Kinetics of Base Hydrolysis of α-Amino Acid Esters Catalyzed by the Copper(II) Complex of N,N,N′,N′-Tetramethylethylene-diamine (Me_4en)

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ABSTRACT: The kinetics of base hydrolysis of glycine-, histidine-, and methionine methyl esters in the presence of $[Cu\text{-}Me_4en]^{2+}$ complex is studied in aqueous solutions and in dioxane–water solutions of different compositions at $T = 25°C$ and $I = 0.1$ mol dm^{-1}. The kinetics of base hydrolysis of glycine and methionine methyl esters is studied at different temperatures. The kinetic data fits assuming that the hydrolysis proceeds in one step. The activation parameters for the base hydrolysis of the complexes are evaluated. © 2006 Wiley Periodicals, Inc. Int J Chem Kinet 38: 737–745, 2006

INTRODUCTION

In recent years there has been considerable interest in the metal-ion-promoted hydrolysis of amino acid esters [1–3]. Angelici and coworkers have studied the hydrolysis of amino acid esters in mixed-ligand complexes of copper(II) with ligands such as H_3nta (nitrilotriacetic acid) [4] and H_2ida (iminodiacetic acid) [5]. Rahman and coworker [6] investigated the hydrolysis of amino acid esters in the presence of $Cu(en)^{2+}$ (en = ethylenediamine). Such systems can be regarded as biomemetic models for certain metalloenzymes, as the metalloenzyme–substrate complex can be considered as a special type of mixed-ligand complex. It is therefore of considerable interest to extend these investigations to the mixed complex of copper(II) with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (Me_4en). The introduction of steric hindrance on the ethylenediamine (en) ligand can be used to tune the lability of this metal center and so controls its reactivity in possible catalytic and biological application.

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EXPERIMENTAL

All reagents were of Analar grade. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine was obtained from Sigma Chemical Co. The glycine-, histidine-, and methionine methyl esters were purchased from Fluka. $Cu(NO_3)_2 \cdot 3H_2O$ was provided by BDH. The copper content of solutions was determined by complexometric EDTA titrations [7]. Carbonate-free NaOH was prepared and standardized against potassium hydrogen phthalate solution. All solutions were prepared in deionized H_2O.

The kinetics of hydrolysis was monitored using a Metrohm 751 Titrino operated with the SET mode. The titroprocessor and electrode were calibrated with standard buffer solutions according to NIST specifications [8]. Hydrolysis kinetics of glycine-, methionine-, and histidine methyl esters in the presence of $[Cu(Me_4en)(H_2O)_2]^{2+}$ was investigated by using pH-state techniques. The kinetics of hydrolysis of the complexed esters was investigated using an aqueous solution (40 cm^3) containing a mixture of copper(II) (6.25×10^{-3} M), (Me_4en) (6.87×10^{-3} M), methyl ester (1.25×10^{-3} M), and $NaNO_3$(0.1 M). In this mixture, the $[Cu(Me_4en)^{2+}]$:[ester] ratio was adjusted to 5:1, so as to maximize the amount of complexed ester present. A 10% excess of Me_4en over copper(II) was used to ensure coordination of all copper(II), which is itself an excellent catalyst. In all cases, the solutions were equilibrated at the desired temperature under a constant nitrogen flow. The ester solution was then added, and the pH of the mixture was progressively raised to the desired value by the addition of 0.05 M NaOH as described previously [9–11]. The hydrolysis was then followed by the automatic addition of 0.05 M NaOH to maintain the desired pH. The data fitting was performed with OLIS KINFIT set of programs [12] as described previously [13]. Values of the hydroxide ion concentration were estimated from the pH using $pK_w = 13.997$, and an activity coefficient of 0.772 was determined from the Davis equation [14]. At the variable temperature studies, the following values of pK_w and γ were employed [15]: at 15°C ($pK_w = 14.35$, $\gamma = 0.776$), at 20°C ($pK_w = 14.16$, $\gamma = 0.774$), at 25°C ($pK_w = 14.00$, $\gamma = 0.772$), at 30°C ($pK_w = 13.83$, $\gamma = 0.770$), and at 35°C ($pK_w = 13.68$, $\gamma = 0.768$).

RESULTS AND DISCUSSION

The hydrolysis of the coordinated esters was monitored over the pH ranges 5.5–7.0 for glycine- and methionine methyl esters and 8.0–9.0 for histidine methyl ester. Throughout these pH ranges, the rate of hydrolysis of the free ester is negligible in the presence of the $Cu(Me_4en)^{2+}$. The kinetic data, the volume of base added to keep the pH constant versus time, could be fitted by one exponential as shown in Fig. 1. Various other kinetic models were tested without leading to satisfying fits of the data. Plots of k_{obs} versus the hydroxide ion concentration is linear (Figs. 2–4). The rate expression can therefore be given in the form (Eq. (1))

$$k_{obs} = k_0 + k_{OH}[OH^-] \quad (1)$$

The term k_0 arises because of the water attack on the mixed-ligand complex and is expressed by the relation (2) [15]

$$k_{H_2O} = \frac{k_0}{55.5} \quad (2)$$

where 55.5 mol dm^{-3} is the molar concentration of water. The value of k_0 can be determined from the intercept of Fig. 2, while the value of k_{OH} can be determined from the slope of the respective plot. The rate constant values k_{obs} and k_{OH} are given in Tables I–III.

Table I Kinetics of Hydrolysis of Coordinated Glycine Methyl Ester at Different Temperatures in Aqueous Solution

Temperature (°C)	pH	$10^4 \times [OH^-]^a$ (mol dm^{-3})	k_{obs} (s^{-1})	$10^4 \times k_{OH}$ (dm^3 mol^{-1} s^{-1})
15	6.00	0.45	0.14	0.97
	6.25	0.79	0.61	
	6.50	1.41	1.36	
	6.75	2.51	2.38	
	7.00	4.47	4.11	
20	6.00	0.68	0.21	1.21
	6.25	1.20	0.80	
	6.50	2.14	1.93	
	6.75	3.80	4.12	
	7.00	6.76	7.49	
25	6.00	1.00	0.40	1.49
	6.25	1.78	1.10	
	6.50	3.16	3.40	
	6.75	5.62	6.95	
	7.00	10.00	13.64	
30	5.75	0.83	0.81	1.73
	6.00	1.48	2.11	
	6.25	2.63	3.70	
	6.50	4.68	6.88	
	6.75	8.32	14.76	
	7.00	14.79	24.60	
35	5.50	0.66	1.09	2.07
	5.75	1.17	2.52	
	6.00	2.09	4.87	
	6.25	3.72	7.25	
	6.50	6.61	13.32	
	6.75	11.75	24.50	

[a] pK_w 14.35 at 15°C; 14.17 at 20°C; 14.00 at 25°C, 13.83 at 30°C, and 13.68 at 35°C. These data were taken from ref. [22].

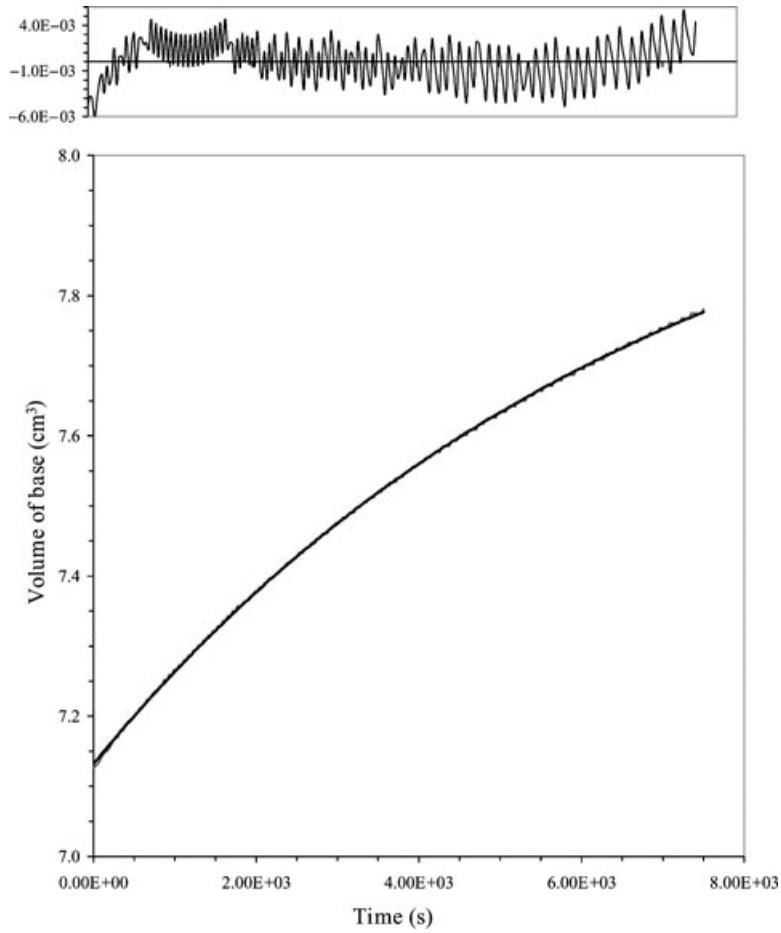


Figure 1 Typical value of the base–time trace for the hydrolysis of coordinated glycine methyl ester fitted with one exponential function. The top of the figure shows the value of base difference between measured and calculated kinetics trace.

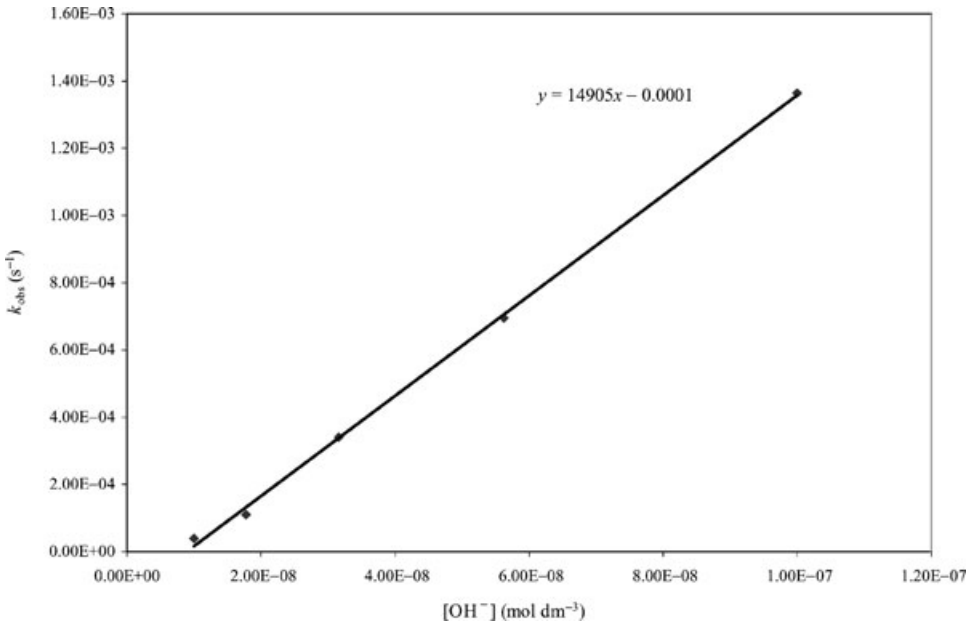


Figure 2 Plots of k_{obs} vs [OH^-] for the hydrolysis of coordinated glycine methyl ester at 25°C.

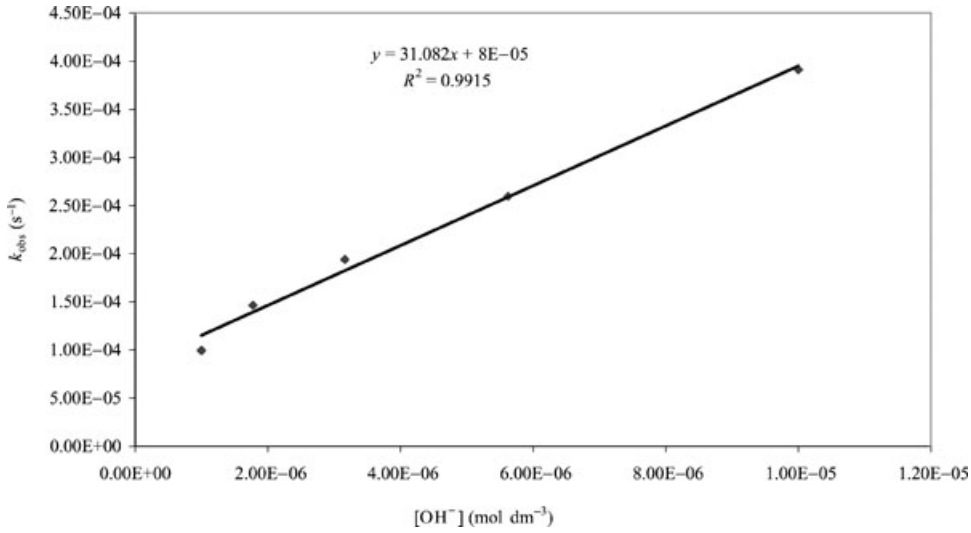


Figure 3 Plots of k_{obs} vs [OH^-] for the hydrolysis of coordinated histidine methyl ester at 25°C.

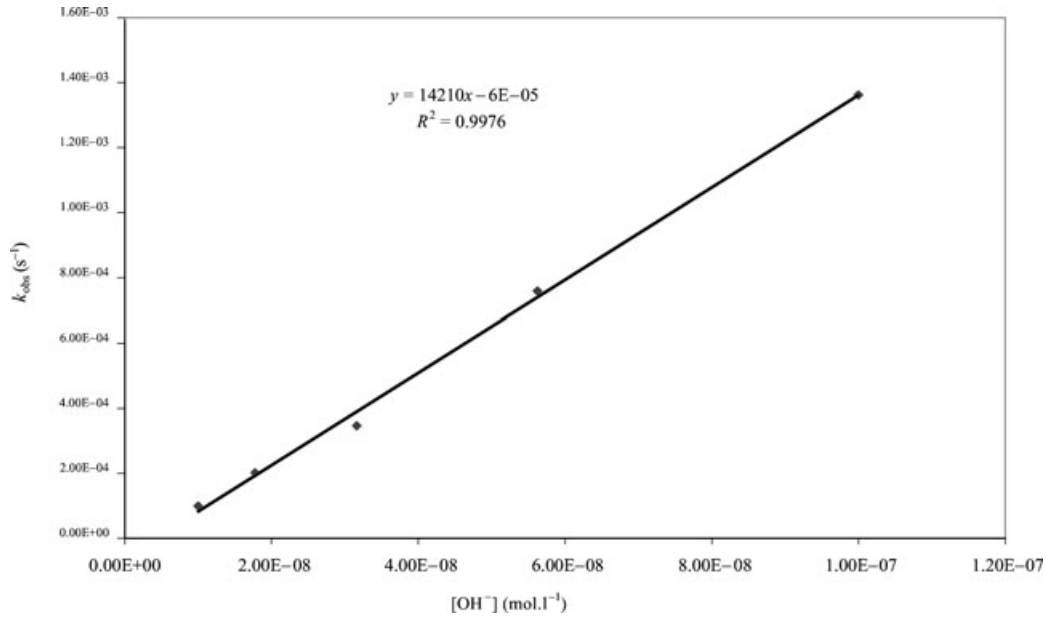
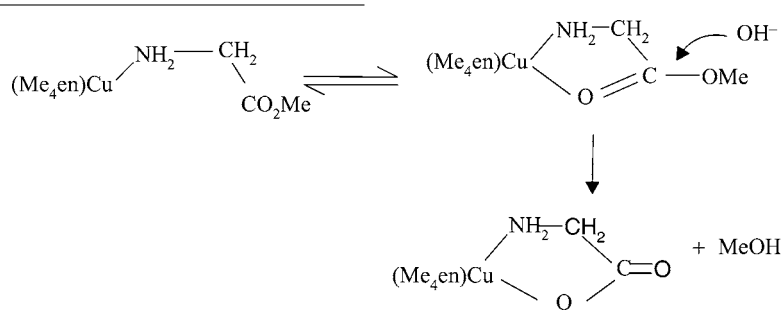


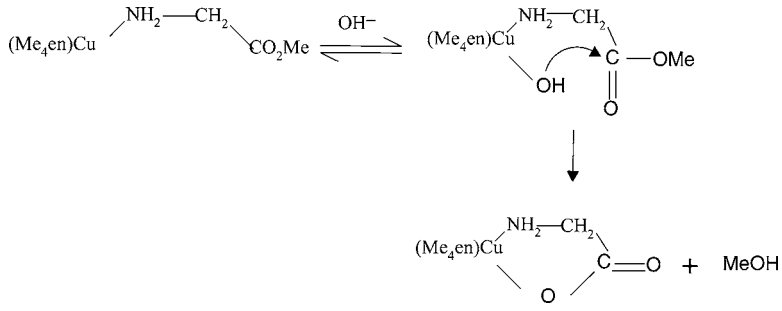
Figure 4 Plots of k_{obs} vs [OH^-] for the hydrolysis of coordinated methionine methyl ester at 25°C.

Metal-ion-promoted hydrolysis of amino acid ester has been studied by a number of research groups [16–19]. The first-order dependence on OH^- concentration may be accounted for by three mechanisms. One involves an initial rapidly established equilibrium in which the carbonyl oxygen of ester group coordinates to the copper ion, followed by rate-determining OH^- attack (Eq. (3)).



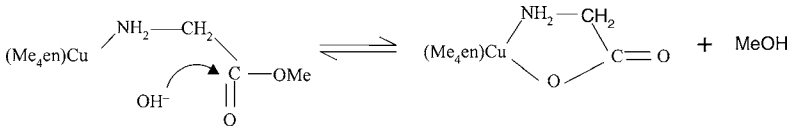
(3)

The second mechanism involves rapid equilibrium formation of a Cu–OH complex, followed by intramolecular OH^- attack (Eq. (4)).



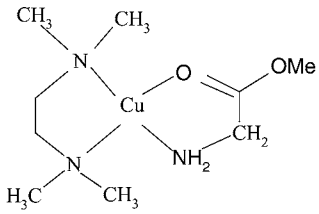
(4)

The third mechanism involves only OH^- attack on the uncoordinated carbonyl carbon of the ester group (Eq. (5)).

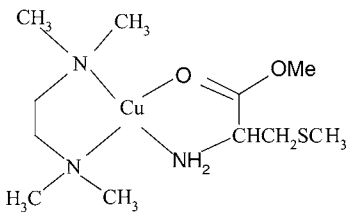


(5)

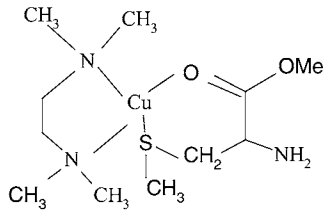
The linear dependence of rate on the OH^- concentration is consistent with the direct attack of OH^- ion on the coordinated ester carbonyl group as given in the first mechanism (Eq. (3)). On the other hand, the second mechanism (Eq. (4)) requires that the plot of k_{obs} versus the hydroxide ion concentration is not linear. The rate acceleration denoted by the catalysis ratio ($C = k_{OH}/k_{OH}^{ester}$) is calculated and found to be approximately 10^4 (Table IV) for glycine- and methionine methyl esters. Rate acceleration of this magnitude is fully consistent with the formation of mixed-ligand complexes where there is a direct interaction between Cu(II) and the alkoxycarbonyl of the ester species as in structure **I** for glycine methyl ester complex or structure **IIa** or **IIb** for methionine methyl ester complex.



Structure **I**



Structure **IIa**



Structure **IIb**

Table II Kinetics of Hydrolysis of Coordinated L-Methionine Methyl Ester at Different Temperatures in Aqueous Solution

Temperature (°C)	pH	$10^8 \times [OH^-]^a$ (mol dm^{-3})	$10^4 \times k_{obs}$ (s^{-1})	$10^4 \times k_{OH}$ (dm^3 mol^{-1} s^{-1})
15.00	6.00	0.45	0.36	6.21
	6.25	0.79	0.51	
	6.50	1.41	0.93	
	6.75	2.51	1.73	
	7.00	4.47	2.80	
20.00	6.00	0.68	0.40	9.46
	6.25	1.20	1.06	
	6.50	2.14	1.83	
	6.75	3.80	3.47	
	7.00	6.76	6.21	
25.00	6.00	1.00	1.00	14.20
	6.25	1.78	2.01	
	6.50	3.16	3.47	
	6.75	5.62	7.59	
	7.00	10.00	13.62	
30.00	5.50	0.47	0.98	19
	5.75	0.83	1.99	
	6.00	1.48	3.30	
	6.25	2.63	5.12	
	6.50	4.68	8.94	
	6.75	8.32	14.70	
	7.00	14.79	28.94	
35.00	5.50	0.66	1.61	23.8
	5.75	1.17	2.88	
	6.00	2.09	4.68	
	6.25	3.72	8.80	
	6.50	6.61	16.80	
	6.75	11.75	29.59	
	7.00	20.89	49.10	

[a] pK_w 14.35 at 15°C, 14.17 at 20°C, 14.00 at 25°C, 13.83 at 30°C, and 13.68 at 35°C. These data were taken from ref. [22].

Table III Kinetics of Hydrolysis of Coordinated L-Histidine Methyl Ester in Aqueous Solution

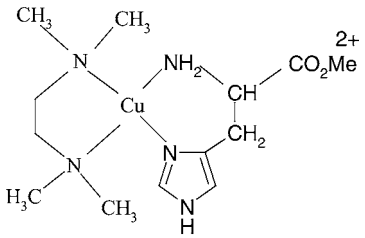
Temperature (°C)	pH	$10^6 \times [OH^-]$ (mol dm^{-3})	$10^4 \times k_{obs}$ (s^{-1})	k_{OH} (dm^3 mol^{-1} s^{-1})
25.00	8.00	1.00	1.00	31.10
	8.25	1.78	1.46	
	8.50	3.16	1.94	
	8.75	5.62	2.60	
	9.00	10.00	3.91	

Structure **IIa**, where methionine coordinates by amino and carbonyl ester groups, is most likely existing, based on the fair agreement between catalysis ratio value of glycine methyl ester complex and that of methionine methyl ester. Structure **IIb** is not assumed to form because of the steric interaction between the methyl group attached to the sulfur atom and the methyl groups attached to the amino group.

Table IV Rate Constant (k, dm^{-3} mol^{-1} s^{-1}) for Base Hydrolysis of Amino Acid Esters and Their Complexes at 25°C in Aqueous Solution

System	k_{OH}	$10^4 \times k_0$	K_{OH}^{ester}	C
Glycine methyl ester	1.49×10^4	1.70	1.28 [25]	1.16×10^4
Methionine methyl ester	1.42×10^4	0.74	0.77 [20]	1.85×10^4
Histidine methyl ester	31.1	0.32	0.62 [25]	50.1

The relatively small rate acceleration observed with methyl L-histidinate complex ($k_{OH}/k_{OH}^{ester} = 50.1$) (Table IV) suggests that in this case the alkoxycarbonyl group is not bounded to the metal ion as given in structure **III**. Such formulation would not lead to a rate acceleration greater than ca. 10^2. Previous studies [20] have shown that the formation of such complexes with nonbonded or pendant ester groups leads to only relatively small rate accelerations (10–10^2).



Structure **III**

Comparative value of k_{OH} at 25°C for the glycine methyl ester incorporated in $[Cu(en)L]^{2+}$ is 7.50×10^{-4} dm^3 mol^{-1} s^{-1} [18]. The k_{OH} value for $[Cu(Me_4en)L]^{2+}$ (Table I) is lower than that of $[Cu(en)L]^{2+}$ complex. This may be due to the steric interaction between the ester and the methyl substituent groups attached to the amine.

The activation parameters for the hydrolysis of coordinated esters are determined using the Eyring plot of $\ln(k_{OH}/T)$ versus $1/T$ (Figs. 5 and 6), from which the values of $\Delta H^{\pm}$ and $\Delta S^{\pm}$ are calculated and presented in Table V. The values obtained for base hydrolysis of glycine methyl ester incorporated in complex are compared with those of the free ester [21]. For base hydrolysis of free glycine methyl ester, the activation parameters were found to be $\Delta H^{\pm} = 39.7$ kJ mol^{-1} and $\Delta S^{\pm} = -117$ J K^{-1} mol^{-1}.

Table V Activation Parameters of Coordinated Glycine and Methionine Methyl Esters

Ester	Slope	Intercept	$\Delta H^{\pm}$ (kJ mol^{-1})	$\Delta S^{\pm}$ (J K mol^{-1})	$\Delta G^{\pm}$ (kJ mol^{-1})
Glycine methyl ester	−3032.8	14.06	25.20 ± 0.1	117.00 ± 0.2	−34.81 ± 0.2
Methionine methyl ester	−5730.7	23.01	47.6 ± 0.2	191 ± 0.2	−56.97 ± 0.1

Table VI Kinetics of Hydrolysis of the Glycine Methyl Ester in Different Dioxane–Water Solutions of Different Compositions at 25°C

Dioxane (%)	pH	$10^9 \times [OH^-]^a$ (mol dm^{-3})	$10^4 \times k_{obs}$ (s^{-1})	$10^4 \times k_{OH}$
12.50	6.50	16.60	2.93	0.67
	6.75	29.51	3.85	
	7.00	52.48	5.17	
	7.25	93.33	7.86	
	7.50	165.96	12.90	
25.00	6.50	6.03	2.63	1.11
	6.75	10.72	3.56	
	7.00	19.05	4.39	
	7.25	33.88	5.77	
	7.50	60.26	8.90	
37.50	6.50	2.34	1.96	2.07
	6.75	4.17	2.74	
	7.00	7.41	3.46	
	7.25	13.18	4.50	
	7.50	23.44	6.54	
50.00	6.00	0.35	0.78	5.07
	6.25	0.62	0.91	
	6.50	1.10	1.26	
	6.75	1.95	1.75	
	7.00	3.47	2.39	
62.50	6.00	0.20	0.38	10.20
	6.25	0.35	0.66	
	6.50	0.63	1.06	
	6.75	1.12	1.53	
	7.00	2.00	2.27	

[a] pK_w are 14.28, 14.72, 15.13, 15.46, and 15.70 for 12.5%, 25.0%, 37.5%, 50.0%, and 62.5% dioxane in water, respectively. These data were taken from ref. [23].

Table VII Kinetics of Hydrolysis of the L-Methionine Methyl Ester in Different Dioxane–Water Solutions of Different Compositions at 25°C

Dioxane (%)	pH	$10^9 \times [OH^-]^a$ (mol dm^{-3})	$10^4 \times k_{obs}$ (s^{-1})	$10^4 \times k_{OH}$
12.50	5.75	2.95	1.17	2.67
	6.00	5.25	2.39	
	6.25	9.33	3.38	
	6.50	16.60	5.32	
	6.75	29.51	8.52	
25.00	5.75	1.07	1.08	5.30
	6.00	1.91	1.77	
	6.25	3.39	2.74	
	6.50	6.03	4.11	
	6.75	10.72	6.30	
37.50	5.75	0.42	0.95	11.30
	6.00	0.74	1.67	
	6.25	1.32	2.34	
	6.50	2.34	3.46	
	6.75	4.17	5.34	
50.00	6.00	0.35	0.63	15.30
	6.25	0.62	0.81	
	6.50	1.10	1.50	
	6.75	1.95	2.92	
	7.00	3.47	5.29	
62.50	6.00	0.20	0.24	19.50
	6.25	0.35	0.46	
	6.50	0.63	1.06	
	6.75	1.12	1.97	
	7.00	2.00	3.71	

[a] pK_w are 14.28, 14.72, 15.13, 15.46, and 15.70 for 12.5%, 25.0%, 37.5%, 50.0%, and 62.5% dioxane in water, respectively. These data were taken from ref. [23].

The values for coordinated glycine methyl ester, as given in Table V, are 25.2 kJ mol^{-1} and 117.0 J K^{-1} mol^{-1}. It could be concluded that the enhanced rate for base hydrolysis is due to contributions from a decreased $\Delta H^{\pm}$ and an increased $\Delta S^{\pm}$. The large increase in $\Delta S^{\pm}$ implies desolvation between the ground and transition states and is indicative of a mechanism involving nucleophilic attack by external OH^- on the complexed ester group as shown in Eq. (3).

It is known that solutions in biochemical microenvironments such as active sites of enzymes and side chain in proteins have dielectric constant values of 30–50 [22–24]. It was suggested that these properties approximately correspond to those (or can be simulated by those) existing in water–dioxane mixtures. Consequently, investigation of amino acid ester hydrolysis in water–dioxane mixture is of biological significance.

In order to examine the effect of organic solvent on the hydrolysis of the ester, the rate constants for the hydrolysis of coordinated esters are determined in various dioxane–water solutions of different compositions. The rate constant values (k_{OH}), given in Tables VI–VIII, increase with increasing amount of dioxane. This may be explained on the premise that as the dioxane

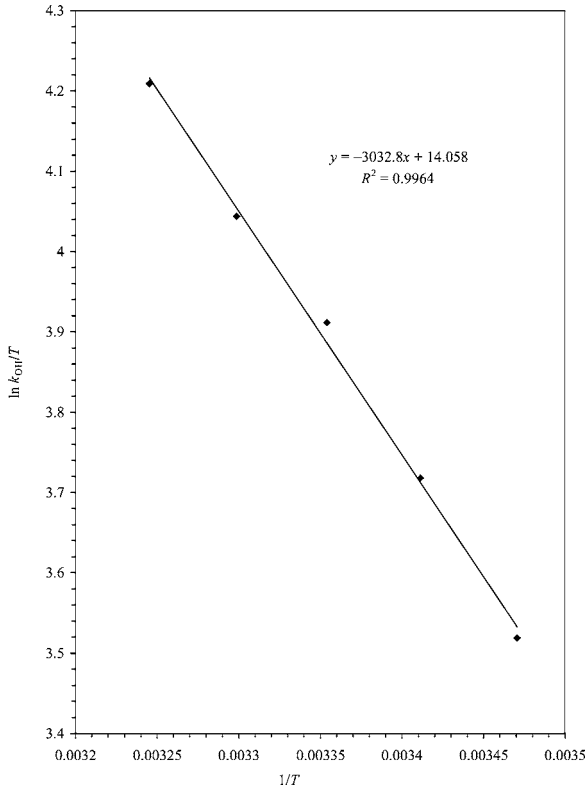


Figure 5 Plots of $\ln k_{OH}/T$ vs $1/T$ for the hydrolysis of coordinated glycine methyl ester.

content increases the dielectric constant of the solution medium decreases. This will favor the interaction of negatively charged OH^- ion with the electropositive carbonyl carbon atom of the ester. Consequently, the hydrolysis will proceed faster.

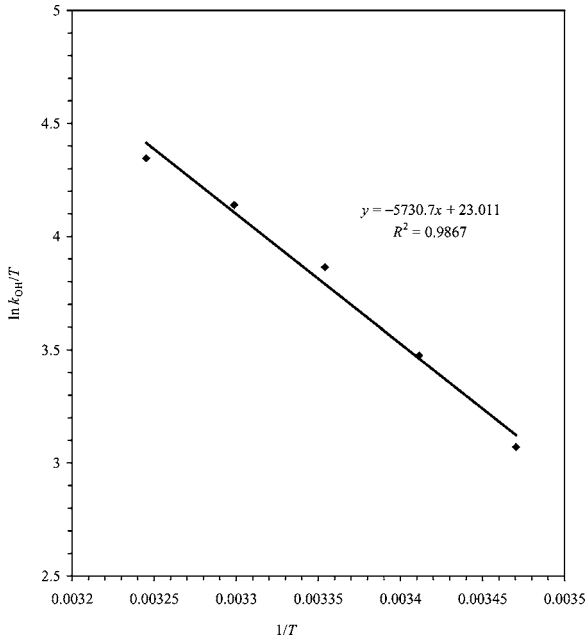


Figure 6 Plots of $\ln k_{OH}/T$ vs $1/T$ for the hydrolysis of coordinated methionine methyl ester.

Table VIII Kinetics of Hydrolysis of the L-Histidine Methyl Ester in Different Dioxane–Water Solutions of Different Compositions at 25°C

Dioxane (%)	pH	$10^6 \times [OH^-]^a$ (mol dm^{-3})	$10^4 \times k_{obs}$ (s^{-1})	k_{OH}
12.50	8.00	0.52	1.56	63.30
	8.25	0.93	1.84	
	8.50	1.66	2.40	
	8.75	2.95	3.09	
25.00	8.00	0.19	1.64	104.0
	8.25	0.34	1.88	
	8.50	0.60	2.10	
	8.75	1.07	2.59	
37.50	8.00	0.07	1.87	240.0
	8.25	0.13	1.98	
	8.50	0.23	2.18	
	8.75	0.42	2.69	
50.00	8.00	0.03	2.09	467.0
	8.25	0.06	2.23	
	8.50	0.11	2.48	
	8.75	0.19	2.84	
62.50	8.00	0.02	2.38	667.0
	8.25	0.04	2.55	
	8.50	0.06	2.69	
	8.75	0.11	3.02	

[a] pK_w are 14.28, 14.72, 15.13, 15.46, and 15.70 for 12.5%, 25.0%, 37.5%, 50.0%, and 62.5% dioxane in water, respectively. These data were taken from ref. [23].

CONCLUSION

The hydrolysis of glycine- and methionine methyl esters is catalyzed by $Cu(Me_4en)^{2+}$ complex with catalysis ratio $C \approx 1.4 \times 10^4$. However, the hydrolysis of histidine methyl ester is not significantly catalyzed, $C = 50.1$.

The catalytic effect is due to the coordination of the ester carbonyl group as in the case of glycine- and methionine methyl ester complexes. The four methyl substituent groups in $Cu(Me_4en)^{2+}$ significantly decrease the hydrolysis of the amino acid esters in comparison with previous study of $[Cu(en)(aminoacidester)]^{2+}$.

The solvent effect of the hydrolysis of ester shows that as the dielectric constant of the medium decreases (by increasing the dioxane content), the hydrolysis of the ester will be more favored. This is interesting from the biological point of view since the solutions in biochemical micro-environment have dielectric constant values of 30–50, and the dielectric constant of water is 76.

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