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Kinetics of base hydrolysis of α-amino acid esters catalyzed by palladium(II) piperazine complex

Research Article

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Abstract: The kinetics of base hydrolysis of glycine, histidine, and methionine methyl esters in the presence of $[Pd(pip)(H_2O)_2]^{2+}$ complex, where pip is piperazine, is studied in aqueous solutions, at T = 25°C, and *I* = 0.1 mol dm^{-3}. The rate of ester hydrolysis for glycine methyl ester is studied at different temperature and dioxane/water solutions of different compositions. The kinetic data are fit under the assumption that the hydrolysis proceeds in one step. The activation parameters for the base hydrolysis of the complexes are evaluated

Keywords: *Palladium(II) • Piperazine • Amino acid esters • Kinetics of base hydrolysis*

1. Introduction

The study of the metal-ion promoted hydrolysis of amino acid esters has been the focus of increasing research efforts [1-4]. The role of metal ions in catalyzing the hydrolysis of amino acid esters has been explored since 1952 [5-7]. Mixed-ligand complexes play an important role in the kinetics and mechanisms of chemical reactions and related bioprocesses. Much work has been published [8] on the hydrolysis of α-amino acid esters coordinated to metals such as cobalt(III), copper(II), and nickel(II). Such systems can be regarded as biomemetic models for certain metalloenzymes, as metalloenzyme-substrate complexes can be viewed as a special type of mixed-ligand complexes. However, only limited information is available for palladium(II) systems. In an interesting study, it has been shown that the mixed-ligand complex $[Pd(en)L]^{2+}$, where (en) denotes ethylenediamine, undergoes hydrolysis by water and hydroxide ion [9]. It would be of considerable interest to know if palladium(II) complexes involving cyclic amines can also undergo an analogous hydrolysis process. In this work, we explore this idea using a palladium(II) complex of the cyclic amine piperazine. The piperazine ligand differs significantly from the previously used chelating ligand ethylenediamine. Coordination of the piperazine ligand to Pd(II) results in decreasing the electron density on the metal center, making it more electrophilic [10]. Furthermore, piperazine has also been explored for its important pharmacological properties and the applicability of its derivatives as antidepressant antihistamines and antiparasitics [11]. In addition, the determination of the activation parameters should be helpful in validating the mechanism of reaction. With this work, we extend our earlier studies [1,12-16] on the hydrolysis of α-amino acid esters in the coordination sphere of metal centers, to study the effects of substituents on reactions of potential biological importance.

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2. Experimental Procedure

2.1. Materials and reagents

All reagents were of Analar grade. $PdCl_2$ and piperazine (pip) are provided by Aldrich. The glycine-, histidine-, and methionine methyl esters were purchased from Fluka. Carbonate-free NaOH was prepared and standardized against potassium hydrogen phthalate solution. All solutions were prepared in deionized H_2O.

2.2. Apparatus and measuring techniques

$[Pd(pip)Cl_2]$ was prepared by heating $PdCl_2$ (1.773 g, 1 mmol) in 40 mL H_2O and KCl (1.4912 g; 2 mmol) at 70°C for 30 min. The clear solution of $[PdCl_4]^{2-}$ was cooled to 20°C and filtered. Piperazine (0.8614 g, 1 mmol) dissolved in 10 mL H_2O was added dropwise to the stirred solution. The pH was adjusted to 2–3 by the addition of $HClO_4$. A yellow precipitate of $[Pd(pip)Cl_2]$ was formed and stirred for another 2 h at 50°C. Afterwards the precipitate was filtered off, and washed sequentially with H_2O, ethanol and diethyl ether. Anal. Calcd. for $C_4H_{10}N_2PdCl_2$: C, 18.22; H, 3.78; N, 10.63%. Found: C, 18.19; H, 3.75; N, 10.56%. Aqueous solutions of the diaqua form of the $[Pd(pip)Cl_2]$ complex were prepared in situ by the addition of slightly less than two molar equivalents of $AgNO_3$ to a solution of a known amount of the dichloro complex and stirred over night. The white precipitate of AgCl that formed was filtered off using a 0.1 μm pore membrane filter. Meticulous precautions were taken to ensure that the resulting solution was free of Ag^+ ions and that the dichloro complex had been converted completely into the diaqua species. The ionic strength of the solutions was adjusted to 0.1 M with $NaNO_3$ (Acros, p.a.). 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 [17]. All measurements were carried out in a double-walled glass cell of 50 mL capacity. The temperature was controlled by circulation of thermostated water through the outer jacket of the cell. The kinetics of the hydrolysis of glycine, methionine, and histidine methyl esters in the presence of $[Pd(pip)(H_2O)_2]^{2+}$ were investigated by pH-state techniques. After equilibrating $[Pd(pip)(H_2O)_2]^{2+}$ solution at the required temperature under nitrogen flow, a solution of ester was added and the pH was brought to the desired value by the addition of 0.05M NaOH solution. The hydrolysis was then followed by the automatic addition of 0.05 M NaOH solution to maintain the given pH constant. The data fitting was performed with the OLIS KINFIT set of programs [18] as previously described [19]. 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 Davies equation [20]. The following values of pK_w and γ were employed for the various temperatures studied: 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 ($pK_w = 13.83$, $\gamma = 0.770$), at 35°C ($pK_w = 13.68$, $\gamma = 0.768$) [21]

3. Results and Discussion

α-amino acid esters react with $[Pd(pip)(H_2O)_2]^{2+}$ according to the Eq. 1.

$$[Pd(pip)(H_2O)_2]^{2+} + {}^{+}NH_3CH(R)CO_2R` \overset{K}{\rightleftharpoons} [Pd(pip)\{NH_2CH(R)CO_2R`\}]^{2+} + H_3O^+ + H_2O \quad (1)$$

The equilibrium constant K is sufficiently large that when the pH is higher than 4.5, at a 1:1 ratio of palladium complex to α-amino acid esters, formation of the mixed-ligand complex is essentially complete. Thus one mole of base is consumed per mole of the palladium complex in the pH-stat measurements. (The hydrolysis of the un-coordinated α-amino-acid ester is extremely slow in this pH range.)

$$[Pd(pip)\{NH_2CH(R)CO_2R`\}]^{2+} + H_2O \xrightarrow{k_o} [Pd(pip)NH_2CH(R)COO]^+ + R`OH + H^+ \quad (2)$$

$$[Pd(pip)\{NH_2CH(R)CO_2R`\}]^{2+} + OH^- \xrightarrow{k_{OH}} [Pd(pip)NH_2CH(R)COO]^+ + R`OH \quad (3)$$

Under the conditions used here, $NH_2CH(R)CO_2R`$ is bound almost entirely as $[Pd(pip)\{NH_2CH(R)CO_2R`\}]^{2+}$. Therefore, the observed rate law represents the second step (k_{OH}) only. The first-order dependence on OH^- concentration for this step may be accounted for by an initial rapidly established equilibrium in which the carbonyl oxygen of the ester group coordinates to the metal, followed by rate determining OH^- attack, as explained by the following mechanism (A)

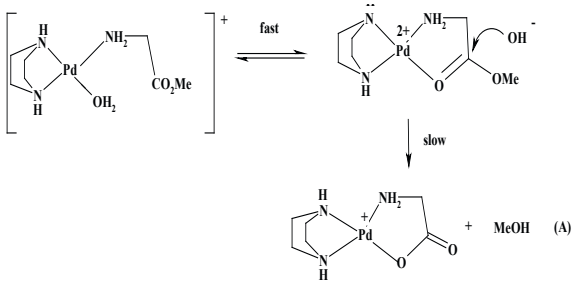


Table 1. Kinetics of the hydrolysis of $[Pd(pip)(ester)]^{2+}$ at 25°C and 0.1 M ionic strength.

Ester	pH	$[OH^-]^a$	k_{obs} (s^{-1})
Glycine methyl ester	4.8	6.31E-10	1.56E-04
	5.0	1.00E-09	1.59E-04
	5.2	1.58E-09	1.61E-04
	5.4	2.51E-09	1.65E-04
	5.6	3.98E-09	1.70E-04
Methionine methyl ester	8.4	2.51E-06	2.11E-04
	8.6	3.98E-06	2.21E-04
	8.8	6.31E-06	2.43E-04
	9	1.00E-05	2.59E-04
	9.2	1.58E-05	2.85E-04
Histidine methyl ester	9.2	1.58E-05	1.08E-04
	9.4	2.51E-05	1.40E-04
	9.6	3.98E-05	1.52E-04
	9.8	6.31E-05	1.71E-04
	10	1.00E-04	2.00E-04

[a] pK_w 14.35 at 15°C; 14.17 at 20°C; 14.00 at 25°C, 13.83 at at 30°C and 13.68

Plots of log (V_∞ - V_t) against time, where V_∞ is the final volume of base consumed and V_t is the volume of base measured at time t, were linear in all cases. The data fitting was performed with the OLIS KINFIT set of programs [18].A typical base-time trace for the hydrolysis of coordinated glycine methyl ester fitted with one exponential function using OLIS KINFIT is shown in Fig. 1. Various other kinetic models were tested and were found to inadequately fit the data. The values of k_{obs} (the observed pseudo-first-order rate constant at constant pH) were obtained and summarized in Tables 1 and 2. Plots of $k_{obs.}$ versus the hydroxide ion concentration were linear with a positive intercept, Fig. 2.

The rate expression can therefore be represented by Eqs. 4 and 5.

$$\text{Rate} = k_{obs}[Pd(N\text{-}N)(ester)] \quad (4)$$

$$k_{obs} = k_o + k_{OH}[OH^-] \quad (5)$$

The term k_o arises due to water attack on the mixed ligand complex. Values of $k_{H2O} = k_o/55.5$, where 55.5 mol dm^{-3} is the molar concentration of water, were determined from the intercept of Fig. 2, and values of $k_{OH} = (k_{obs.} - k_o)/[OH^-]$ from the slope. The linear dependence of the rate on the OH^- concentration is consistent with the direct attack of the OH^- ion on the coordinated ester carbonyl group as proposed in mechanism A. The rate constants k_{OH} obtained are summarized in Tables 3 and 4. In addition, Table 3 also contains the previously reported

Table 2. Kinetics of the hydrolysis of $[Pd(pip)(GlyOMe)]^{2+}$ at different temperatures in aqueous solution and 0.1 M ionic strength.

T (°C)	pH	$[OH^-]^a$	k_{obs} (s^{-1})
15	4.8	3.55E-10	1.42E-04
	5	5.62E-10	1.43E-04
	5.2	8.91E-10	1.44E-04
	5.4	1.41E-09	1.46E-04
	5.6	2.24E-09	1.48E-04
20	4.8	5.37E-10	1.50E-04
	5	8.51E-10	1.51E-04
	5.2	1.35E-09	1.53E-04
	5.4	2.14E-09	1.55E-04
	5.6	3.39E-09	1.58E-04
25	4.8	7.94E-10	1.56E-04
	5	1.26E-09	1.59E-04
	5.2	2.00E-09	1.61E-04
	5.4	3.16E-09	1.65E-04
	5.6	5.01E-09	1.70E-04
30	4.8	1.15E-09	1.64E-04
	5	1.82E-09	1.68E-04
	5.2	2.88E-09	1.70E-04
	5.4	4.57E-09	1.74E-04
	5.6	7.24E-09	1.81E-04
35	4.8	1.29E-09	2.04E-04
	5	2.04E-09	2.07E-04
	5.2	3.24E-09	2.13E-04
	5.4	5.13E-09	2.18E-04
	5.6	8.13E-09	2.30E-04

[a] pK_w 14.35 at 15°C; 14.17 at 20°C; 14.00 at 25°C, 13.83 at at 30°C and 13.68 at 35°C. These data were taken from [33].

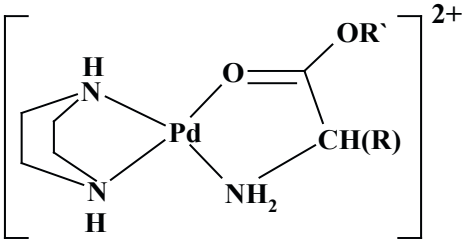
Table 3. Hydrolysis data ($dm^3 mol^{-1} s^{-1}$) of $[Pd(pip)(ester)]^{2+}$ at 25°C and 0.1 M ionic strength.

Ester	k_{OH}	k_{H2O}	[a]	$C = k_{OH}/k_{OH}^{ester}$
Glycine Methyl Ester	4.0E+03	2.8E-06	1.28	3.12E+03
Methionine Methyl Ester	5.50E+00	3.64E-06	0.77	7.14E+00
Histidine Methyl Ester	0.82E+00	1.34E-06	0.62	1.32 E+00

[a] Data from [7,12].

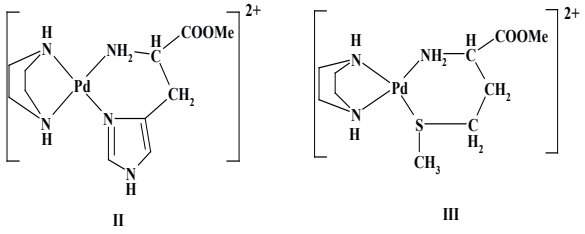
Table 4. Hydrolysis data ($dm^3 mol^{-1} s^{-1}$) of $[Pd(pip)(GlyOMe)]^{2+}$ at different temperatures in aqueous solution.

T (°C)	k_{OH}	k_{H2O}
15	1.73 E+03	2.5E-06
20	2.55 E+03	2.7E-06
25	3.98 E+03	2.8E-06
30	4.91 E+03	2.9E-06
35	7.65 E+03	3.6E-06



I

Scheme 1. Pd(pip)complex coordinated to glycine methyl ester



II III

Scheme 2. Pd(pip)complex coordinated to histidine methyl ester (structure II) and methionine methyl ester (structureIII)

[7,16,22] rate constants k_{OH}^{ester} for the base hydrolysis reaction:

$$NH_2CH(R)CO_2R` + OH^- \xrightarrow{k_{OH}^{ester}} NH_2CH(R)CO_2^- + R`OH \quad (6)$$

For glycine methyl ester (GlyOMe), the rate acceleration denoted by the catalysis ratio C= (k_{OH}/k_{OH}^{ester}) has the value 3.11×10^3. Rate acceleration of this magnitude is fully consistent with the formation of the mixed-ligand complex as in mechanism (A), where there is a direct interaction between Pd(II) and the alkoxycarbonyl group of the ester species (Structure I).

Histidine and Methionine esters act as bidentate ligands without invoking any interaction with the alkoxycarbonyl group [7].The kinetic data of HisOMe and MethOMe complexes (the volume of base added to keep the pH constant versus time) could be fitted by applying only one exponential. Values of k_{obs} versus the hydroxide ion concentration are given in Table 1. The linear plots of k_{obs} versus the hydroxide ion concentrations are represented in Figs. 3 and 4. They reveal that hydrolysis proceeds via an intermolecular mechanism. The catalysis ratio C, of methionine methyl ester (MethOMe) and histidine methyl ester (HisOMe) complexes amounts to 7.14 and 1.32, respectively (Table 3). The relative small catalysis ratio values suggest that in these cases the alkoxycarbonyl group is not bonded to the metal ion. The HisOMe complex is expected to have structure (II) in which the donor atoms are the α-amino group and the unprotonated nitrogen of the imidazole ring. A similar situation (III) is likely with MethOMe, where thiolate sulphur and the α-amino group act as donors. A number of previous studies [23-28] have shown that the formation of such complexes with pendant ester groups lead to only relatively small rate accelerations, *i.e.* if the ester carbonyl was instead directly bonded to Pd(II), we would have obtained much higher catalysis ratios.

The activation parameters for the hydrolysis of coordinated ester were determined using the Eyring plot [21] of $\ln(k_{OH}/T)$ versus 1/T, Fig. 5, according to Eq. 7:

$$\ln(k_{OH}/T) = (\ln(k_B/h) + \Delta S^{\neq}/R) - \Delta H^{\neq}/R(1/T) \quad (7)$$

$\Delta H^{\neq}$ and $\Delta S^{\neq}$ are the activation parameters of enthalpy change and entropy change, respectively. The slope is $-\Delta H^{\neq}/R$ and $\Delta S^{\neq}$ can be extracted from the intercept by using Eq. 8,

$$\Delta S^{\neq} = [\text{intercept}-\ln(k_B/h)]R \quad (8)$$

where k_B, h and R are the Boltzmann, Planck and gas constants, respectively [29]. The values for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ obtained for the base hydrolysis of complexed glycine methyl ester are compared with those for the base hydrolysis of free glycine methyl ester. The values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated to be 13.6 (±0.2) kJ mol^{-1} and -95.2 (±0.4) J K^{-1} mol^{-1}, respectively. For the base hydrolysis of free glycine methyl ester, the activation parameters were found to be $\Delta H^{\neq}$ = 39.7 kJ mol^{-1} and $\Delta S^{\neq}$ = -117 J K^{-1} mol^{-1} [7]. It could therefore be concluded that the enhanced rate of base hydrolysis when the ester is incorporated in the complex $[Pd(N\text{-}N)L]^{2+}$ is due to contributions from a decreased $\Delta H^{\neq}$ and an increased $\Delta S^{\neq}$. The large increase in $\Delta S^{\neq}$ implies disolvation between the complex and transition state and is indicative of a mechanism involving nucleophilic attack by external OH^- on the complexed ester group as shown in mechanism (A).

Generally, biochemical micro-environments such as active sites of enzymes and side chains in proteins have dielectric constant values of 30-50 [30-32]. It

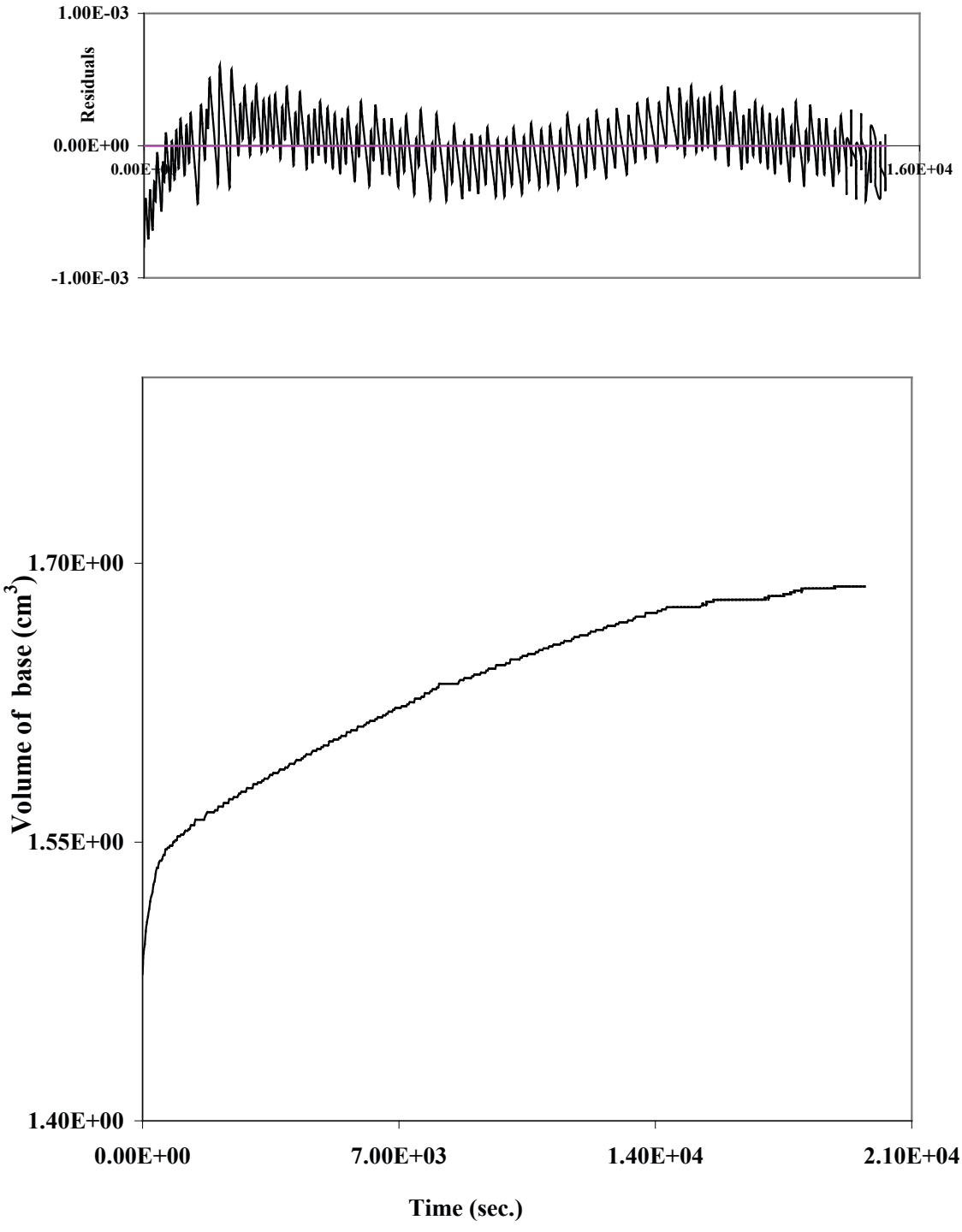


Figure 1. Typical volume of base vs. time trace, fitted with one exponential, for the hydrolysis reaction of $[Pd(pip)GlyOMe]^{2+}$ at 25°C and 0.1 M ionic strength

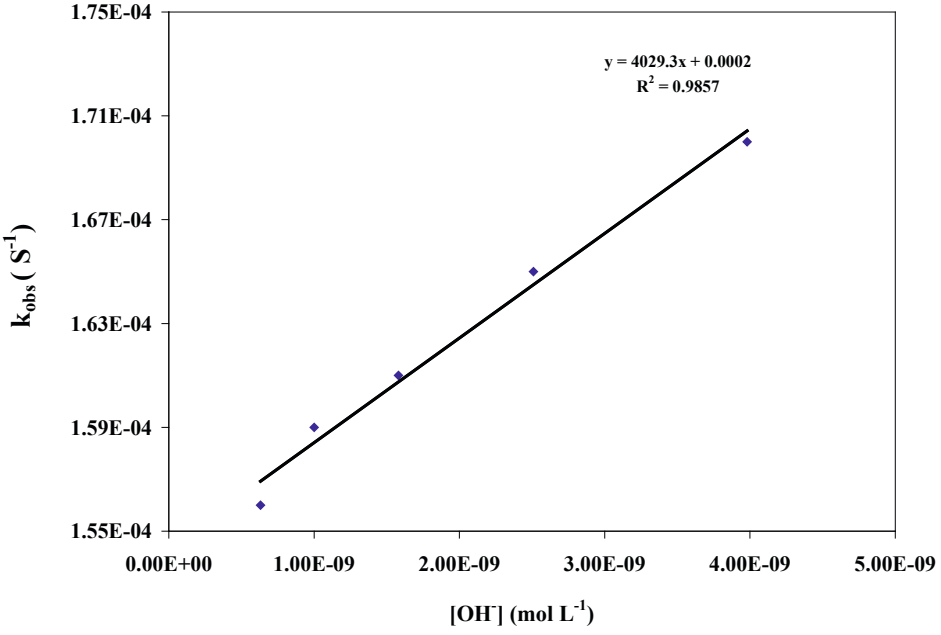


Figure 2. Effect of OH- concentration on k_{obs} for the hydrolysis of glycine methyl ester coordinated to Pd(pip) complex at 25°C

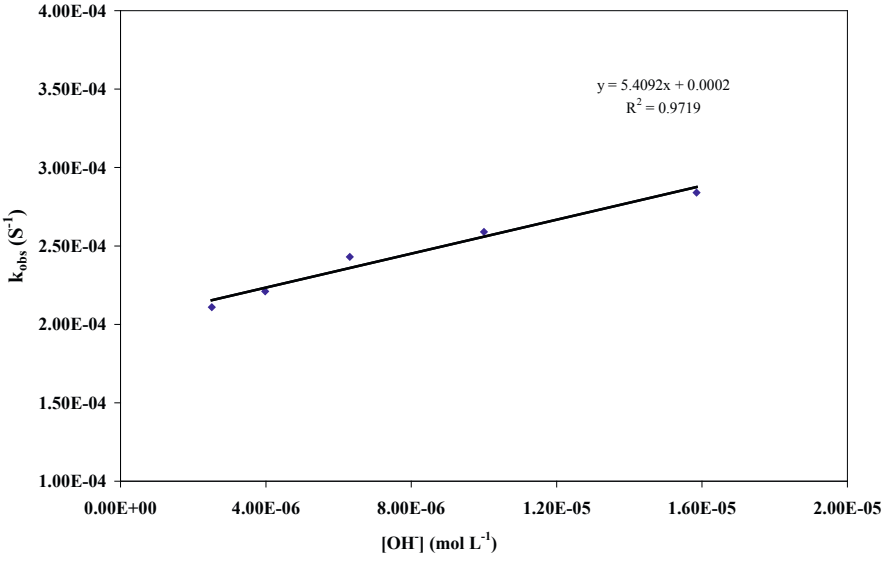


Figure 3. Effect of OH- concentration on kobs for the hydrolysis of methionine methyl ester coordinated to Pd(pip) complex at 25°C.

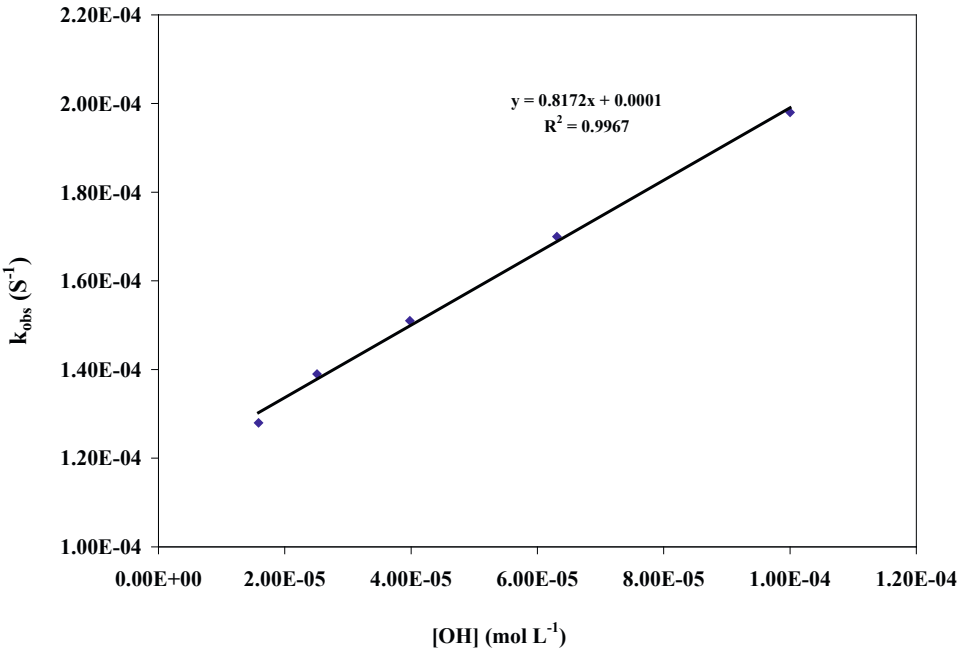


Figure 4. Effect of OH- concentration on kobs for the hydrolysis of histidine methyl ester coordinated to Pd(pip) complex at 25°C.

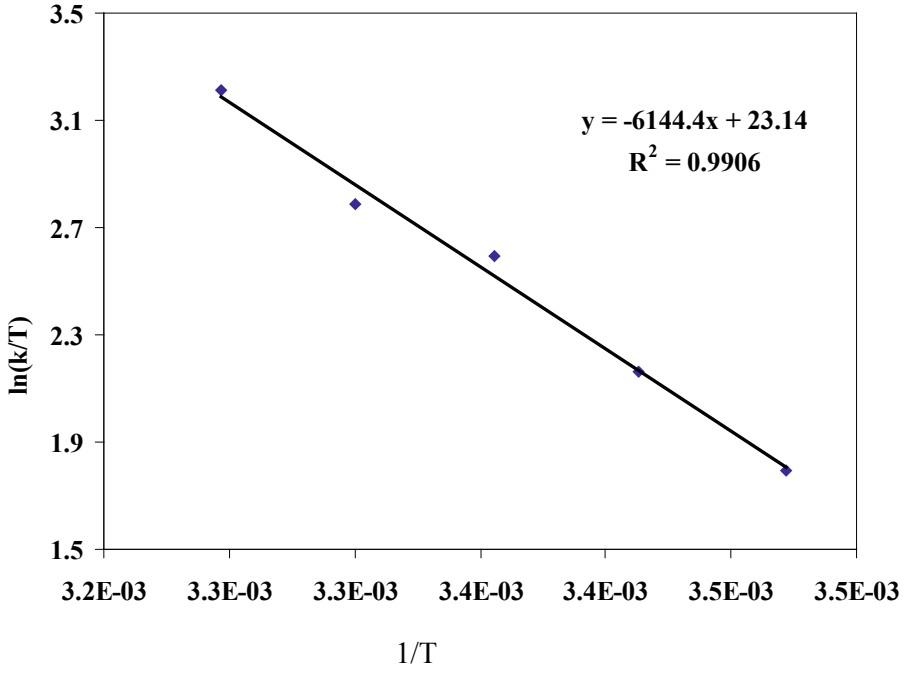


Figure 5. Effect of temperature on the hydrolysis of glycine methyl ester

Table 5. Kinetics of the hydrolysis of $[Pd(pip)(GlyOMe)]^{2+}$ in dioxane/water solutions of different compositions at 25°C, pH 5.2, and 0.1 M ionic strength.

Dioxane %	k_{obs} (s^{-1})
12.5	1.329E-04
25.0	1.400E-04
37.5	1.595E-04
50	1.730E-04

pK_w are 14.28, 14.72, 15.13, and 15.46, for 12.5%, 25.0%, 37.5%, and 50.0%, dioxane in water, respectively. These data were taken from [31].

was suggested that these properties approximately correspond to those (or can be simulated by those) existing in the water/dioxane mixtures. Consequently, the investigation of amino acid ester hydrolysis in water/dioxane mixtures is of biological significance.

In order to examine the effect of organic solvent on the hydrolysis of ester, the rate constants for the hydrolysis of free and coordinated ester were determined in various dioxane-water solutions of different compositions. The rates for the hydrolysis of $[Pd(pip)(GlyOMe)]^{2+}$ were investigated at pH=5.2, temperature 25°C, and using dioxane/water solutions of several different compositions (12.5%, 25%, 37.5%, 50%). The ensuing rate constants are provided in Table 5. The rate constant k_{obs} increases with increasing amount of dioxane. This may be explained on the premise that as the dioxane content increases the dielectric constant of the solution medium decreases. This will favor the interaction of the negatively charged OH^- ion with the electropositive carbonyl carbon atom of the ester. Consequently the hydrolysis will proceed faster.

4. Conclusions

The hydrolysis of glycine methyl esters is catalyzed by $[Pd(pip)(H_2O)_2]^{2+}$ complex with catalysis ratio C ≈ 3.12E+03. The catalytic effect is due to a direct interaction between Pd(II) and the alkoxycarbonyl group of the ester species. However, the hydrolysis of histidine and methionine methyl ester is not significantly catalyzed. The relative small catalysis ratio values suggest that in these cases the alkoxycarbonyl group is not bonded to the metal ion. The solvent effect on the hydrolysis of ester shows that, as the dielectric constant of the medium decreases (by increasing the dioxane content), the hydrolysis of the ester becomes increasingly favored. This is interesting from a biological point of view since the solutions in biochemical micro-environments have dielectric constant values of 30-50, and the dielectric constant of water is 76.

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