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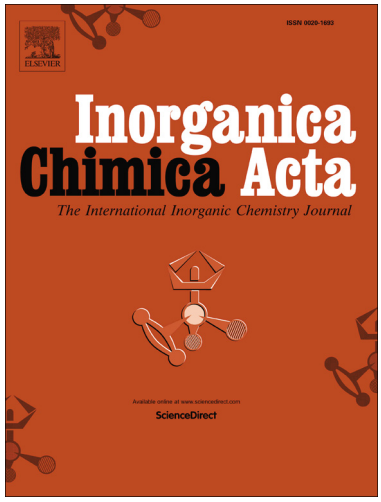

Base hydrolysis of α-amino acid esters catalysed by [Pd(N-ethylethylenediamine)$(H_2O)_2$]$^{2+}$. Kinetic study and DFT calculations

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Base hydrolysis of α-amino acid esters catalysed by [Pd(N-ethylethylenediamine)$(H_2O)_2]^{2+}$. Kinetic study and DFT calculations

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Abstract

Amino acid esters (L) react with $[Pd(Eten)(H_2O)_2]^{2+}$ (Eten = N-ethyl ethylenediamine) giving mixed ligand complexes of the type $[Pd(Eten)L]^{2+}$. Base hydrolysis of $[Pd(Eten)L]^{2+}$ was studied by pH-stat technique from which rate constants for the base hydrolysis of the esters were obtained. The glycine methyl ester hydrolysed significantly, whereas the methionine methyl and histidine methyl esters hydrolysed much slower. The mode of coordination of the ester plays a role in the catalysis, and possible mechanisms for these reactions are considered. Activation parameters were determined for the hydrolysis of the glycine methyl ester. The effect of the dielectric constant of the medium on the hydrolysis process was also investigated. The B3LYP/LANL2DZ method was used for geometric optimization of the free ligand and the complex using the Gaussian 09 program. The calculations are compared with the kinetic data. In addition, the vibrational frequencies of the molecules were computed for the optimized geometries.

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Keywords: N-ethylethylenediamine, Amino acid ester hydrolysis, Pd(II), pH-stat technique. DFT calculation.

INTRODUCTION

Metal ion catalysis of the amino acid ester hydrolysis was reported in 1952 by Kroll [1]. Since that time these reactions have been investigated by a number of research groups with hopes of elucidating the nature of the hydrolytic process and the role of metal ions in biological systems. Certain metalloenzymes [2] were reported to catalyse the hydrolysis of amino acid esters. While the metal ion is known to be the active site in some of these enzymes, the protein groups binding and neighbouring the metal ion also play a major role in determining the overall catalytic properties of the enzymes.

Metal ions in metalloenzymes, such as carbonic anhydrase [3], carboxypeptidase A [4] and alkaline phosphatase [5], play a key role in many biological processes [6]. In these metalloenzymes, the metal ions in the active sites are considered to serve as primary catalytic centre for bringing substrate and nucleophile together through formation of a coordination complex, in order to activate the substrate carbonyl group facilitating attack of the nucleophile in carboxypeptidase A [7], to activate the water molecule in the reversible hydration process of carbon dioxide in carbonic anhydrase [6], and to activate the serine hydroxyl group in alkaline phosphatase [8]. To probe the mechanism by which the metalloenzyme operates and to provide a theoretical basis for designing highly effective artificial metalloenzymes, previous reports [9-13] have developed biomimetic models for metalloenzymes which catalyse the hydrolysis of carboxylic acid esters in the models.

Work in our laboratories [14-19] has focused on the catalysed hydrolysis of various amino acid esters by metal complexes. The mixed ligand complex $[Pd(en)L]^{2+}$ undergoes hydrolysis by water and hydroxide ion [20]. This work has now been extended to the mixed ligand complex involving N-ethylethylenediamine. The introduction of the bulky ethyl substituent can tune the lability of the metal centre and so control its reactivity in catalytic and biological applications. Density functional theory (DFT) calculations for geometry optimization and vibrational frequencies of all complexes and ligands are reported.

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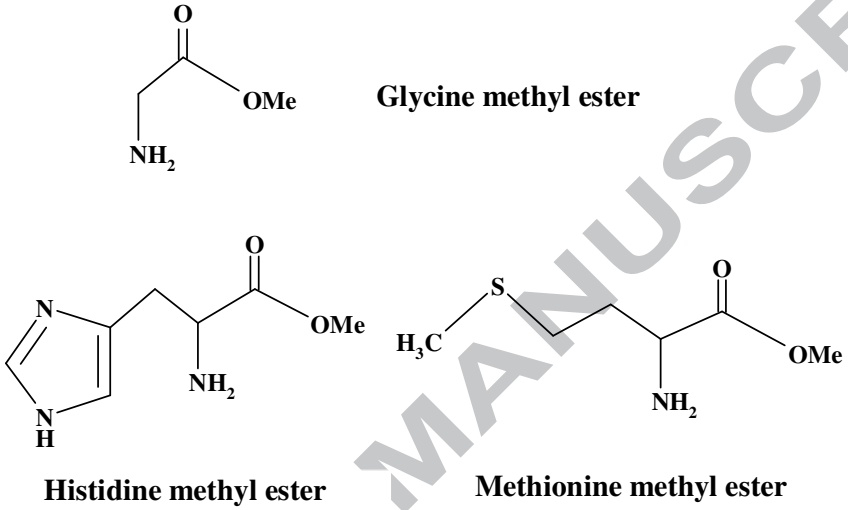
2. Experimental

2.1 Materials and reagents

All reagents were of analytical grade. K_2PdCl_4 and N-ethylethylenediamine were provided by Aldrich. The glycine-, histidine-, and methionine-methyl esters, Scheme 1, were purchased from Fluka. Carbonate-free NaOH was prepared and standardized against potassium hydrogen phthalate solution. All solutions were prepared in de-ionized water.



Scheme 1. Structural formula of the amino acid esters investigated

2.2 Apparatus and measuring techniques

$Pd(Eten)Cl_2$ was prepared following a procedure described for similar complexes [15]. K_2PdCl_4 (2.82 mmol) is dissolved in 10 ml water with stirring. The clear solution of $[PdCl_4]^{2-}$ was filtered and N-ethylethylenediamine (2.82 mmol) dissolved in 10 ml H_2O, was added drop wise to the stirred solution. The pH was adjusted to 2-3 by the addition of HCl and/or NaOH. A yellowish-brown precipitate of $Pd(Eten)Cl_2$ was formed and stirred for a further 30 min at 50 °C. After filtering off the precipitate, it was thoroughly washed with water, ethanol and diethyl ether. An orange crystalline precipitate was obtained; yield 92%. Anal. Calc. for $C_4H_{12}N_2PdCl_2$ (F.wt = 265.48), Anal. Found: C, 18.04; H, 5.40; N, 10.29. Calc.: C, 18.08; H, 4.52; N, 10.55 %.)

Aqueous solutions of the diaqua form of the $Pd(Eten)Cl_2$ complex were prepared *in situ* by the addition of slightly less than two mole equivalents of $AgNO_3$ to a solution of a known amount of the dichloro complex and stirred overnight. The white

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precipitate of AgCl that formed was filtered off using a 0.1 μm pore membrane filter. Great care was taken to ensure that the resulting solution was free of Ag^+ ion 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.).

2.3. Kinetic measurements

The kinetics of the hydrolysis process was monitored using a Metrohm 751 Titrino operated in the SET mode (titration to a pre-set end point). The titroprocessor and electrode were calibrated with standard buffer solutions according to NIST [21]. Hydrolysis kinetics of glycine-, methionine-, and histidine-methyl esters in the presence of $[Pd(Eten)(H_2O)_2]^{2+}$ was investigated by pH-stat technique [22,23]. After equilibrating a solution mixture (40 cm^3) containing $[Pd(Eten)(H_2O)_2]^{2+}$ (2.5 x 10^{-3}M), ester (2.5 x 10^{-3}M) and $NaNO_3$ (0.1 M) at the required temperature under nitrogen flow, the pH was brought to the desired value by the addition of 0.05 M NaOH solution. The hydrolysis was then followed by the automatic addition of 0.05 M NaOH solution to maintain the given pH. The data fitting was performed with the OLIS KINFIT set of programs [24] as described previously [25]. The precision of the kinetic data was estimated from plots as obtained from the OLIS program output. The accepted residual values are less than 10^{-2}. 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 [26]. For the variable temperature studies, the following values of pK_w and γ were employed [27], at 15 ^oC ($pK_w = 14.35$, $\gamma = 0.776$), at 20 ^oC ($pK_w = 14.16$, $\gamma = 0.774$), at 25 ^oC ($pK_w = 14.00$, $\gamma = 0.772$), at 30 ^oC ($pK_w = 13.83$, $\gamma = 0.770$) and at 35 ^oC ($pK_w = 13.68$, $\gamma = 0.768$).

2.4 DFT calculations

The density functional theory was applied to calculate the optimized geometries using the Gaussian09 program [28]. A full optimization of all complexes and ligands geometries were obtained at the B3LYP (Becke's three-parameter exchange functional, in combination with Lee-Yang-Parr correlation function) [29-30] level of theory using the LANL2DZ (Los Alamos National Laboratory 2 double-zeta) [31-34] basis set.

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This basis set has been widely used along with density functional methods for studies of transition metals complexes.

The GaussView 5.0 by Gaussian Inc. program was used for inspecting the input and output files generated by Gaussian09, for pre-processing, structure modification, and post-processing analyses of structures, frequencies, and forces. To identify the most stable structures (the minima), a frequency analysis was performed for each stationary point. These analyses were performed to ensure that all minima had no imaginary frequencies in the vibrational mode calculations.

3. Results and Discussion

α-Amino acid esters react with $[Pd(Eten)(H_2O)_2]^{2+}$ according to reaction (1). The equilibrium constant (K_f) is sufficiently large that when pH is higher than 4.5 for a 2:1 ratio of palladium complex to amino acid ester, formation of the mixed-ligand complex is complete. The resulting mixed-ligand complexes $[Pd(Eten)L]^{2+}$ [L = $NH_2CH(R)CO_2R`$] undergo hydrolysis by water and hydroxide ion according to reactions (2) and (3),

$$[Pd(Eten)(H_2O)_2]^{2+} + NH_2CH(R)CO_2R' \rightleftharpoons [Pd(Eten)(NH_2CH(R)CO_2R')]^{2+} + 2H_2O \quad (1)$$

$$[Pd(Eten)(NH_2CH(R)CO_2R')]^{2+} + H_2O \xrightarrow{k_o} [Pd(Eten)(NH_2CH(R)CO_2)]^{+} + R'OH + H^{+} \quad (2)$$

$$[Pd(Eten)(NH_2CH(R)CO_2R')]^{2+} + OH^{-} \xrightarrow{k_{OH}} [Pd(Eten)(NH_2CH(R)CO_2)]^{+} + R'OH \quad (3)$$

The kinetic data, the volume of base added to keep the pH constant versus time, could be fitted by a single exponential function. Various other kinetic models were tested without leading to satisfying fits of the data. The values of k_{obs} (the observed first-order rate constant at constant pH) were obtained. Plots of k_{obs} versus the hydroxide ion concentration were linear with a positive intercept, Figure 1. The rate expression is therefore of the form given in Eqs. (4) and (5).

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

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

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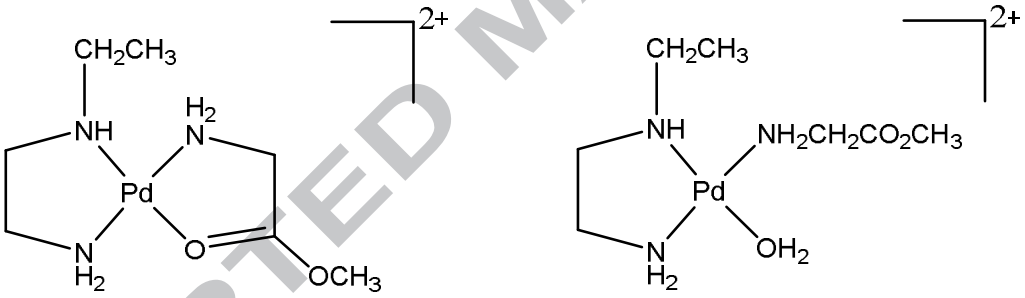
The term k_o arises due to water attack on the mixed-ligand complex. Values of $k_{H2O} = k_o/55.5$, where 55.5 mol dm^{-3} is the molar concentration of water, were determined from the intercept, and values of $k_{OH} = (k_{obs} - k_o)/[OH]$ from the slopes of the plots. The observed rate constants are given in Table 1.

The hydrolysis of the coordinated glycine methyl ester was monitored in the lower pH range (4-5), where the ester group is coordinated and the hydrolysis is activated. The linear dependence of k_{obs} on the OH^- concentration is consistent with the direct attack of OH^- ion on the coordinated ester carbonyl group. The rate acceleration denoted by the catalysis ratio ($C = k_{OH}/k_{OH}^{free\ ester}$) was calculated, see Table 2, and found to be 2.8×10^5 for the glycine methyl ester. Rate acceleration of this magnitude is fully consistent with the formation of mixed–ligand complex where there is a direct interaction between Pd(II) and the carbonyl group of the ester [15,20] as in structure **I** and not structure **II**, where the carbonyl group is not involved in chelation (see below).



(I) **(II)**

The formation of the bidentate ester complexes as in **I**, with both copper(II) and cobalt(II), led to rate accelerations of 10^5 - 10^6 [35,36], and the situation with palladium(II) appears to be similar. The base hydrolysis of coordinated histidine- and methionine-methyl esters was studied in a relatively high pH range 9-10. This is because the ester group is not coordinated and hence the hydrolysis is not activated as in the case of the glycine methyl ester. Throughout this pH range the reaction shows a first-order dependence on the hydroxide ion concentration. The relative catalysis ratio (C) observed with L-methylmethionate (L-MethOMe) [$k_{OH}/k_{OH}^{free\ ester} = 52.47$] and

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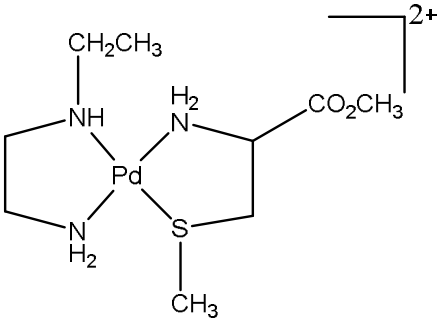
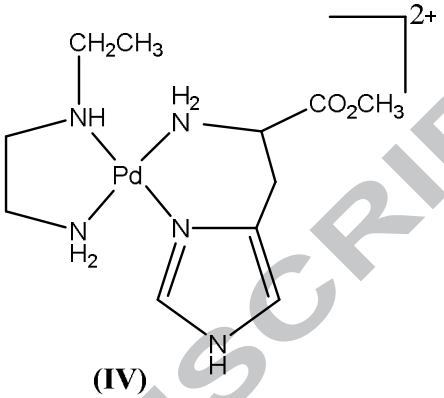
methyl-L-histidinate (L-HisOMe) [$k_{OH}/k_{OH}^{free\ ester}$ = 15.43], Table 2, suggests that in these cases the alkoxycarbonyl group is not bound to the metal ion.



(III)



(IV)

The L-MethOMe complex is expected to have the structure (**III**)**,** in which the donor atoms are thiolato-sulphur and the α-amino group. A similar situation (**IV**) is likely for L-hisOMe, where the α-amino group and the pyridine nitrogen of the imidazole ring act as donors. Previous studies have shown that the formation of such complexes with non-bonded or pendant ester groups leads to only relatively low catalytic effects [37,38].

The relative catalysis ratio at 25 °C for the base hydrolysis of the glycine methyl ester incorporated in $[Pd(Et_4en)L]^{2+}$ is 2.25 x 10^4 [39]. The corresponding value for $[Pd(Eten)L]^{2+}$ (2.8 x 10^5) is significantly higher. This can be accounted for on the premise that the steric interaction associated with the four ethyl substituents on the $[Pd(Et_4en)L]^{2+}$ complex with the entering amino acid esters will decrease the efficient binding to the Pd(II) centre. In addition, the electrophilicity of the Pd(II) centre is expected to be lower for the Et_4en complex and controls the donor-acceptor interaction between the ester and the Pd(II) ion. The complex that binds the ester more tightly will withdraw more electron density from the ester making it more susceptible to OH^- attack. This will lead to a higher catalytic effect as expressed by C.

Effect of temperature on the hydrolysis of coordinated glycine methyl ester

The activation parameters ($\Delta H^{\#}$ and $\Delta S^{\#}$) were determined for the hydrolysis of the coordinated glycine methyl ester from the temperature dependence of the rate

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constants in Table 3. The activation parameters were obtained using the Eyring plot of ($\ln k_{OH}$/T) versus 1/T, Figure 2, from which the values $\Delta H^{\#}$ = 16.1 ± 0.9 kJ mol^{-1} and $\Delta S^{\#}$ = -85 ± 3 J K^{-1} mol^{-1} were calculated. For the base hydrolysis of free glycine methyl ester the activation parameters were found [23] to be $\Delta H^{\#}$= 39.7 kJ mol^{-1} and $\Delta S^{\#}$ = -117 J K^{-1} mol^{-1}. The enhanced rate for base hydrolysis of the ester incorporated in the complex $[Pd(Eten)L]^{2+}$ is therefore due to a significant lowering of the activation enthalpy and an increase in the activation entropy. This suggests desolvation between the ground and transition states and is indicative of a mechanism involving nucleophilic attack by external OH^- on the coordinated ester group.

Effect of solvent on hydrolysis of the coordinated glycine methyl ester

It is known that solutions in biochemical microenvironments such as active sites of enzymes and side chains in proteins have dielectric constants of 30-50 [40-42]. It was suggested that these properties approximately correspond to those existing in water-dioxane mixtures. Consequently, studies on amino acid ester hydrolysis in water-dioxane mixtures are of biological significance. In order to examine the effect of an organic solvent on the hydrolysis of the 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 k_{OH} and $k_{OH}^{\text{free ester}}$ increase with increasing concentration of dioxane, see Table 4. This can be accounted for on the basis that as the dioxane content increases, the dielectric constant of the solution medium decreases. This will favour the interaction of the negatively charged OH^- ion with the electropositive carbonyl carbon atom of the ester. Consequently the hydrolysis will proceed faster.

The hydrolysis of the free glycine methyl ester is governed by two factors. The first is the decrease in the rate constant $k_{OH}^{\text{free ester}}$ in going from pure water as a solvent ($k_{OH}^{\text{free ester}}$ = 1.28 dm^3 mol^{-1} s^{-1}) to dioxane-water solution ($k_{OH}^{\text{free ester}}$ = 0.092 dm^3 mol^{-1} s^{-1} for 12.5% dioxane-water solution). This is explained on the basis that the non-polar solvent such as dioxane will suppress the polarization of the carbonyl group and consequently will decrease the interaction of OH^- with the carbonyl carbon atom of the ester. The second factor is associated with the increase in $k_{OH}^{\text{free ester}}$ on increasing the dioxane content (Table 4). This can be explained on the assumption that the non-polar dioxane will increase the interaction between the negatively charged OH^- ion and the

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polarized carbonyl group carbon atom of the ester. However, upon coordination of the ester carbonyl group to Pd(II), the carbonyl group becomes more polarized and will be more susceptible to interact with the negatively charged OH^- ion. Then dioxane will enhance such interaction.

Geometry Optimization with DFT method

The optimized molecular structure of the amino acid ester and its $Pd(Eten)^{2+}$ complex before and after hydrolysis are shown in Figure 3. The optimized molecular geometry, bond lengths, bond angles and atomic charge, Table 5, were evaluated. The electronic energies and dipole moment of the amino acid esters as well as the complexes are given in Table 6. The dipole moments of the complexes after hydrolysis are significantly higher than those of the free amino acid esters and their complexes before hydrolysis. This indicates that the complexes are more polarized than the other species. The energies of the HOMO and LUMO orbitals of the amino acid esters and the complexes are stable. The energy gap $\Delta E(E_{HOMO} - E_{LUMO})$, is an important stability index that helps to characterize the chemical reactivity and kinetic stability of the molecule [43]. A molecule with a small gap is more polarized and is known as soft molecule. The results indicate that the gap for the complexes after hydrolysis is smaller than those for the complexes before hydrolysis and free ester. This indicates that the complexes after hydrolysis are more polarized. The optimised bond lengths, bond angles and atomic charges of the amino acid esters and their complexes are reported below.

Glycine methyl ester

The Pd-NH_2 bond length for the complex before and after hydrolysis is of the same order. The Pd-O bond formed between the Pd(II) ion and amino acetate (after hydrolysis) is shorter than the Pd-O(ester) (before hydrolysis). This is due to the stronger electrostatic interaction between the Pd(II) ion and the negatively charged oxygen atom of the amino acetate than between the Pd(II) ion and the neutral carbonyl oxygen atom of the ester. The angle around the Pd(II) ion with O and N atoms of the ester after hydrolysis is 82.62. This bond angle is in agreement with that found for the Pd(phenanthroline)-glycine system (83.02) [44].

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The calculation of atomic charge is an important parameter in the application of quantum mechanical calculations used to describe the electronic characteristics of the molecular system [45-47]. The charge densities found on the carbonyl carbon atom of the ester before and after binding to $Pd(Eten)^{2+}$ are 0.293 and 0.482, respectively. The increase in charge density after binding will facilitate the interaction of the negatively charged OH^- ion with the ester carbonyl carbon atom. Consequently the hydrolysis will proceed faster. This is in agreement with the high catalysis ratio found for the $Pd(Eten)(glycine\ methyl\ ester)^{2+}$ complex.

Methionine methyl ester

The Pd–NH_2 and Pd–SCH_3 bond lengths are 2.11 and 2.45 Å for the complex before hydrolysis, respectively. The same bond lengths are 2.104 and 2.45 Å for the complex after hydrolysis. The Pd–SCH_3 bond is longer than that of Pd – NH_2. This is due to the fact that the Pd–NH_2 bond is more stable than the Pd–SCH_3 bond. The bond angle S–Pd–N for the complexes before and after hydrolysis are of the same order. The charge density on the carbonyl carbon atom of the methionine methyl ester increased from 0.306 (before coordination) to 0.328 (after coordination). The very slight increase in charge density suggests that the carbonyl group is not involved in complex formation and consequently not subjected to polarization. This is in line with the low catalytic ratio found for the $[Pd(Eten)(methionine\ methyl\ ester)]^{2+}$.

Histidine methyl ester

The coordination bonds formed between Pd(II) and the imidazole nitrogen and amino nitrogen atoms are 2.046 and 2.112 Å, respectively, for the complex before hydrolysis. The corresponding bond lengths are 2.043 and 2.063 Å, respectively, for the complex after hydrolysis. The Pd–imidazole nitrogen bond is shorter than the Pd–amino nitrogen bond. This is due to the back donation of the aromatic imidazole group [48]. The bond angle for the imidazole (N)–Pd–amino(N) are of the same order as that found for the methionine complex. The charge densities on the carbonyl carbon atom are 0.299 and 0.291 for the free and coordinated histidine methyl ester, respectively. The charge density did not change significantly upon coordination. This is due to no participation of the carbonyl group in coordination with the Pd(II) ion. It is interesting to find that the charge density on the carbonyl carbon atom of the histidine methyl

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ester after coordination is lower than that of methionine methyl ester. This is in agreement with the observation that the hydrolysis rate constant for the coordinated histidine methyl ester (9.58), is lower than that of the coordinated methionine methyl ester (40.40) in Table 2.

Calculated Infrared Spectra of Ligands and Complexes

In the absence of experimental IR spectra, we explored the calculated IR spectra of the complexes before and after hydrolysis from a theoretical point of view. The calculated IR spectra of the free ligands and the complexes before and after hydrolysis are shown in Figures 4 and 5, respectively. No imaginary vibrational frequencies were observed in all calculated spectra of the ligands and complexes. The assignments of the calculated vibrational frequencies of the free ligands and their complexes are listed in Table 7. The theoretical assignments were obtained by visualization of the normal mode displacement vectors utilizing the GaussView program. The assignments listed in Table 7 are only for the vibrational modes of the amino, sulphide and carboxylate group vibrations, since they are most sensitive to changes in the metal-nitrogen, metal-sulphur and metal-oxygen interactions, which are also the coordination sites. Furthermore, we also identified the Pd-N, Pd-O and Pd-S stretching vibrations.

In the spectra of the methionine methyl ester and methionine methyl ester complexes, the $\nu(S-CH_3)$ vibration mode is shifted to lower frequency in comparison with that found in the uncoordinated methionine methyl ester ligand (Table 7). Also in the spectrum of the glycine methyl ester complex, the $\nu(C=O)$ vibration mode is shifted with 116 cm^{-1} to lower frequency in comparison with that found in the uncoordinated glycine methyl ester ligand. This decrease in the $\nu(S-CH_3)$ and $\nu(C=O)$ vibration modes is related to the fact that the sulphur and oxygen atoms that are involved in these vibrations, participate in coordination to the Pd atom in the complexes. In the glycine complex, the coordination with the oxygen atom of the carbonyl group is absent and the $\nu(C=O)$ vibration mode appears at 1702 cm^{-1}, which is very close to that of the glycine methyl ester ligand (1696 cm^{-1}). All calculated Pd-N, Pd-O and Pd-S stretching vibrations of the complexes appear in the range of those reported for related complexes [49-53].

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4. CONCLUSIONS

The hydrolysis of the glycine methyl ester is catalysed by the $[Pd(Eten)(H_2O)_2]^{2+}$ complex with a catalysis ratio of $C = 2.80 \times 10^5$. The catalytic effect is due to a direct interaction between Pd(II) and the alkoxycarbonyl group of the ester species. However, the hydrolysis of the histidine- and methionine-methyl esters is not significantly catalysed. The relative small catalysis-ratio values suggest that in these cases the alkoxycarbonyl group is not bound to the metal ion. The activation parameters for the hydrolysis of coordinated glycine methyl ester were determined. The effect of solvent on the hydrolysis of the ester shows that as the dielectric constant of the medium decreases (by increasing the dioxane content) the hydrolysis of the ester is more favoured. This is interesting from a biological point of view since solutions in a biochemical micro-environment have dielectric constant values of 30-50, compared to the dielectric constant for water of 76.

The optimized molecular structures of the amino acid esters and their $Pd(Eten)^{2+}$ complexes before and after hydrolysis were investigated. The electronic energies and dipole moments of the complexes were calculated. The reported DFT data support the kinetic findings.

REFERENCES

[1] H. Kroll, J. Am. Chem. Soc., 74 (1952) 2036.

[2] H.R. Mahler, E.H. Cordes, *Biological Chemistry*, Harper and Row, New York, N.Y. 1966.

[3] M. J. Pesando, Biochemistry, 14 (1975) 681.

[4] T. Zenchenko, V. Morozov, Protein Sci., 4 (1995) 251.

[5] L. Zhang, R. Buchet, G. Azzar, Biochem. Biophys. Res. Commun., 328 (2005) 591.

[6] B. L. Vallee, D. S. Auld, Biochemistry, 29 (1990) 5647.

[7] D. W. Christianson, W. N. Lipscomb, Acc. Chem. Res., 22 (1989) 62.

[8] J. M. Harrowfield, V. Morris, A. M. Sargeson, J. Am. Chem. Soc., 98 (1976) 7282.

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[9] J. E. Coleman, J. F. Chlebowski in L.G. Marzilli (Eds) *Advances in Inorganic Chemistry,* Elsevier, New York, vol. 1, 1979.

[10] R. Jairam, M. L. Lau, J. Adorante, P. G. Potvin, J. Inorg. Biochem., 84 (2001) 113.

[11] X. Kou, X. Meng, J. Xie, Z. Zeng, Transition Met. Chem., 28 (2003) 777.

[12] J. Xia, S. Li, Y. Shi, K. Yu, W. Tong, J. Chem. Soc., Dalton Trans., 2109 (2001).

[13] X. Su, H. Sun, Z. Zhou, H. Lin, L. Chen, S. Zhu, Y. Chen, Polyhedron, 20 (2001) 91.

[14] M. R. Shehata, M. M. Shoukry, F. M. H. Nasr, R. van Eldik, Dalton Trans., 779 (2008).

[15] M. R. Shehata, M. M. Shoukry, F. H. Abdel-Shakour, R. van Eldik, Eur. J. Inorg. Chem., 3912 (2009).

[16] M. M. A. Mohamed, A. A. Shoukry, M. M. Shoukry, Int. J. Chem. Kinet., 38 (2006) 737.

[17] M. A. Mohamed, M. M. Shoukry, Polyhedron, 21 (2002) 167.

[18] A. A. El-Sherif, M. M. Shoukry, Inorg. Chim. Acta, 360 (2007) 473.

[19] M. M. Shoukry, E. M. Khairy, A. Saeed, Transition Metal Chem., 12 (1987) 315.

[20] R.W. Hay, P. Banerjee, J. Chem. Soc. Dalton. Trans., 362 (1981).

[21] R. G. Bates, *Determination of pH - Theory and Practice*, Wiley-Interscience, New York, USA, 2nd Edition, 1975.

[22] R.W. Hay, A.K. Basak, J. Chem. Soc. Dalton. Trans., 1819 (1982).

[23] R.W. Hay, P.J. Morris, in *"Metal Ions in Biological Systems"*, Ed., H. Sigel, Marcel Dekker, New York, Vol. 5, 1976.

[24] OLIS KIFET, Olis Inc., Borgart GA, 1993.

[25] A. Mijatović, R. Jelić, J. Bogojeski, Ž. D. Bugarčić , B. Petrović, Monatsh. Chem., 144 (2013) 1489.

[26] C. W. Davis, *Ion Association*, Butterworths, London, 1962.

[27] R. A. Robinson, R. H. Stokes, *Electrolyte Solutions,* Butterworths, London 2nd Edition, 1979.

[28] M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J.

ACCEPTED MANUSCRIPT

Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dap prich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, (2009).

[29] C. Lee, W. Yang, R. G. Parr, Phys. Rev. B., 37 (1988) 785.

[30] A. D. Becke, J. Chem. Phys., 98 (1993) 5648.

[31] A. D. Becke, J. Chem. Phys., 104 (1996) 1040.

[32] P. J. Hay, W. R. Wadt, J. Chem. Phys., 82 (1985) 270.

[33] W. R. Wadt, P. J. Hay, J. Chem. Phys., 82 (1985) 284.

[34] P. J. Hay, W. R. Wadt, J. Chem. Phys., 82 (1985) 299.

[35] P. A. Sutlon, D. A. Buckingham, Acc. Chem. Res., 20 (1987) 357.

[36] R. Angelici, D. Hopgood, J. Am. Chem. Soc., 90 (1968) 2514; B. E. Leach, R. Angelici, Inorg. Chem., 8 (1969) 907; H. Charaborty, M. L. Rahman, Transition Met. Chem., 18 (1993) 545; M. R. Shehata, M. M. Shoukry, F. M. H. Nasr, R. van Eldik, Dalton Trans., 779 (2008).

[37] M. M. Shoukry, E. M. Khairy, A. A. El-Sherif, Transition Met. Chem., 27 (2002) 656.

[38] M. M. A. Mohamed, M. M. Shoukry, Polyhedron, 21 (2002) 167.

[39] M. M. Shoukry, A. Al-Najjar, A. K. Abdel Hadi, A. E. Mahgoub, P. A. Khalf Alla, J. Coord. Chem., 63 (2010) 2498.

[40] D. O. Rees, J. Mol. Biol., 141 (1980) 323.

[41] N. K. Rogers, G. R. Roore, M. J. E. Strenberg, J. Mol. Biol., 182 (1985) 613.

[42] H. Sigel, R. B. Martin, R. Tribolet, U. K. Haring, R. Malini-Balakrishran, Eur. J. Biochem., 152 (1985) 187.

[43] V. P. Singh, M. Mishra, K. Tiwari, Inorg. Chim. Acta, 398 (2013) 89.

[44] M. Yodoshi, N. Okabe, Chem. Pharm. Bull., 56 (2008) 908.

[45] C. R. Bhattacharjee, P. Goswami, P. Mondal, J. Coord. Chem., 63 (2010) 2002.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

[46] A. Akbari, M. Ahmadi, R. Takjoo, F.W. Heinemann, J. Coord. Chem., 65 (2012) 4115.

[47] M. Landman, R. Fraser, L. Twigge, J. Conradie, J. Coord. Chem., 68 (2015) 2388.

[48] N. T. Abdel Ghani, A. M. Mansour, Inorg. Chim. Acta 273 (2011) 249.

[49] G. W. Watt, D. S. Klett., Inorg. Chem., 5 (1966) 1278.

[50] R. llavarasi, M. N. S. Rao, M. R. Udupa, Indian J. Chem., 38A (1999) 161.

[51] N. Trendafilova, I. Georgieva, Vib. Spectrosc., 20 (1999) 133.

[52] R. A. Condrate, K. Nakamoto, J. Chem. Phys., 42 (1965) 2590.

[53] K. Misra, G. K. Ghosh, I. Mitra, S. Mukherjee, V. P. Reddy, W. Linert, B. Misini, J. C. Bose, S. Mukhopadhyay, S. C. Moi , RSC Adv., 5 (2015) 12454.

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Table 1. Kinetics of hydrolysis of coordinated amino acid esters $[Pd(Eten)(ester)]^{2+}$ in aqueous solution as function of pH at 25 °C.

System	***pH***	$10^{10}[OH^-]$ *mol dm^{-3}*	k_{obs} s^{-1}
Glycine methyl ester	4.2	1.58	3.62E-4
	4.4	2.51	3.84E-4
	4.6	3.98	4.25E-4
	4.8	6.31	5.12E-4
	5.0	10.00	6.60E-4
Methionine methyl ester	8.6	4.00E-6	3.84E-4
	8.8	6.30E-6	5.08E-4
	9.0	1.00E-5	6.99E-4
	9.2	1.58E-5	9.02E-4
	9.4	2.51E-5	12.60E-4
Histidine methyl ester	9.0	1.00E-5	3.36E-4
	9.2	1.58E-5	4.20E-4
	9.4	2.51E-5	5.06E-4
	9.6	3.98E-5	6.28E-4
	9.8	6.31E-5	8.60E-4

Table 2. Rate constants for base hydrolysis of amino acid esters and their Pd(Eten) complexes at 25 °C in aqueous solution.

System	k_{OH} $dm^3\,mol^{-1}\,s^{-1}$	$10^4 k_o$, s^{-1}	$k_{OH}^{(free\ ester)\,a}$ $dm^3\,mol^{-1}\,s^{-1}$	**C**
Glycine methyl ester	$(3.6 \pm 0.2) \times 10^5$	2.9 ± 0.1	1.28	2.80×10^5
Methionine methyl ester	41 ± 2	2.5 ± 0.3	0.77	53
Histidine methyl ester	9.3 ± 0.2	2.69 ± 0.06	0.62	15

[a] Data from ref. [30].

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

Temp. ***°C***	$10^{-5} k_{OH}$ $dm^3 mol^{-1} s^{-1}$	$10^4 k_o$ s^{-1}
15	2.7 ± 0.1	2.05 ± 0.03
20	3.2 ± 0.2	2.21 ± 0.06
25	3.6 ± 0.2	2.9 ± 0.1
30	4.0 ± 0.2	3.1 ± 0.2
35	4.5 ± 0.2	4.2 ± 0.2

Table 4. Rate constants for base hydrolysis of free and coordinated glycine methyl ester in dioxane-water solution of different compositions at 25 °C.

% Dioxane	$10^{-6} k_{OH}$ $dm^3 mol^{-1} s^{-1}$	$10^4 k_o$ s^{-1}	$10^2 k_{OH}^{(free\ ester)}$ $dm^3 mol^{-1} s^{-1}$
12.5	0.63 ± 0.04	2.5 ± 0.1	9.2 ± 0.6
25.0	1.54 ± 0.06	2.34 ± 0.06	24 ± 1
37.5	3.7 ± 0.2	2.27 ± 0.06	56 ± 3

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Table 5. Selected bond lengths (Å), bond angles and Mulliken atomic charges of the optimized structures according to B3LYP/LanL2DZ level.

Glycine methyl ester complex (Before hydrolysis)				
Bond Length (Å)		Bond angles (°)		Charges
Pd(1)-N(19)	2.13	N(4)-Pd(1)-N(2)	84.1	Pd(1)= 0.46
Pd(1)-O(26)	2.07	N(19)-Pd(1)-N(2)	101.6	N(2)= -0.44
Pd(1)-N(4)	2.08	O(26)-Pd(1)-N(4)	93.6	N(4)= -0.65
Pd(1)-N(2)	2.09	N(19)-Pd(1)-O(26)	80.8	N(19)= -0.67
C(25)-O(26)	1.28	C(25)-C(23)-N(19)	109.7	C(23)= -0.41
N(19)-C(23)	1.52	O(26)-C(25)-C(23)	120.7	C(25)= 0.48
C(23)-C(25)	1.52	C(25)-O(26)-Pd(1)	115.5	O(26)= -0.34
C(25)-O(27)	1.31	C(23)-N(19)-Pd(1)	110.0	O(27)= -0.22

Glycine complex (After hydrolysis)				
Bond Length (Å)		Bond angles (°)		Charges
Pd(1)-N(2)	2.15	N(2)-Pd(1)-N(19)	105.2	Pd(1)= 0.40
Pd(1)-N(19)	2.11	N(2)-Pd(1)-N(4)	83.9	N(2)= -0.44
Pd(1)-O(27)	1.99	N(19)-Pd(1)-O(27)	82.6	N(4)= -0.64
Pd(1)-N(4)	2.08	O(27)-Pd(1)-N(4)	88.2	N(19)= -0.66
C(25)-O(27)	1.36	C(25)-C(23)-N(19)	111.2	C(23)= -0.41
C(25)-O(26)	1.24	O(27)-C(25)-C(23)	114.4	C(25)= 0.31
N(19)-C(23)	1.52	C(23)-N(19)-Pd(1)	107.2	O(26)= -0.23
C(23)-C(25)	1.54	C(25)-O(27)-Pd(1)	117.6	O(27)= -0.40

Histidine methyl ester complex (Before hydrolysis)				
Bond Length (Å)		Bond angles (°)		Charges
Pd(1)-N(20)	2.12	N(20)-Pd(1)-N(2)	94.7	Pd(1)= 0.44
Pd(1)-N(2)	2.13	N(20)-Pd(1)-N(42)	87.7	N(4)= -0.65
Pd(1)-N(42)	2.05	N(2)-Pd(1)-N(4)	83.7	N(2)= -0.45
Pd(1)-N(4)	2.10	N(42)-Pd(1)-N(4)	93.9	N(42)= -0.33
N(20)-C(26)	1.52	C(23)-C(26)-N(20)	114.3	N(20)= -0.70
C(38)-N(42)	1.41	C(38)-N(42)-Pd(1)	121.2	C(28)= 0.29
N(20)-C(26)	1.52	C(26)-N(20)-Pd(1)	120.8	O(29)= -0.27
C(26)-C(28)	1.55	C(38)-C(23)-C(26)	112.2	O(30)= -0.29

Histidine complex (After hydrolysis)				
Bond Length (Å)		Bond angles (°)		Charges
Pd(1)-N(4)	2.13	N(4)-Pd(1)-N(2)	83.8	Pd(1)= 0.41
Pd(1)-N(2)	2.13	N(4)-Pd(1)-N(38)	94.2	N(4)= -0.65
Pd(1)-N(38)	2.04	N(2)-Pd(1)-N(20)	93.2	N(2)= -0.44
Pd(1)-N(20)	2.06	N(38)-Pd(1)-N(20)	88.8	N(38)= -0.32
N(20)-C(26)	1.52	C(23)-C(26)-N(20)	115.7	N(20)= -0.69
C(34)-N(38)	1.40	N(38)-C(34)-C(23)	121.2	C(28)= 0.21
C(23)-C(26)	1.54	C(34)-N(38)-Pd(1)	122.2	O(29)= -0.44
C(23)-C(34)	1.50	C(26)-N(20)-H(21)	109.9	O(30)= -0.34

Methionine methyl ester complex (Before hydrolysis)				
Bond Length (Å)		Bond angles (°)		Charges
Pd(1)-S(23)	2.45	S(23)-Pd(1)-N(20)	84.6	Pd(1)=0.26
Pd(1)-N(20)	2.12	S(23)-Pd(1)-N(4)	94.4	N(4)= -0.65
Pd(1)-N(2)	2.14	N(20)-Pd(1)-N(2)	97.1	N(2)= -0.44
Pd(1)-N(4)	2.10	N(2)-Pd(1)-N(4)	83.7	N(20)= -0.67
S(23)-C(24)	1.92	C(27)-C(24)-S(23)	109.8	S(23)= 0.33
N(20)-C(27)	1.51	C(24)-C(27)-N(20)	111.2	C(33)= 0.33
C(24)-C(27)	1.53	C(27)-N(20)-Pd(1)	112.2	O(34)= -0.28
C(27)-C(33)	1.55	C(24)-S(23)-Pd(1)	97.4	O(35)= -0.29

Methionine complex (After hydrolysis)				
Bond Length (Å)		Bond angles (°)		Charges
Pd(1)-S(23)	2.45	S(23)-Pd(1)-N(20)	83.8	Pd(1)=0.20
Pd(1)-N(20)	2.10	S(23)-Pd(1)-N(4)	93.6	N(4)= -0.64
Pd(1)-N(4)	2.10	N(20)-Pd(1)-N(2)	98.7	N(2)= -0.42
Pd(1)-N(2)	2.15	N(4)-Pd(1)-N(2)	83.4	N(20)= -0.65
S(23)-C(24)	1.93	C(27)-C(24)-S(23)	108.8	S(23)= 0.34
N(20)-C(27)	1.52	C(24)-C(27)-N(20)	111.5	C(33)= 0.24
C(24)-C(27)	1.52	C(27)-N(20)-Pd(1)	104.2	O(34)= -0.45
C(27)-C(33)	1.60	C(24)-S(23)-Pd(1)	95.9	O(35)= -0.33

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Table 6. Calculated energy properties of the amino acid ester complexes before and after hydrolysis according to B3LYP/LANL2DZ level of theory.

Complex	HOMO (eV)	LUMO (eV)	ΔE (E_{LUMO} -E_{HOMO}) (eV)	Total energy (a.u.)	Dipole moment (Debye)
Glycine methyl ester complex (before hydrolysis)	-14.80	-10.16	4.64	-719.1	1.5595
Glycine complex (after hydrolysis)	-10.08	-5.99	4.09	-679.5	10.8287
Histidine methyl ester complex (before hydrolysis)	-13.44	-9.01	4.43	-983.4	5.8756
Histidine complex (after hydrolysis)	-8.17	-5.68	2.49	-943.8	16.4949
Methionine methyl ester complex (before hydrolysis)	-14.20	-9.79	4.41	-807.8	4.4337
Methionine complex (after hydrolysis)	-8.85	-6.40	2.45	-768.2	11.2947

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Table 7. Calculated infrared absorption (cm^{-1}) data for the ligands and complexes.

Compounds	ν(Pd–O)	ν(Pd–N)	ν(Pd–S)	$\beta_{as}(NH_2)$	$\gamma_s(NH_2)$	ν(C–N)	ν(C=O)	$\beta_s(NH_2)$	ν(S−CH_3)
Glycine methyl ester	-	-	-	711	640	1157	1696	1704	-
Histidine methyl ester	-	-	-	751	656	1121	1685	1691	-
Methionine methyl ester	-	-	-	755	637	1119	1691	1680	671
Glycine methyl ester complex	421	520	-	744	667	1020	1580	1690	-
Glycine complex	449	516	-	750	670	1095	1702	1685	-
Histidine methyl ester complex	-	518	-	746	709	1079	1698	1651	-
Histidine complex	-	519	-	797	697	1090	1711	1692	-
Methionine methyl ester complex	-	546	305	753	704	1096	1685	1692	626
Methionine complex	-	541	320	751	700	1097	1656	1611	612

[a] Calculated value according to B3LYP/LANL2DZ level, ν_s: symmetric stretching, ν: stretching, γ_{as}: twisting, γ_s: wagging, β_s: scissoring, β_{as}: Rocking

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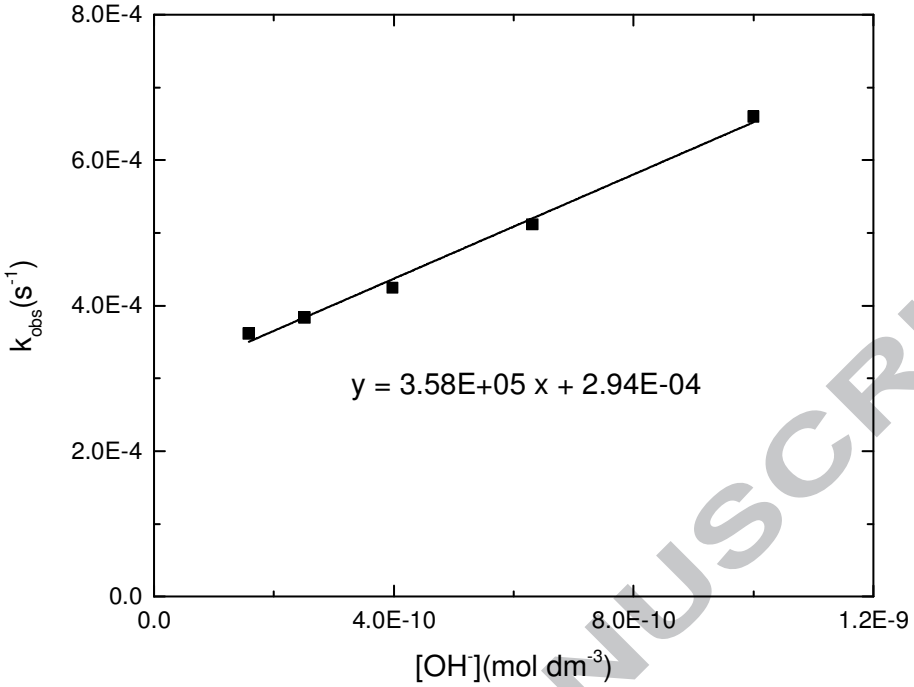

Figure 1. Plot of k_{obs} (s^{-1}) *vs.* [OH^-] (mol dm^{-3}) for the hydrolysis of coordinated glycine methyl ester at 25°C.

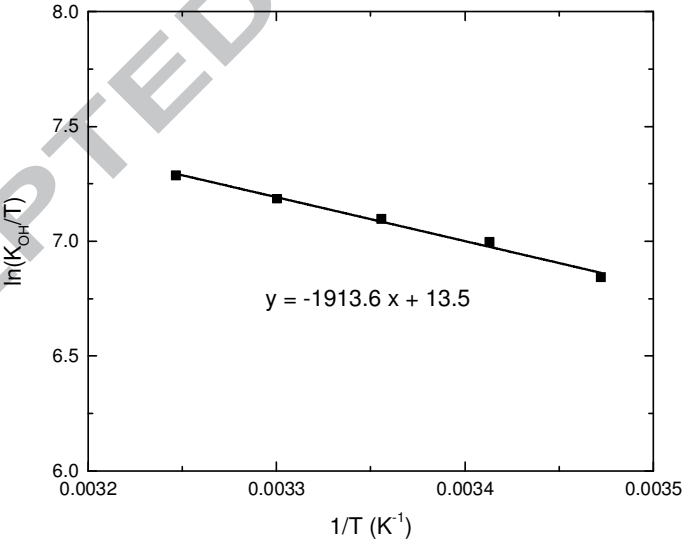

Figure 2. Plot of ln k_{OH}/T *vs.* 1/T for the hydrolysis of coordinated glycine methyl ester

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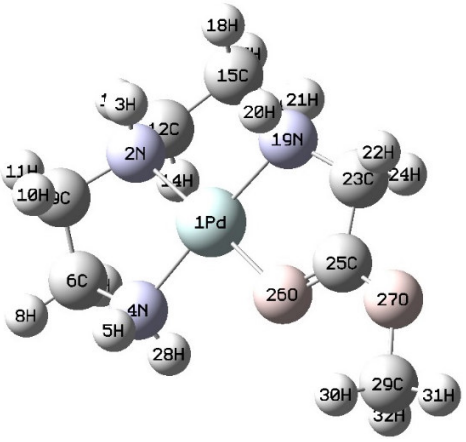
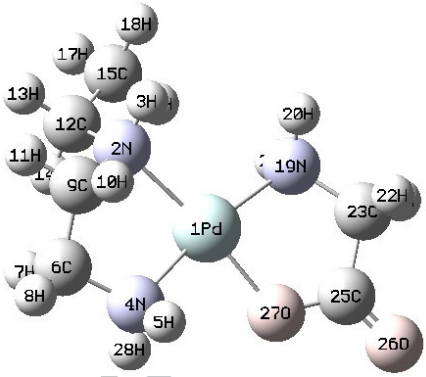
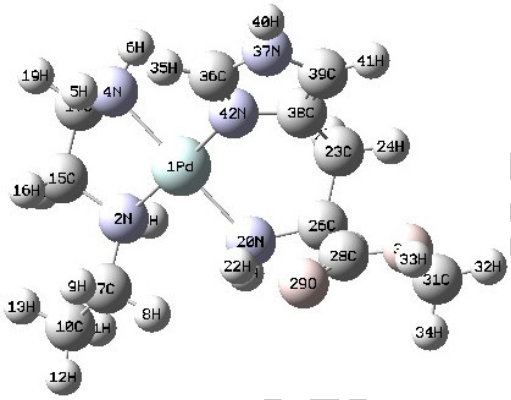
(a) Glycine methyl ester complex



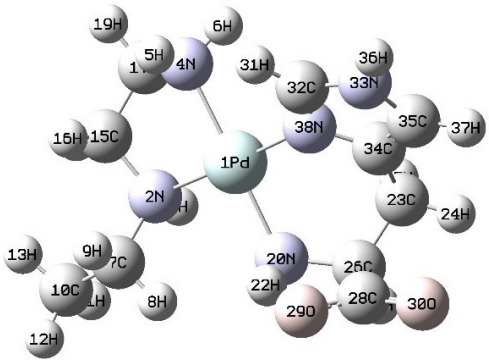
(a') Glycine complex



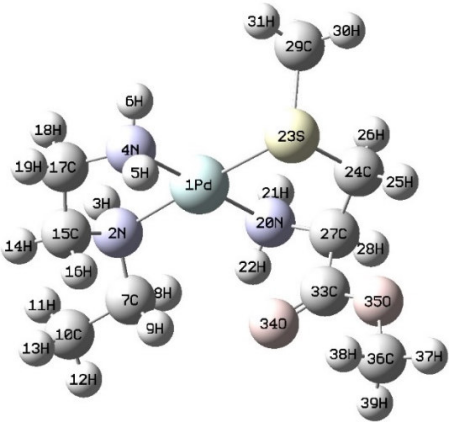
(b) Histidine methyl ester complex



(b') Histidine complex



(c) Methionine methyl ester complex



(c') Methionine complex

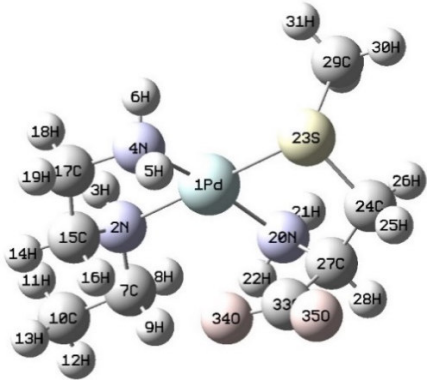


Figure 3. The optimized structure of the complexes before and after hydrolysis according to B3LYP/LANL2DZ level of theory.

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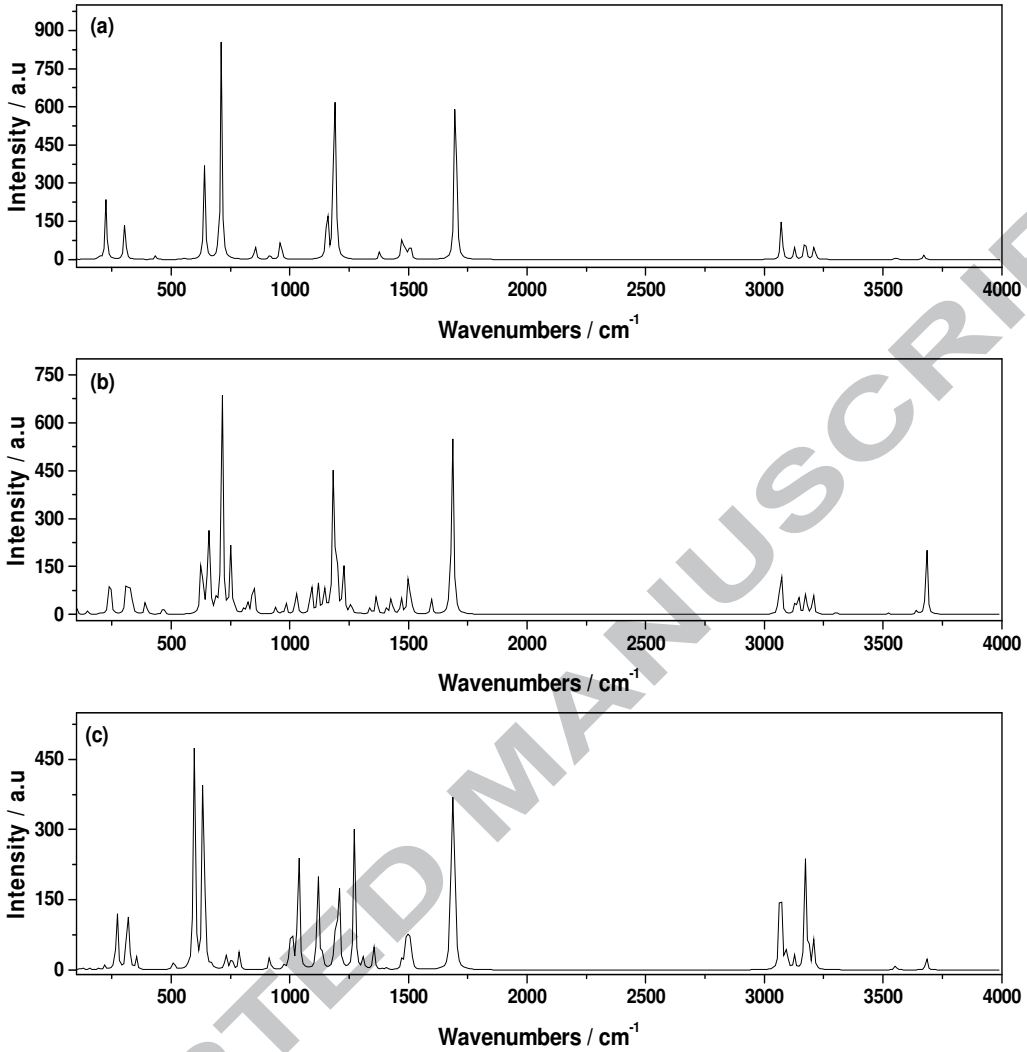

Figure 4. Calculated Infrared spectra of the (a) Glycine methyl ester, (b) Histidine methyl ester and (c) Methionine methyl ester according to B3LYP/LANL2DZ level of theory.

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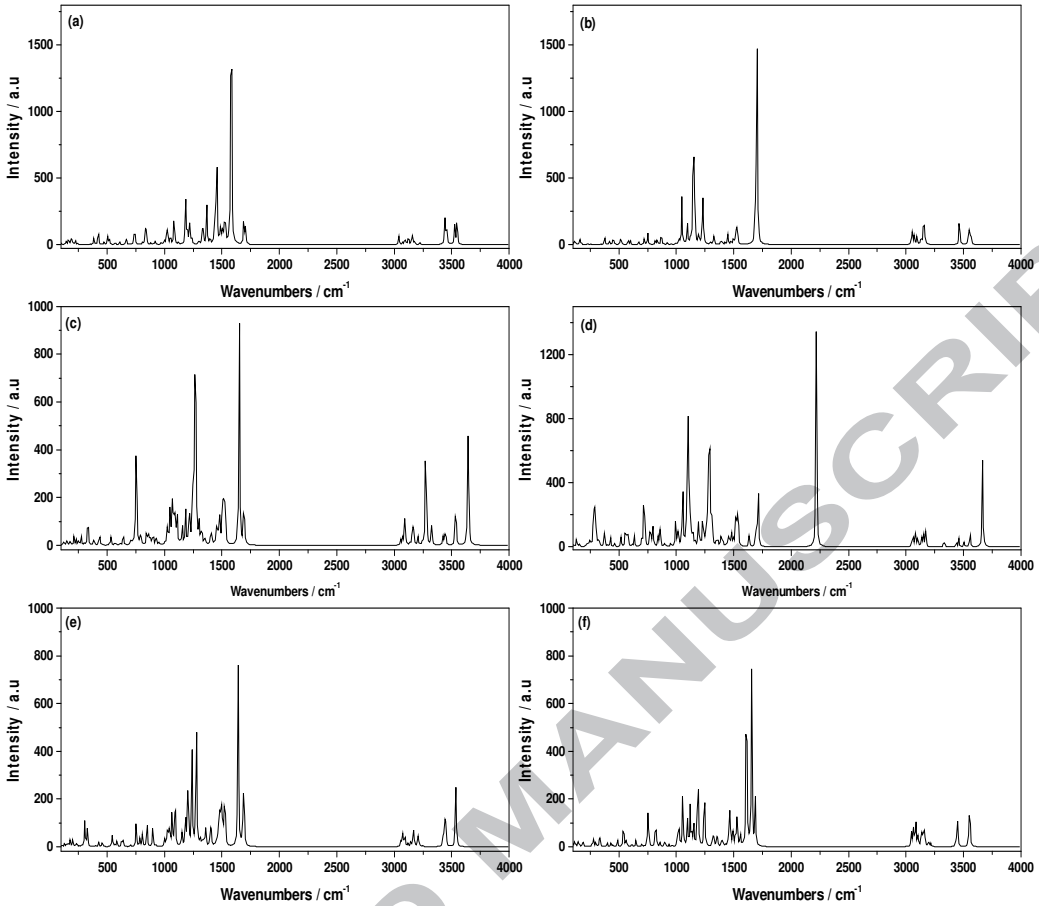

Figure 5. Calculated Infrared spectra of the (a) Glycine methyl ester complex, (b) Glycine complex, (c) Histidine methyl ester complex, (d) Histidine complex, (e) Methionine methyl ester complex and (f) Methionine complex according to B3LYP/LANL2DZ level of theory.

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Graphical Abstract

Base hydrolysis of α-amino acid esters catalysed by [Pd(N-ethylethylenediamine)(H_2O)$_2$]$^{2+}$. Kinetic study and DFT calculations

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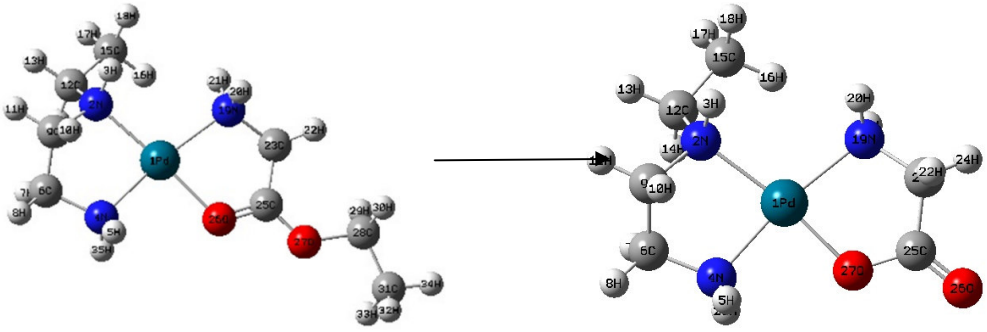

The hydrolysis of the glycine ethyl ester coordinated to Pd(Eten)$^{2+}$ was studied by pH-stat technique and occurs 3 x 10^5 times faster than the spontaneous hydrolysis of the ester.

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Highlights

Base hydrolysis of α-amino acid esters catalysed by [Pd(N-ethylethylenediamine)(H_2O)$_2$]$^{2+}$. Correlation between kinetic data and DFT calculations

Perihan A. Khalaf–Alla, Mohamed M. Shoukry, Abdel Aziz Jbara and Rudi van Eldik

1. The hydrolysis kinetics of glycine ethyl ester coordinated to Pd(Eten)$^{2+}$ was studied by pH-stat technique and occurs 3 x 10^5 times faster than the spontaneous hydrolysis of the ester.

2. Similar hydrolysis reactions for methionine methyl and histidine methyl esters also show a catalytic effect for coordination to Pd(Eten)$^{2+}$, but orders of magnitude less efficient.

3. The optimized molecular structures of the amino acid esters and their Pd(Eten)$^{2+}$ complexes before and after hydrolysis were investigated by DFT calculations. The electronic energies and dipole moments of the complexes were calculated and correlated with the kinetic data.

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