.1×10^{-9}	—

a) Acetone: 5×10^{-4} M, iodine: 1×10^{-4} M; b) acetone: 1×10^{-1} M, iodine: 2×10^{-3} M; c) acetone: 1×10^{-3} M, iodine: 2.5×10^{-5} M; d) acetone: 5×10^{-1} M, iodine: 2.5×10^{-5} M; e) $k°$ is defined by the following equation, $v=k°[A]_0$.

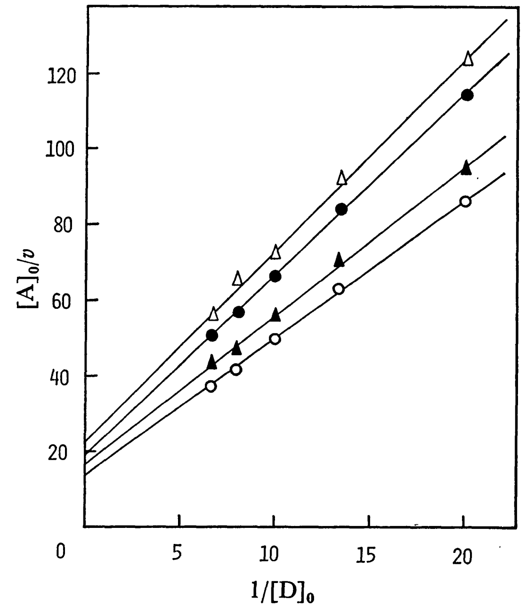


Fig. 7. Iodination reaction of acetone in the DAP reversed micellar system at 25.0 °C. Plot according to Eq. 4 at various [DAP]/[water] ratios; (○): 1.20, (▲): 0.901, (●): 0.719, and (△): 0.599; where acetone and iodine concentrations are 5×10^{-4} and 1×10^{-4} M, respectively.

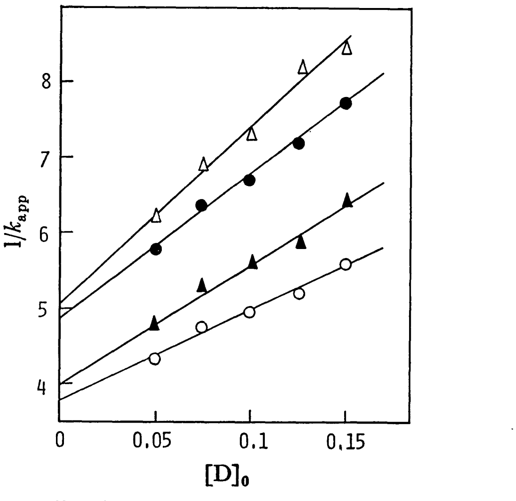


Fig. 8. Iodination reaction of acetone in the DAP reversed micellar system at 25.0 °C. Plot according to Eq. 5 at various [DAP]/[water] ratios; (○): 1.20, (▲): 0.901, (●): 0.719, and (△): 0.599; where acetone and iodine concentrations are 5×10^{-4} and 1×10^{-4} M, respectively.

Table 2. Iodination reaction of acetone in DAP reversed micellar systems at 25.0 °C

Substrate	$\frac{[\mathrm{DAP}]}{[\mathrm{Water}]}$	K_i (M^{-1})	k_1 (M^{-1} s^{-1})	k_{-1} (s^{-1})	k_2 (s^{-1})	K_m (K_m^{calcd}) (M)
Acetone	1.20	6.8	4.0×10^{-1}	5.8×10^{-2}	8.3×10^{-2}	0.31 (0.35)
Acetone	0.599	6.9	3.2×10^{-1}	4.7×10^{-2}	4.2×10^{-2}	0.21 (0.28)
Acetone-d_6	0.599	6.9	3.2×10^{-1}	4.6×10^{-2}	1.6×10^{-2}	0.16 (0.19)

Substrate: 5×10^{-4} M, iodine: 1×10^{-4}, DAP: 5×10^{-2} -1.5×10^{-1} M.

Table 3. Iodination rates of other ketones (R–CO–R′) in DAP reversed micellar and DAP aqueous systems at 25.0 °C

R	R′	Reversed Micellar[a)]		Aqueous[b)]			Values in Ref[d)]	
		k_{aqq}^{r} [c)]	k_{rel}^{r}	k_{app}^{w}	k_{rel}^{w}	$\left(\frac{k_{app}^{r}}{k_{app}^{w}}\right)$	k_{rel}^{OH}	k_{rel}^{H}
Methyl	Methyl	1.4×10^{-1}	1	1.9×10^{-3}	1	74	1	1
Methyl	Ethyl	3.8×10^{-2}	0.27	1.3×10^{-3}	0.67	29	0.54	—
Ethyl	Ethyl	1.6×10^{-3}	0.011	5.3×10^{-4}	0.27	3.0	0.20	0.96
Isopropyl	Isopropyl	9.2×10^{-5}	0.00066	2.0×10^{-5}	0.010	4.6	0.014	0.064
Isobutyl	Isobutyl	2.6×10^{-4}	0.0019	3.0×10^{-4}	0.15	0.87	—	—
Methyl	Phenyl	2.5×10^{-4}	0.0018	2.5×10^{-4}	0.13	1.0	—	—
Ethyl	Phenyl	6.1×10^{-5}	0.00044	2.4×10^{-4}	0.12	0.25	—	—

a) DAP: 1×10^{-1} M, ketone: 5×10^{-4} M, iodine: 1×10^{-4} M, water: 1.67×10^{-1} M. b) DAP: 4×10^{-2} M, ketone: 1×10^{-3} M, iodine: 2.5×10^{-5} M. c) M^{-1} s^{-1}. d) See Refs. 8 and 9.

kinetically from the iodination rate, v. For this purpose, Eq. 3 is transformed into the following equations.

$$\frac{[\mathrm{A}]_0}{v} = \frac{K_m}{k_2}\cdot\frac{1}{[\mathrm{D}]_0} + \frac{1}{k_2} \qquad (4)$$

$$\frac{1}{k_{app}} = \frac{1}{k_2}\cdot[\mathrm{D}]_0 + \frac{K_m}{k_2} \qquad (5)$$

The plots of $[\mathrm{A}]_0/v$ against $1/[\mathrm{D}]_0$ and of $1/k_{app}$ against $[\mathrm{D}]_0$ give straight lines (Figs. 7 and 8), and the k_2 and K_m values can be determined from their slopes. The [DAP]/[water] ratio was kept constant so as not to affect the state of DAP reversed micelles in these experiments.[3,4]

The values of k_1 and k_{-1} can be determined by the measurements on the ketimine formation reaction between DAP and acetone; the k_1 value was obtained directly from the measurement on the increase in absorption of ketimine at 250 nm, and the k_{-1} value was estimated from k_1 and K_i values. The results are summarized in Table 2. The K_m values can be calculated from k_1, k_{-1}, and k_2 values, and the calculated values are given in Table 2 as K_m^{calcd} in parentheses. The values are close to those obtained experimentally, indicating the validity of the reaction mechanism.

Iodination Reactions of Other Ketones. The iodination rate constants of higher analogs of acetone in the DAP reversed micellar system, k_{app}^{r}, and those in the DAP aqueous system, k_{app}^{w}, are given in Table 3, where k_{rel}^{r} and k_{rel}^{w} represent the relative rates of higher ketones to acetone. For the sake of comparison the reported values of relative rates of higher ketones to acetone in the iodination reaction catalyzed by hydroxide anion, k_{rel}^{OH}, and by hydronium cation, k_{rel}^{H}, in aqueous system are also given.[9,10]

Discussion

Catalytic Effect of DAP Reversed Micellar Systems in Iodination Reaction of Acetone. The results given in Table 1 indicate that the rate constant of iodination of acetone in the DAP reversed micellar system is 10^6—10^7 times greater than that in the system without DAP, and about 100 times greater even in comparison with that in the DAP aqueous system. The second-order rate constants of the iodination reactions in aqueous solutions catalyzed by various catalysts are given in Table 4.[5,11]

Table 4. Iodination rate constants of acetone catalyzed by various acid-base catalysts at 25.0 °C[5,11]

Catalyst	k (M^{-1} s^{-1})
OH^-	1.7×10^{-1}
CH_3COO^-	2.4×10^{-7}
CH_3NH_2	1.9×10^{-2}
H_2O	8.3×10^{-12}
H_3O^+	2.5×10^{-5}
CH_3COOH	1.0×10^{-7}
$CH_3NH_3^+$	3.0×10^{-4}

These reactions proceed *via* prototropic mechanism catalyzed by general acid-base catalysts, the rate constants obeying the Brønsted relationship.[11] However, the ammonium ion catalyzed reaction is much faster than that expected from this relationship. As a reason for this acceleration, the reaction mechanism *via* ketimine formation has been proposed.[5]

Since the pK_a values of methylamine ($pK_a=10.26$) and dodecylamine ($pK_a=10.63$), or those of acetic acid ($pK_a=4.76$) and propionic acid ($pK_a=4.87$) are nearly equal to each other at 25.0 °C, no large difference should exist between them as general acid-base catalysts. Then, it could be anticipated that the contribution of DAP as a general acid-base catalyst would be very small in the DAP aqueous system of pH=6.8. In fact, the catalytic effect of DAP in aqueous media is very high, and the reaction is considered to proceed mainly *via* ketimine formation. This catalytic mechanism could be applied to the DAP reversed micellar system, although a rate acceleration is enhanced by the micellar effect.

The catalytic effect of reversed micellar system can be discussed in detail by considering the role of micelles in each step of Scheme (2). The K_i value in DAP reversed micellar system is 6.8—6.9 (Table 2). In aqueous system the absorption band of ketimine was not clearly observed. However, the K_i value could be roughly estimated from the decrease in absorption band of acetone at 280 nm, where the absorption due to ketimine and DAP is negligibly small. The K_i value obtained for DAP and acetone in aqueous system is 0.2 ± 0.1 at 25.0 °C, close to the values 0.21—0.23 for methylamine and acetone, and 0.08 for butylamine and acetone.[12,13] The K_i value in aqueous system is much smaller than that in the reversed micellar system. It is therefore concluded that the stabilization of ketimine as a reaction intermediate would be one of the important factors for determining the catalytic effect of the reversed micellar system.

The results on hexadeuterated acetone are included Table 2. An isotope effect is observed only at the enolization step (k_2), ensuring also the reaction mechanism illustrated in Scheme (2).

Dependence of Iodination Rate on Water Concentration. The enolization rate, k_2, of ketimine is affected by water concentration. A major part of water in the DAP reversed micellar system in hexane is solubilized in the cores of reversed micelles,[4] iodine existing in the cores of reversed micelles. The k_2 value is nearly proportional to the [DAP]/[water] ratio (Fig. 9). A similar effect was observed for the ATP hydrolysis and was explained by a change in the microenvironment of substrate solubilized in the cores of reversed micelles.[3] This suggests that the enolization of ketimine occurs in the cores of reversed micelles to afford enamine, to which iodine adds rapidly.

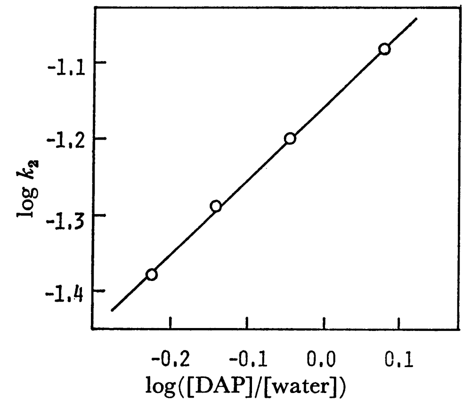


Fig. 9. Dependence of enolization rate constant of ketimine (k_2) on [DAP]/[water] ratio in the DAP reversed micellar system at 25.0 °C, where acetone and iodine concentrations are 5×10^{-4} and 1×10^{-4} M, respectively.

We see from the rate Eq. 3 that, when the k_2 value increases, the K_m value increases and approaches the value of k_2/k_1, the k_{app} value becoming governed mainly by the k_1 value. On the other hand, it is clear from Table 2 that the water concentration largely affects the value of k_2, but not k_1. Therefore, it can be expected that the dependence of the reaction rate on water concentration becomes smaller with the lowering in water concentration or increase in the k_2 value. This expectation agrees with the results shown in Fig. 3.

Iodination Reactions of Other Ketones. It is supposed that the rate-determining step of the base-catalyzed reaction is the proton transfer from ketone, while that of the acid-catalyzed reaction is the proton transfer from protonated ketone.[14] Therefore, it could be expected that the acid-catalyzed reaction would be less affected by the electronic effect of substituents than the base-catalyzed reaction. The reaults in Table 3 show that k_{rel}^{w} values are similar to k_{rel}^{OH} values suggesting that the enolization of ketimine in the DAP aqueous system proceeds *via* proton transfer from the form $(CH_3)_2C{=}NR$.

On the other hand, in the DAP reversed micellar system the k_{rel}^{r} values of higher alkyl ketones are much smaller than the k_{rel}^{w} values. The ratio k_{app}^{r}/k_{app}^{w} is the largest for acetone, and decreases remarkably as the substituents become larger. The selectivity of the iodination reaction catalyzed by the reversed micellar system would be caused by the steric factor rather than the electronic factor of the substituents. Existence of the microscopic heterogeneous phase, *i.e.* a bulk hexane phase and a reversed micellar phase with core water, would play an important role in governing the selectivity through the distribution of substrate or intermediate between these two phases. The results are of interest in relation to the specificity of enzyme.

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