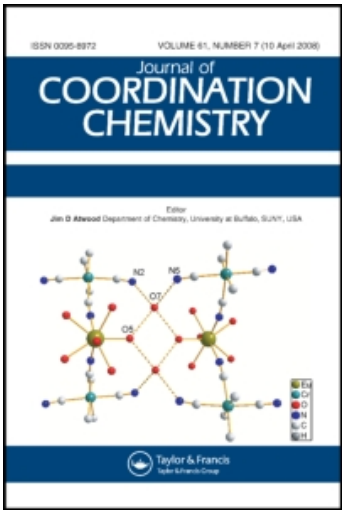

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Copper(II) complexes of imino-bis(methyl phosphonic acid) with some bio-relevant ligands. Equilibrium studies and hydrolysis of glycine methyl ester through complex formation

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To cite this Article El-Sherif, Ahmed A. and Shoukry, Mohamed M.(2005) 'Copper(II) complexes of imino-bis(methyl phosphonic acid) with some bio-relevant ligands. Equilibrium studies and hydrolysis of glycine methyl ester through complex formation', Journal of Coordination Chemistry, 58: 16, 1401 — 1415
To link to this Article: DOI: 10.1080/00958970500055435
URL: http://dx.doi.org/10.1080/00958970500055435

Journal of Coordination Chemistry
Vol. 58, No. 16, 10 November 2005, 1401–1415

Copper(II) complexes of imino-bis(methyl phosphonic acid) with some bio-relevant ligands. Equilibrium studies and hydrolysis of glycine methyl ester through complex formation

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(*Received 2 June 2004; revised 23 August 2004; in final form 19 January 2005*)

Binary and ternary complexes of Cu(II) involving imino-bis(methyl phosphonic acid) (IdP) abbreviated as H_4A and some selected bio-ligands, amino acids, peptides and DNA constituents (L), were examined. Cu(II) forms CuA and CuAH complexes with IdP. Ternary complexes are formed in a stepwise mechanism whereby iminodiphosphonic acid binds to Cu(II), followed by coordination of amino acid, peptide or DNA. The concentration distribution of the various complex species has been evaluated. The kinetics of base hydrolysis of glycine methyl ester in the presence of Cu(II)-IdP was studied in aqueous solution at different temperatures, and in dioxane-water solutions of different compositions at 25°C. The activation parameters are evaluated and discussed.

Keywords: Cu(II); Imino-bis(methyl phosphonic acid); Amino acids; Glycine methyl ester; Hydrolysis; Equilibria

1. Introduction

Aminopolyphosphonic acids and their derivatives have received considerable attention because of their interesting biological activity and include a variety of herbicides, plant growth regulators, antibodies and inhibitors of metallo-enzymes [1]. For example, N,N′-di(phosphenomethyl)glycine is an active component of polaris, a known plant growth regulator [2], whereas N-(phosphenomethyl)glycine is an active ingredient of a popular herbicide [3,4]. As potent metal binders, aminophosphonates could be involved in interactions relevant for the fate of metal ions in the natural environment or biological systems [5,6]. Numerous studies were aimed at understanding the chelating properties of this class of ligands and determining the stability of the complexes formed [7,8].

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Journal of Coordination Chemistry
ISSN 0095-8972 print: ISSN 1029-0389 online © 2005 Taylor & Francis
DOI: 10.1080/00958970500055435

Formation equilibria of mixed ligand complexes involving aminophosphonic acid derivatives and some bio-relevant ligands provide information regarding the behavior of this class of ligands in biological systems. In continuation of our published work on binary and ternary complexes of transition metal ions involving amino acids [9,10], peptides [11,12] and DNA units [13,14], as well as the base hydrolysis of the mixed-ligand complexes with α-amino acid esters [15–17], we now describe the equilibria associated with the formation of binary and ternary complexes involving Cu(II) and imino-bis(methyl phosphonic acid) and amino acid, peptides, DNA constutitents or amino acid ester. The study also includes the base hydrolysis of glycine methyl ester in its ternary complex in aqueous solution and in dioxane-water solutions of different composition and at different temperatures.

2. Experimental

2.1. *Materials and reagents*

Imino-bis(methyl phosphonic acid) IdP, the bis phosphonic derivative of iminodiacetic acid (Ida) was obtained from Aldrich Chem. Co. The amino acids: glycine, alanine, imidazole, threonine iso-leucine, histamine dihydrochloride, histidine monohydrochloride and methylamine hydrochloride were provided by Sigma Chem.Co. The peptides used were glutamine and glycylglycine, also provided by Sigma Chem.Co. BDH-Biochemicals Ltd supplied the DNA constituents, uridine, thymine, thymidine, inosine and adenine. The glycine methyl ester hydrochloride was purchased from Fluka. $Cu(NO_3)_2$ was provided by BDH. The copper content of solutions was determined by complexometric EDTA titrations [18]. Carbonate-free NaOH (titrant) was prepared and standardized against potassium hydrogen phthalate solution. All solutions were prepared in deionized H_2O.

2.2. *Apparatus and measuring techniques*

Potentiometric measurements were made using a Metrohm 686 titroprocessor equipped with a 665 Dosimat. The electrode and titroprocessor were calibrated with standard buffer solutions prepared according to NBS specifications [19]. The kinetics of hydrolysis were monitored using the titroprocessor operated with (Set) mode. All titrations were carried out at $25.0 \pm 0.1^{\circ}C$, in a double-walled glass cell, through the outer jacket of which water was circulated from a constant temperature bath.

2.3. *Equilibrium measurements*

The acid dissociation constants of the ligands were determined potentiometrically by titrating the ligand ($40\,cm^3$) solution (1.25×10^{-3}M) of constant ionic strength 0.1M, (adjusted with $NaNO_3$). The stability constants of the Cu-IdP complex were determined by titrating $40\,cm^3$ of a solution mixture of Cu(II) (1.25×10^{-3}M), IdP (2.5×10^{-3}M) and $NaNO_3$ (0.1M). The stability constants of the ternary complexes were determined using potentiometric data obtained from mixtures of Cu(II) (1.25×10^{-3}M), IdP and the bio-relevant ligand solutions in a concentration ratio 1:1:1. All titrations were performed in a purified N_2 atmosphere, using aqueous 0.05 M NaOH as titrant.

The stability constants of Cu(IdP)L complexes, where HL is amino acid, peptide, DNA or amino acid ester, were determined using the data obtained within the pH range corresponding to complete formation of Cu-IdP complex. Hence, in calculation only complex formation between Cu(IdP) and ligand (HL) is considered and each of these systems could be treated as a binary one. All pH-metric titrations were carried out at $25.0 \pm 0.1^{\circ}C$ in a purified N_2 atmosphere.

The calculations were obtained from ≈90 data points in each titration using the computer program [20] MINIQUAD-75. The stoichiometries and stability constants of the complexes formed were determined by trying various possible composition models. The model selected gave the best statistical fit and was chemically consistent with the titration data without giving any systematic drifts in the magnitudes of various residuals, as described elsewhere [20]. The results obtained are shown in table 1. Species distribution diagrams were obtained using the program SPECIES (L. Pettit, personal communication) under the experimental conditions used.

2.4. *Kinetic measurements*

The kinetics of hydrolysis of the complexed ester were investigated using aqueous solutions ($40\,cm^3$) of a mixture of Cu(II) (6.25×10^{-3}M), IdP (6.87×10^{-3}M), glycine methyl ester (1.25×10^{-3}M) and $NaNO_3$ (0.1M). In this mixture the [Cu-IdP]:[ester] ratio was adjusted to 5:1, so as to maximize the amount of complexed ester present. A 10% excess of IdP over Cu(II) was used to ensure coordination of all Cu(II), which is itself an excellent catalyst. The pH of the mixture was progressively raised to the desired value. The reaction was monitored by the addition of aqueous NaOH solution to maintain the given pH as described previously [15–17]. Data fitting was performed with the OLIS KINFIT set of programs [21] as indicated 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. For the variable temperature studies the following values of pK_w and γ were employed [22] at 20°C ($pK_w = 14.146$, $\gamma = 0.774$), at 30°C ($pK_w = 13.833$, $\gamma = 0.770$), at 35°C ($pK_w = 13.680$, $\gamma = 0.768$) and at 40°C ($pK_w = 13.535$, $\gamma = 0.766$). The activity coefficients were obtained using the Davies equation [23].

3. Results and discussion

3.1. *Equilibrium studies*

Imino-bis(methyl phosphonic acid) (H_4A) has two phosphonic groups. Three of the four protonation processes can be measured by pH potentiometry and log K_{HnA} values of 10.78, (NH), 6.36 (PO_3^{2-}) and 5.08 (PO_3^{2-}), are calculated (see table 1). Comparable values (10.77, 6.30 and 4.86) have been reported [24], while values of (10.79, 6.08 and 4.86) have been determined by another study [25]. In this case too, two protons of PO_3H_2 groups appear very acidic and have pKa values less than 2, and thus they are fully deprotonated in the pH range studied and do not take part in metal coordination equilibria. The acid dissociation constants of amino acids, peptides, DNA constitutents and glycine methyl ester.HCl have been reported.

Table 1. Formation constants of $M_pL_qH_r$ species.

System	p	q	r[a]	$\log \beta$[b]	S[c]	$\log K_{CuL}^{Cu}$[d]	$\Delta \log K$
Cu-IdP	0	1	1	10.78(0.06)	3.2E-6	12.98	
	0	1	2	17.14(0.06)			
	0	1	3	22.22(0.03)			
	1	1	0	12.98(0.01)	2.0E-8		
	1	1	1	17.74(0.01)			
	1	1	2	21.09(0.09)			
	1	1	−1	2.66(0.02)			
Glycine	0	1	1	9.60(0.01)	1.5E-7	8.19	−5.01
	0	1	2	11.93(0.03)			
	1	1	0	3.18(0.06)	1.2E-8		
Alanine	0	1	1	9.69(0.01)	9.2E-8	7.99	−4.89
	0	1	2	11.88(0.02)			
	1	1	0	3.1(0.05)	7.6E-9		
Threonine	0	1	1	9.06(0.01)	7.9E-9	8.22	−5.15
	0	1	2	11.03(0.02)			
	1	1	0	3.07(0.09)	7.1E-9		
Imidazole	0	1	1	7.04(0.01)	2.6E-9	4.15	−1.54
	1	1	0	2.61(0.08)	7.0E-9		
Methylamine	0	1	1	10.55(0.004)	8.9E-9	6.82	−2.82
	1	1	0	4.01(0.07)	6.7E-8		
Iso-leucine	0	1	1	9.76(0.01)	3.4E-7	8.23	−4.79
	0	1	2	12.22(0.01)			
	1	1	0	3.44(0.04)	7.7E-9		
Histidine	0	1	1	9.53(0.01)	1.6E-7	10.66	−5.59
	0	1	2	15.81(0.03)			
	0	1	3	17.81(0.06)			
	1	1	0	5.07(0.09)	2.2E-8		
Histamine	0	1	1	9.88(0.01)	2.4E-8	9.5	−4.78
	0	1	2	15.97(0.01)			
	1	1	0	4.77(0.05)	5.7E-9		
Glycylglycine	0	1	1	7.99(0.006)	4.6E-8	5.4	−2.66
	1	1	0	2.74(0.07)	4.9E-9		
Glutamine	0	1	1	9.06(0.01)	4.5E-8	7.69	−4.88
	1	1	0	2.81(0.09)	1.3E-8		
Adenine	0	1	1	9.95(0.01)	5E-9	6.77	−3.7
	0	1	2	14.63(0.01)			
	1	1	0	3.07(0.06)	1.3E-8		
Uridine	0	1	1	9.01(0.01)	1.1E-7	6.04	−2.75
	1	1	0	3.29(0.09)	5.9E-8		
Thymidine	0	1	1	9.77(0.01)	8.7E-8	5.87	−2.91
	1	1	0	2.96(0.07)	1.3E-8		
Thymine	0	1	1	9.58(0.006)	8.1E-8	5.77	−3.02
	1	1	0	2.75(0.09)	8.6E-8		
Inosine	0	1	1	8.43(0.01)	4.1E-8	4.61	−1.64
	1	1	0	2.97(0.07)	2.6E-8		

[a] p, q and r are the stoichiometric coefficients corresponding to Cu(IdP), amino acids, peptides or DNA units and H^+; [b] Standard deviations are given in parentheses; [c] Sum of square of residuals. [d] These data, except that of Cu-IdP are taken from reference [16].

We redetermined them under the experimental conditions used for determining the stability constants of the mixed-ligand complexes. The results obtained are in good agreement with the literature values [26].

The potentiometric data of Cu-IdP solution were fitted assuming the formation of 110, 111 and 112 species but not a 120 species. The formation of the 1:2 complex seems to be hindered because IdP is tridentate with two five-membered chelate rings. Also the electrostatic replusion of the negatively charged phosphonate groups

precludes coordination of the second ligand: the charge of the 1:2 complex would be 6−. In the 1:1 complex $Cu(IdP)^{2-}$ the ligand is tridentate with nitrogen and phosphate groups bound in three equatorial positions. A comparison between IdP and Ida complexes with Cu(II) indicates that $Cu(IdP)^{2-}$ is more stable than the corresponding Ida complex (10.41) [24]. Thus substitution of carboxylate by phosphonate increases the stability of the complexes due to the higher basicities of the phosphonic functions.

Ternary complex formation may proceed either through a stepwise or simultaneous mechanism depending on the chelating potential of IdP and the other ligand (L) [L = amino acid, peptide or DNA]. The formation constant of 1:1 Cu(II)-IdP complex is larger than 1:1 Cu(II)-Ligand (L) complex, (table 1). It is resonable to propose that in the presence of both ligands, one molecule of IdP is coordinated to the Cu(II) ion, with subsequent coordination of the secondary ligand (L). This assumption was supported by potentiometric data. A representative set of pH titration curves for Cu(II)-IdP-glycine system is shown in figure 1. The Cu(II)-IdP(1:1) mixture titration curve has a sharp inflection at a = 4 (a = number of moles of base added per mole of ligand), corresponding to complete formation of the 1:1 complex. The Cu(II)-IdP complex is formed first due to its greater stability compared to the Cu(II)-L complex (table 1). Beyond a = 4, the formation of a ternary complex was ascertained by comparison of the mixed-ligand titration curve with the composite curve obtained by graphical addition of glycine titration data to that of the Cu(II)-IdP titration curve. The mixed ligand system was found to deviate considerably from the composite curve, indicating formation of a ternary complex. Thus, formation of ternary complex can be described by the following stepwise equilbria (equations 1, 2).

$$Cu + IdP \rightleftharpoons Cu(IdP) \tag{1}$$

$$Cu(IdP) + L \rightleftharpoons Cu(IdP)L \tag{2}$$

(Charges are omitted for simplicity)

The stability constant value of the monodentate methylamine complex is slightly higher than that of glycine, indicating that glycine most likely coordinates with Cu(IdP) as a monodentate rather than a bidentate ligand. The extra stability of the methylamine complex may be due to higher basicity of its amino group than that of glycine amino group (as reflected by their pK_a values). This finding is further supported by the fact that the stability constant of Cu(ethylenediamine)-glycine complex is 7.47 [27], significantly higher than that of its corresponding complex with Cu(IdP), (3.18), further evidence that glycine is monodentate. Ring opening in Cu(IdP), allowing for chelation of glycine as a bidentate ligand or chelation of glycine to equatorial and apical sites, would be unlikely.

The ionized amide residue of the peptide, [–CONH–], is an important ligating group and coordinates to Cu(II) [11]. The β-alcoholato-group, in the side chain of serine and threonine plays an essential role in the functions of protolytic enzymes such as chymotrypsin and subtilisin [28] and previously [29] was reported to bind to Cu(II). The potentiometric data reported for the peptides and threonine complexes reveals the formation of Cu(IdP)(L) rather than $Cu(IdP)LH_{-1}$ species which supports the view that ring opening of Cu(IdP) and induced ionization of peptide hydrogen and β-alcoholato-group would be unfavored. This is in agreement

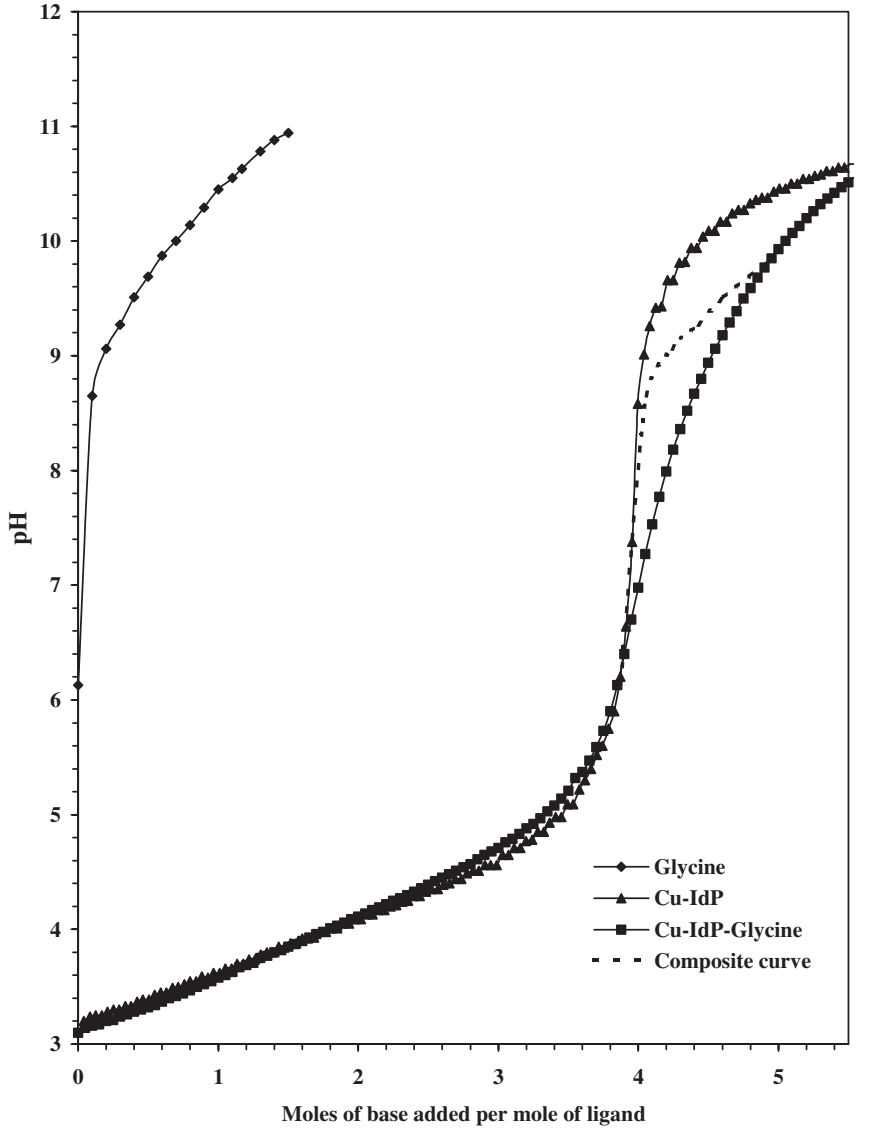


Figure 1. Potentiometric titration curves for Cu-IdP-Glycine system.

with our previous investigation carried out on the Cu(II)-diethylenetriamine-peptide system [30].

The pyrimidines uridine, thymine and thymidine have only basic nitrogen (N_3). Consequently the pyrimidines coordinate through this site and do not form protonated complexes. Inosine may become protonated at N(7) with formation of [N(1)H–N(7)H] monocations. In the present study, the pK_a of N(1)H was only determined since the pK_a of N(7)H is too low to be detected by the potentiometric technique. The potentiometric data of the mixed ligand complexes involving inosine showed the formation of the Cu(IdP)L species, where L is the monoanion of inosine.

In the acidic pH range, N(1) remains protonated, while the metal ion is attached to N(7). The gradual change from N(7)-binding to N(1)-binding with increasing pH has been frequently documented by ^{1}HNMR [31] and EPR [32] spectroscopic measurments. Consequently, it is proposed that N(1) serves as a coordination site in the mixed ligand complexes of inosine at higher pH values.

The relative stabilities of the ternary and binary complexes can be quantitatively expressed in different ways. It has been argued that a comparison can best be made in terms of $\Delta\log K$ [33]. The relative stability of the ternary complexes formed through a stepwise mechanism, as compared to those of binary complexes, is expressed in terms of $\Delta\log K$ as defined by equation (3).

$$\Delta\log K = \log K^{Cu(IdP)}_{Cu(IdP)L} - \log K^{Cu}_{CuL} \tag{3}$$

One expects to obtain negative values for $\Delta\log K$ (table 1), since more coordination positions are available for the bonding of ligand (L) in the binary than in the ternary complexes. This indicates that the secondary ligand (L, amino acid, peptide or DNA) forms more stable complexes with Cu(II) ion alone than with the Cu(II)-IdP complex. Imidazole has the less negative $\Delta\log K$ value, evidence for enhanced stability involving π-back donation from the negatively charged IdP^{4-} ion to the π-system of the imidazole. The $\Delta\log K$ value of the mixed-ligand amino acid complexes are more negative than those of methylamine. This may be explained on the premise that the amino acid is bidentate and methylamine is monodentate and there is one equatorial coordination site available in $Cu(IdP)^{2-}$ complex. The negative values obtained for $\Delta\log K$, are of the order:– tridentate (as histidine) > bidentate (as glycine) > monodentate (as imidazole) ligand. This observation can be justified by the fact that Cu-IdP provides only one available coordination site.

Estimation of the concentration distribution of the various species in solution provides a useful picture of metal ion binding. The main features observed in the species

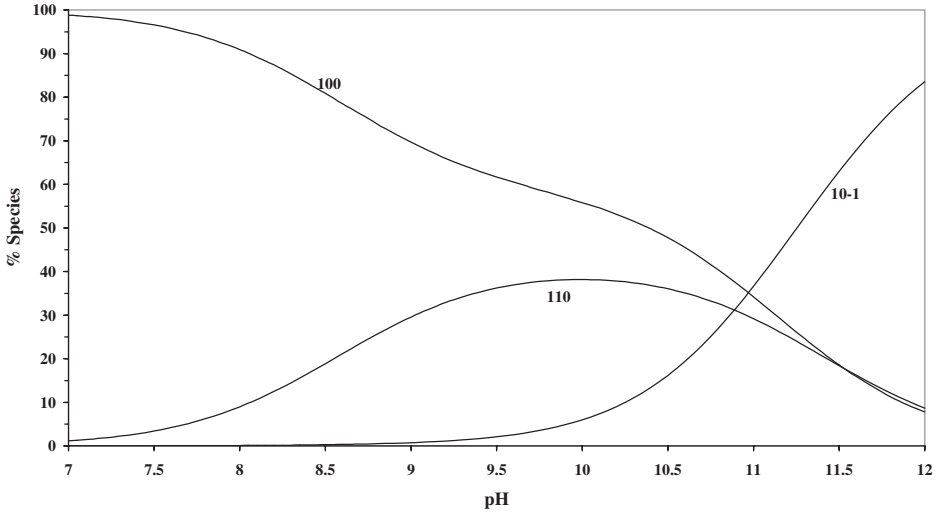


Figure 2. Concentration distribution of various species as a function of pH in the Cu-IdP-Uridine system.

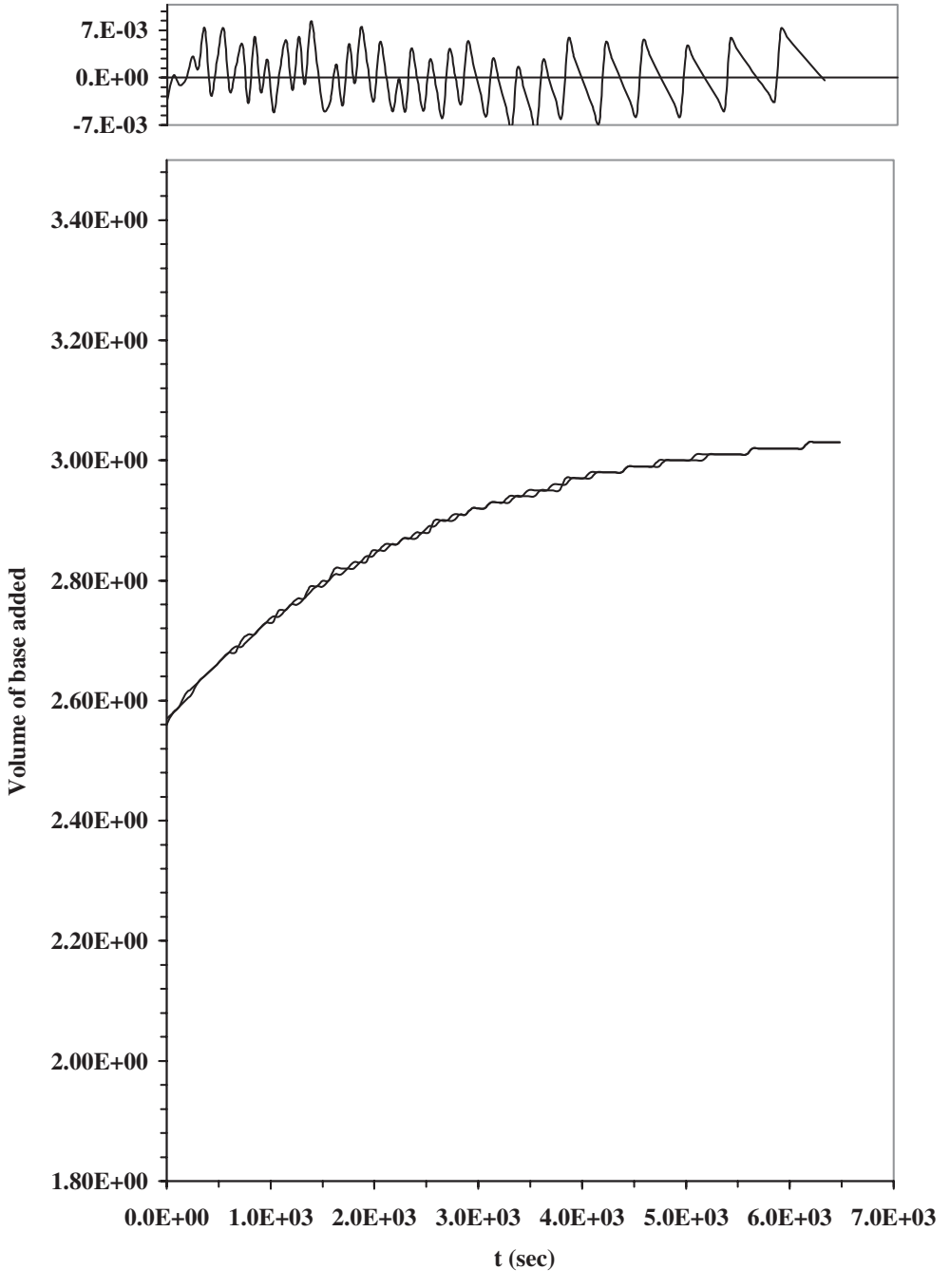


Figure 3. Typical volume of base added-time trace for the hydrolysis of Cu-IdP-Glycine methyl ester fitted with one exponential function. The top of the figure shows the volume of base difference between the measured and calculated kinetic traces at I = 0.1M; pH = 8.6 and T = 25°C.

Table 2. Kinetics of hydrolysis of the coordinated glycine methyl ester at different temperatures in aqueous solution.

Temp.	pH	10^6 [OH][a]/mol dm^{-3}	10^4 k_{obs}/s^{-1}
20	8.20	1.46	1.05
	8.40	2.32	1.55
	8.60	3.67	2.41
	8.80	5.82	3.44
	9.00	9.23	5.52
25	8.20	2.06	1.54
	8.40	3.27	2.57
	8.60	5.19	3.89
	8.80	8.22	5.69
	9.00	13.04	8.90
30	8.20	3.02	2.94
	8.40	4.79	4.16
	8.60	7.59	5.81
	8.80	12.03	9.41
	9.00	19.02	15.0
35	8.20	4.31	4.95
	8.40	6.83	6.25
	8.60	10.83	9.5
	8.80	17.16	16.4
	9.00	27.20	24.7
40	8.20	6.03	7.15
	8.40	9.56	9.8
	8.60	15.16	16.0
	8.80	24.03	24.1
	9.00	38.08	38.8

[a] pK_w 14.146 at 20°C; 13.997 at 25°C, 13.833 at 30°C , 13.68 at 35°C. and 13.535 at 40°C. These data were taken from reference [38].

distribution plots in these systems are shown in the speciation diagram obtained for the Cu-IdP-uridine system, figure 2. The mixed ligand species [Cu(IdP)L] (110) starts to form at pH ~ 7 and with increasing pH, whereby its concentration reaches the maximum of 37% at pH = 10.

3.2. *Hydrolysis Kinetics*

Hydrolysis of the coordinated ester was monitored over the pH range (8.2–9). In this range, the rate of hydrolysis of MeGly is negligible in the absence of $Cu(IdP)^{2-}$. Kinetic data, the volume of base added to keep the pH constant *vs.* time, could be fitted by one exponential as shown in figure 3. Various other kinetic models were tested without leading to satisfying fits of the data. The values of k_{obs} at different pH and temperatures are given in table 2. Plots of k_{obs} *vs.* the hydroxide ion concentration are linear, figure 4. The rate expression can therefore be given in the form equation 4.

$$k_{obs} = k_o + k_{OH}[OH^-] \tag{4}$$

The k_o term arises from attack of water being expressed by the relation (5) [34].

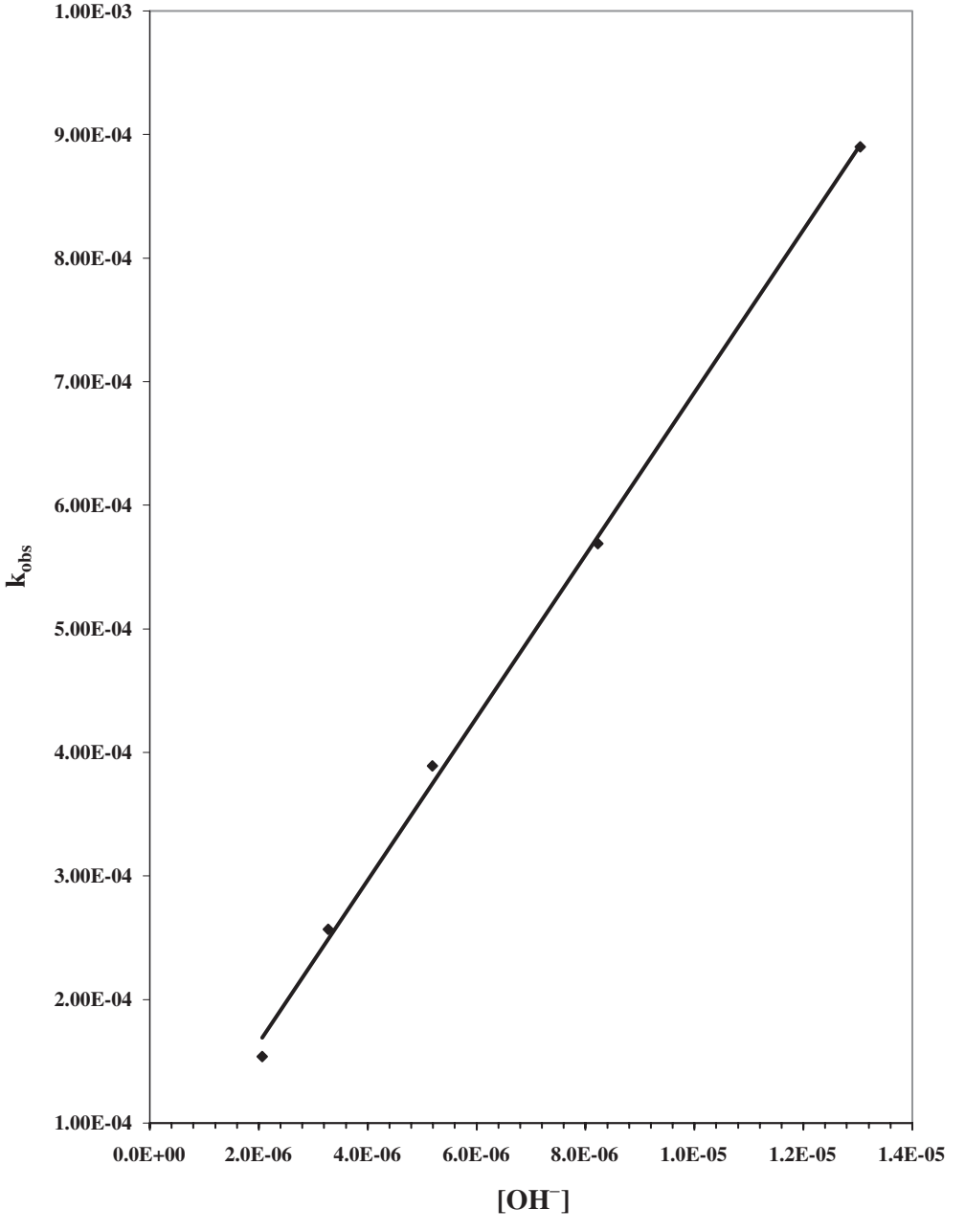
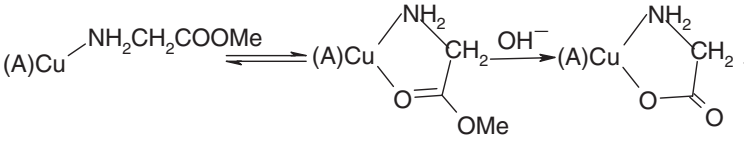


Figure 4. Kinetic plot of k_{obs} *vs.* the hydroxide ion concentration for the hydrolysis of Cu-IdP-glycine methyl ester in water solutions at 25°C and I = 0.1M.

$$k_{H_2O} = \frac{k_o}{55.5} \tag{5}$$

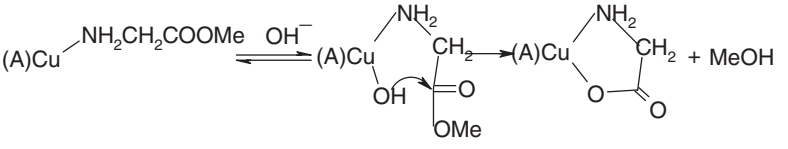
where 55.5 mol dm^{-3} is the molar concentration of water. The value of k_o can be determined from the intercept of figure 4, and the value of k_{OH} from the slope of the respective plot. The rate constants k_{H_2O} and k_{OH} values are given in table 3.

Metal-ion-promoted hydrolysis of amino acid esters has been studied by a number of research groups [34–37] with three mechanisms proposed. One involves an initial rapid equilibrium in which the carbonyl oxygen of the ester group coordinates, followed by a stage of determining OH^- attack (equation 6).



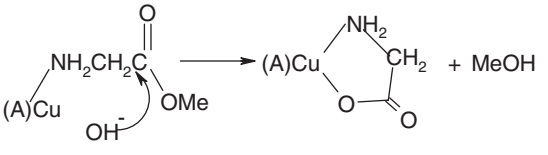
(6)

The second mechanism involves rapid equilibrium formation of an M–OH complex, followed by intramolecular OH^- attack (equation 7).



(7)

The third mechanism inolves only OH^- attack on the uncoordinated carbonyl carbon of the ester group (equation 8).



(8)

The catalysis constant, $C = k_{OH}/k_{OH}^{ester}$ obtained for glycine methyl ester is 50. The formation of monodentate N-coordinated ester species would not lead to rate accelerations greater than ca. 10^2 [38] therefore, a rate enhancement ($C = 50$) is consistent with the third mechanism, equation (8) in which a monodentate ester coordination species is formed. Formation of bidentate ester complexes with Cu(II) leads to rate accelerations of 10^5–10^6 [39–43]. On the other hand the second mechanism equation (7) requires that the plot of k_{obs} *vs.* the hydroxide ion concentration is not linear [34]. Also it is unlikely that an OH^- ion would add to form a stable five-coordinate derivative since Cu(II) is known to prefer four coordination [44]. Evidence for the formation of such complex species, in which the ester is coordinated by the amino group only,

Table 3. Rate constants for base hydrolysis of coordinated glycine methyl ester at different temperatures.

Temp.°C	$10^5\ k_o/s^{-1}$	$10^7\ k_{H_2O}/dm^3mol^{-1}s^{-1}$	$10^{-1}\ k_{OH}/dm^3mol^{-1}s^{-1}$
20	2.33	4.2	5.68
25	3.30	5.93	6.58
30	4.25	7.67	7.57
35	5.31	9.58	8.92
40	7.23	13.02	9.93

is also proved by the results of the potentiometric measurements. The amino acid is coordinated as a monodentate ligand; it is unlikely that the carboxylate group occupies the apical site as a result of the Jahn-Teller effect operative in Cu(II), causing elongation of the bonds in the apical site. Also, the binding of negatively charged carboxylate to Cu(II) ion already coordinated to tetranegatively charged $(IdP)^{4-}$ ion seems to be disfavored.

The activation parameters ($\Delta S^{\pm}$ and $\Delta H^{\pm}$) were obtained from ln (k_{OH}/T) *vs.* $1/T$ using the Eyring equation [45] . The slope of the plot, displayed in figure 5, is $\Delta H^{\pm}/R$ and the intercept is related to $\Delta S^{\pm}$ by equation (9)

$$\Delta S^{\pm} = \left[\text{intercept} - \ln\left(\frac{K}{h}\right)\right]R \tag{9}$$

where K, h and R are the Boltzmann, Plank and gas constants, respectively.

The activation parameters were determined for the hydrolysis of $[Cu(IdP)(GlyOMe)]^{2-}$ at $I = 0.1M$. The temperature dependence of the rate constants k_{OH} and k_{H_2O} are summarised in table 3. For $k_{OH,}$ $\Delta H^{\pm} = 19.2 \pm 0.61\,kJ\,mol^{-1}$, $\Delta S^{\pm} = -145 \pm 0.24\,J\,K^{-1}\,mol^{-1}$, while for k_{H_2O} $\Delta H^{\pm} = 39.3 \pm 0.62\,kJ\,mol^{-1}$, $\Delta S^{\pm} = -162 \pm 1.57\,J\,K^{-1}\,mol^{-1}$. For base hydrolysis of free glycine methyl ester the activation parameters were found [46] to be $\Delta H^{\pm} = 39.7\,kJ\,mol^{-1}$, $\Delta S^{\pm} = -117\,J\,K^{-1}\,mol^{-1}$. The enhanced rate for base hydrolysis of the ester incorporated in the complex is therefore due to contribution from a decreased $\Delta H^{\pm}$. Attack of water on the $[Cu(Idp)GlyOMe]^{2-}$ complex is some 10^9 slower than that of hydroxide ion as determined by k_{OH}/k_{H_2O} ratio. This large difference in nucleophilicities between OH^- and H_2O is also observed for a variety of Cu(II) complexes [47].

Previously, it was proposed that [48] the catalytic activity of metal chelates toward amino acid ester hydrolysis could be correlated with the formation constant of metal chelate (equation 10)

$$M^{2+} + A^{X-} \overset{K_f}{\rightleftharpoons} MA^{(2-X)} \underset{K_x}{\overset{GlyOMe}{\rightleftharpoons}} MAGlyOMe^{(2-X)} \tag{10}$$

Large formation constants (K_f) result in reduced Lewis acid character (K_x) of the metal chelate toward esters and, therefore, lower catalytic activities for a series of Cu^{2+} chelates [48]. Metal chelates of the highest Lewis acidity are the most effective promoters of ester hydrolysis. According to the data in (table 4), the Cu(II) complexes exhibit significant catalytic effects which decrease in the order $Cu^{2+} > Cu(Ida) > Cu(IdP)^{2-}$, this is the same order observed for K_x (table 4) in the complexation of glycine esters by these Cu^{2+} complexes. Although the decrease in k_{OH} follows an increase in the formation constant of the metal chelate (K_f), we can also interprete this trend in terms of the magnitude of positive charge on the metal chelates *i.e.*, complexes with high positive charge yielded the highest k_{OH}.

Traditionally, water has been considered as the solvent that best represents biological conditions. Although this is a general assumption, lower polarity has been detected in some bio-chemical micro-environments such as active sites of enzymes and side chain in proteins with dielectric constant values of 30–50 [49–51]. It was suggested that these properties approximately correspond to those (or can be simulated by those) existing

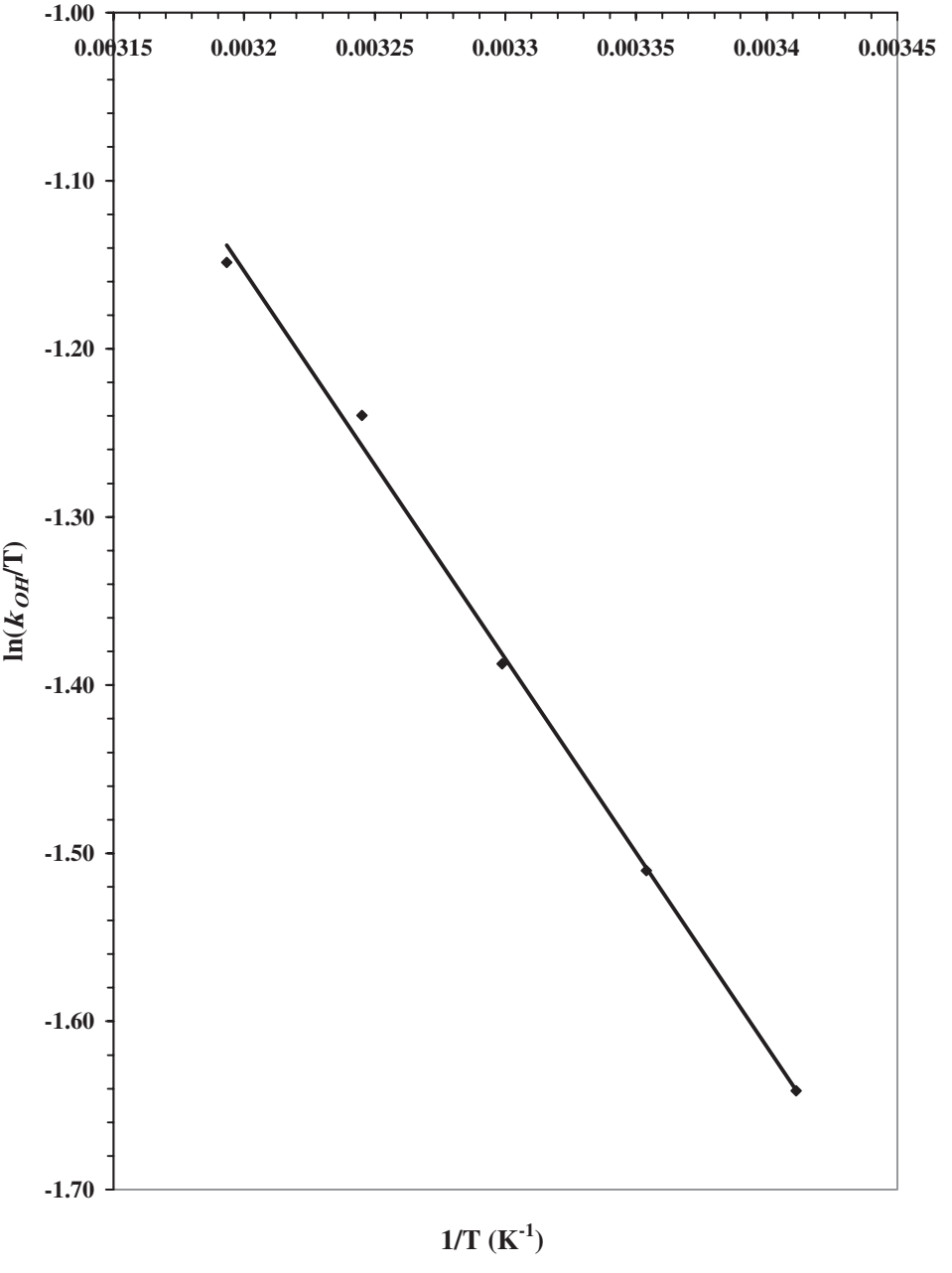


Figure 5. Eyring plot of $\ln(k_{OH}/T)$ versus $1/T$ for the base hydrolysis of Cu-IdP-glycine methyl ester system.

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 ester, the rate constants for the hydrolysis of free and coordinated ester were determined in various dioxane-water solutions of different compositions. The rate constants are given in tables 5 and 6. The rate constant k_{OH}

Table 4. Rate (k_{OH}) and equilibrium costants associated with Cu(II)-catalyzed hydrolysis of MeGly at 25°C.

$CuL(MeGly)^n$	$k_{OH}/dm^3mol^{-1}s^{-1}$	log K_x(ester)	log K_f
$Cu(EtGly)^{2+}$	7.6×10^4 [a]	4.04 [b]	–
Cu(Ida)(MeGly)	7.6×10^3 [c]	3.69 [d]	10.63(e)
$Cu(IdP)(MeGly)^{2-}$	0.66×10^2	2.98	12.98

[a] Although not reported, the rate for $Cu(MeGly)^{2+}$ would be somewhat faster(~2 times) than for $Cu(EtGly)^{2+}$ given above, reference [52]. [b] Reference [53]. [c,d] Reference [54]. [e] Reference [55].

Table 5. Kinetics of hydrolysis of the coordinated glycinemethyl ester in different dioxane-water solutions of different compositions at 25°C.

Dioxane%	pH	10^7 [OH][a]/mol dm^{-3}	10^4 k_{obs}/s^{-1}
12.5	8.2	8.32	5.70
	8.4	13.20	6.24
	8.6	20.90	6.93
	8.8	33.10	7.99
25.0	8.2	3.02	4.79
	8.4	4.79	5.10
	8.6	7.59	5.90
	8.8	12.02	6.89
37.5	8.2	1.17	3.90
	8.4	1.86	4.20
	8.6	2.95	4.90
	8.8	4.68	5.80
50	8.2	0.55	3.50
	8.4	0.87	3.90
	8.6	1.38	4.40
	8.8	2.19	5.28

[a] 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 references [46].

Table 6. Rate constants ($k/dm^3mol^{-1}s^{-1}$) for base hydrolysis of free and coordinated glycine methyl ester in dioxane-water solutions of different compositions at 25°C.

Dioxane (% V/V)	10^{-2} $k_{OH}/dm^3mol^{-1}s^{-1}$ (coord. ester)	10^5 k_o/s^{-1}	10^7 $k_{H_2O}/dm^3mol^{-1}s^{-1}$	10^2 k_{OH}[a]$/dm^3mol^{-1}s^{-1}$ Free ester
12.5	1.36	1.55	2.79	9.24
25.0	2.80	1.06	1.91	24.24
37.5	5.92	0.62	1.12	55.99
50.0	9.6	0.25	0.45	108.85

[a] These data were taken from reference [56].

increases with increasing amount of dioxane, attributable to dioxane content decreasing the dielectric constant of the solution. This will favor the interaction of negatively charged OH^- ion with the electropositive carbonyl carbon atom of the ester and the hydrolysis will proceed faster.

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