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Abstract

$Pd(AEMP)Cl_2$ (AEMP = 2-(2-aminoethyl)-1-methylpyrrolidine) was synthesized and characterized by spectral and thermal measurements.$[Pd(AEMP)(H_2O)_2]^{2+}$ reacts with amino acid esters (L) to form mixed ligand $[Pd(AEMP)L]^{2+}$ complexes. The kinetics of the base hydrolysis of $[Pd(AEMP)L]^{2+}$ was studied by a pH-stat technique and the corresponding rate constants are reported. The coordinated glycine methyl ester is hydrolyzed efficiently, whereas the coordinated methionine- and histidine- methyl esters undergo hydrolysis with a much lower catalytic activity. The catalytic effect is controlled by the mode of coordination of the ester to the Pd(II) complex. Possible mechanisms for these reactions are considered. Activation parameters were determined experimentally for the hydrolysis of the coordinated glycine

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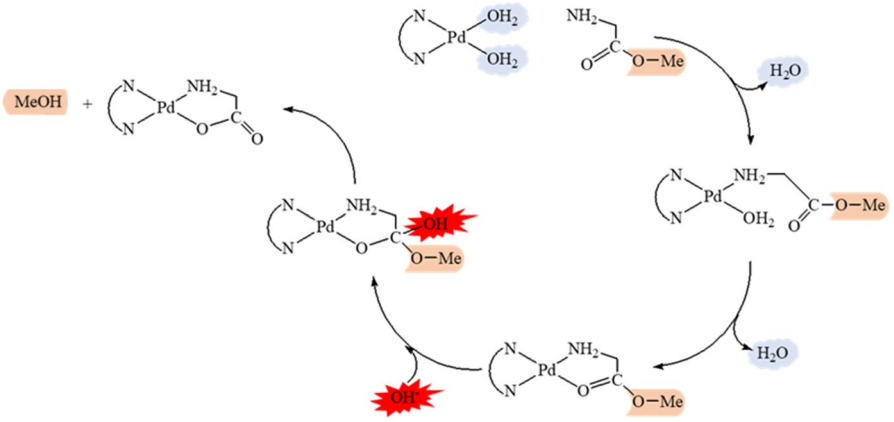
methyl ester. DFT calculations (B3LYP/def2svp) were applied to gain further insight into the possible mechanism of the base hydrolysis of the amino acid esters. The calculations are discussed in reference to the reported experimental data.

Graphic abstract



Keywords 2-(2-Aminoethyl)-1-methylpyrrolidine · Amino acid ester · Catalytic hydrolysis · Pd(II) · pH-stat technique · DFT calculations

Introduction

Metal ions incorporated in metalloenzymes such as carbonic anhydrase [1], carboxypeptidase A [2] and alkaline phosphatase [3], play a significant role in many biological processes [4]. Metal ions in the active site of metalloenzymes serve as catalytic center by bringing substrate and nucleophile together during formation of a coordination complex to activate the substrate carbonyl group and hence facilitate attack of the nucleophile in carboxypeptidase A [5]. Furthermore, the metal ion can activate the water molecule in the reversible hydration process of carbon dioxide involved in carbonic anhydrase [6], and activate the serine hydroxyl group in alkaline phosphatase [7]. In order to illustrate the mechanism by which the metalloenzyme may operate and consequently provide a theoretical base for designing highly effective artificial metalloenzymes, previous reports [8–11] have examined biomimetic models for metalloenzymes which catalyze the hydrolysis of carboxylic acid esters in biomimetic models for certain metalloenzymes, e.g. the metalloenzyme-substrate complex. Palladium(II) complexes are used as functional mimics of hydrolytic enzymes (hydrolases) and oxidoreductases [12]. Also, Pd(II) being a soft metal ion is expected to promote the hydrolysis of amino acid esters that have a soft donor sulfur atom as in the case of esters having the biologically active methionine moiety [13].

Pyrrolidines are known for their pharmacological activities such as antimicrobial [14–16], antitumor [17], anti-HIV-1 [18], anticonvulsant [19, 20], sphingosine-1-phosphate (S1P) receptor agonists [21, 22], malic enzyme inhibitors [23], ketoamide-based cathepsin K inhibitors [24], and human melanocortin-4 receptor agonists [25]. Pyrrolidine complexes may undergo catalytic hydrolysis of the ester group, existing as functional group in biological fluids. Work in our laboratory [26–31] has focused on catalysis of the hydrolysis of various amino acid esters by metal complexes. Based on the above, it is of considerable interest to study the catalysis of base hydrolysis of amino acid esters by $[Pd(AEMP)(H_2O)_2]^{2+}$. DFT (B3LYP/def-2svp) calculations were used to account for the catalytic activity of ester hydrolysis, where every species in the DFT calculated mechanism for hydrolysis were treated as a different isomer of the same compound.

Experimental

Materials and reagents

All the reagents used were of analytical reagent grade. K_2PdCl_4 and 2-(2-aminoethyl)-1-methylpyrrolidine were provided by Aldrich. The glycine methyl ester (GlyOMe), methionine methyl ester (MethOMe) and histidine methyl ester (HistOMe) were obtained from Fluka. The $Pd(AEMP)Cl_2$ complex was prepared as described previously [32]. The aqueous solution of the diaqua form, $[Pd(AEMP)(H_2O)_2]^{2+}$ was prepared as outlined before [32] and used in the kinetic measurements. NaOH solutions (carbonate-free) were prepared and standardized against solutions of potassium hydrogen phthalate. All solutions were prepared in deionized water.

Kinetic measurements

Metrohm 751 Titrino was used to monitor the kinetics of hydrolysis using SET mode (titration with preset end point). The electrode and titroprocessor were calibrated according to NIST [33], with standard buffer solutions. The hydrolysis kinetics of glycine-, methionine-, and histidine-methyl esters coordinated to $[Pd(AEMP)(H_2O)_2]^{2+}$ were investigated by pH–stat technique [34, 35]. A solution mixture (40 cm^3) containing $[Pd(AEMP)(H_2O)_2]^{2+}$ (2.5×10^{-3} M), ester (2.5×10^{-3} M) and $NaNO_3$ (0.1 M) was equilibrated at the required temperature under nitrogen atmosphere and the pH was brought to the desired value by the addition of 0.05 M NaOH solution. The hydrolysis was then followed by the addition of 0.05 M NaOH solution to maintain a constant pH. The fitting of the data was done using the OLIS KINFIT program [36] as previously described [37]. The precision of the data was tested from plots obtained from the OLIS program where the accepted residual values were less than 3 mV. The hydroxide ion concentration values were estimated from the pH using $pK_w = 13.997$, and an activity coefficient (γ) of 0.772 that was determined from the Davies equation [38]. For the variable temperature studies, the following

values of pK_w and γ were employed [39], at 15 °C ($pK_w = 14.35$, $\gamma = 0.776$), at 20 °C ($pK_w = 14.16$, $\gamma = 0.774$) at 25 °C ($pK_w = 14.00$, $\gamma = 0.772$), at 30 °C ($pK_w = 13.83$, $\gamma = 0.770$), and at 35 °C ($pK_w = 13.68$, $\gamma = 0.768$).

Quantum chemical method

Due to convergence problems when optimizing the structures in which the OH^- species was present, the energy of this species was calculated by the difference between the energy of a water cluster consisting of ten water molecules and the OH^- species, and the energy of the same water cluster but without the presence of the OH^- species, where the number and strength of the hydrogen bonds formed in the cluster were preserved:

$$E(OH^-) = E(10H_2O + OH^-) - E\left(10H_2O\right)$$

For all calculations the B3LYP functional [40–42] in combination with the def-2svp basis set was applied [43–47]. The characterization as minima was done by computation of vibrational frequencies at the same level. Relative energies were corrected for zero-point vibrational energies (ZPE). Single point calculations were performed using the CPCM formalism [48, 49] on the same level and water as a solvent to investigate the influence of the bulk solvent and to compensate exaggerated energies, originating from the Coulomb term. All calculations were performed using the Gaussian 09 program package [50].

Results and discussion

$Pd(AEMP)Cl_2$ was synthesized and characterized as described previously [32]. The complex in the solid state was further characterized by thermal measurements reported in the Supporting Information. In a previous study [32] the acid–base equilibria of $[Pd(AEMP)(H_2O)_2]^{2+}$ were investigated; the pK_a values of coordinated water were found to be 5.04 and 10.78.

The reaction between α-amino acid esters and $[Pd(AEMP)(H_2O)_2]^{2+}$ can be presented as the following equilibrium::

$$[Pd(AEMP)(H_2O)_2]^{2+} + {}^{+}NH_3CH(R)CO_2R' \rightleftharpoons [Pd(AEMP)\{NH_2CH(R)CO_2R'\}]^{2+} + H_3O^+ + H_2O \quad (1)$$

The equilibrium constant K is sufficiently large that in a medium with pH larger than 5.0 for 1:1 ratios of the palladium complex to α-amino acid esters, formation of the mixed-ligand complex is effectively complete [34]. Thus one mole of base is consumed per mole of complex formed and $NH_2CH(R)CO_2R`$ is bound almost entirely as $[Pd(AEMP)\{NH_2CH(R)CO_2R`\}]^{2+}$. The possible hydrolysis of uncoordinated α-amino acid ester may be neglected.

The coordinated α-amino acid ester can be hydrolyzed by H_2O and OH^- as given in Eqs. 2 and 3, respectively.

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

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

Kinetic data

On the basis of reactions (1)–(3), the rate expression is given in Eq. 4, for which k_{obs} can be expressed as in Eq. 5.

$$\text{Rate} = -dc/dt = k_{obs}[Pd(AEMP)(ester)] \quad (4)$$

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

The OLIS KINFIT program [36] was used to fit the kinetic data. A typical volume of base as a function of time for the hydrolysis of coordinated glycine methyl ester fitted to a single exponential function using OLIS KINFIT is shown in Fig. 1.

The values of k_{obs} (the pseudo-first-order rate constant observed at constant pH) were obtained and are summarized in Table S2 (Supporting Information) for all three systems. Plots of k_{obs} versus $[OH^-]$ were linear with either a positive or negligible intercept, see Figs. 2, 3 and 4. 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 M is the molar concentration of water, were determined from the intercept, and the values of $k_{OH} = (k_{obs} - k_o)/[OH^-]$ from the slopes of the plots. The linear dependence of the rate on the $[OH^-]$ is in agreement with the direct attack of OH^- ion on the coordinated carbonyl group of the ester as given in mechanism A (see further discussion) [51, 52]. The rate constants k_{OH}^{ester} previously reported [53, 54] for the base hydrolysis reaction of the selected amino acid esters, are included in Table 1.

For the glycine methyl ester the rate of acceleration denoted by the rate ratio (k_{OH}/k_{OH}^{ester}) is 1.15×10^5, see Table 1. The large magnitude of the rate acceleration for this complex is consistent with the formation of the mixed-ligand complex as in path A shown below, where there is a direct attachment between Pd(II) and the alkoxy carbonyl group of the ester species (Structure I).

The linear plots of k_{obs} versus the hydroxide ion concentration are represented in Figs. 2, 3 and 4. They reveal that hydrolysis proceeds by an intermolecular mechanism. The catalysis ratio of the histidine methyl ester and methionine methyl ester complexes amount to 17.6 and 21.8, respectively, see Table 1. The relatively small catalytic ratios suggest that in these cases the alkoxycarbonyl group is not bound to the metal ion. The histidine methyl ester complex is expected to have structure II in which the donor atoms are the alpha amino group pyridine nitrogen of the imidazole group. A similar situation III is most likely for methionine methyl ester complex, where the sulfur and alpha amino groups act as donors. Previous studies [53–55]

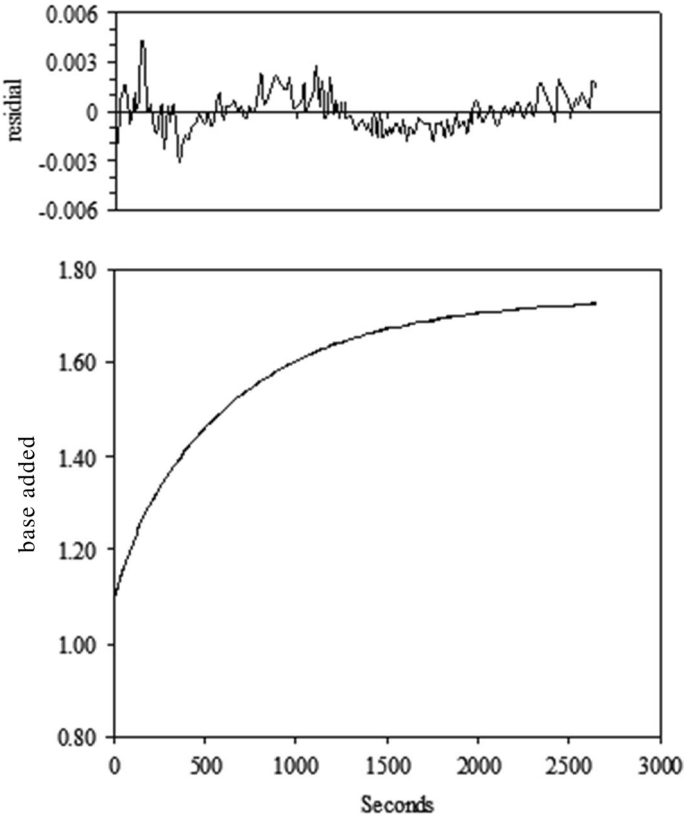


Fig. 1 Typical volume of base versus time trace, fitted with a single exponential function, for the hydrolysis reaction of $[Pd(AEMP)GlyOMe]^{2+}$ at 25 °C and 0.1 M ionic strength

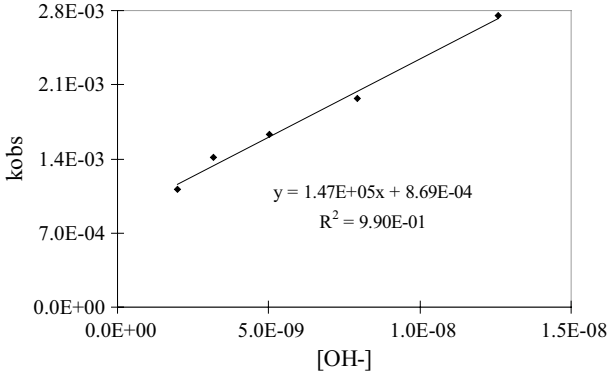


Fig. 2 Plot of k_{obs} (s^{-1}) vs. [OH^-] (M) for hydrolysis of the $[Pd(AEMP)(GlyOMe)]^{2+}$ complex at 25 °C

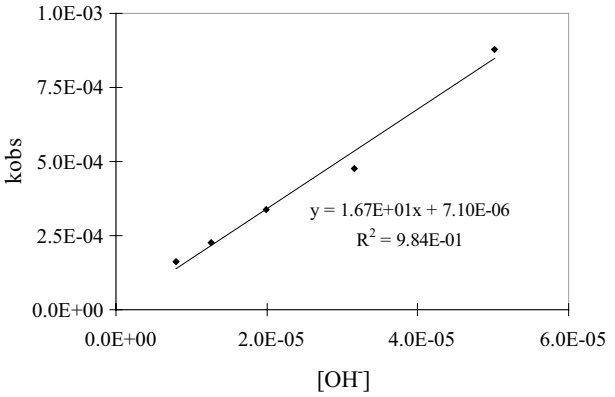


Fig. 3 Plot of k_{obs} (s^{-1}) vs. [OH^-] (M) for hydrolysis of the $[Pd(AEMP)(MetOMe)]^{2+}$ complex at 25 °C

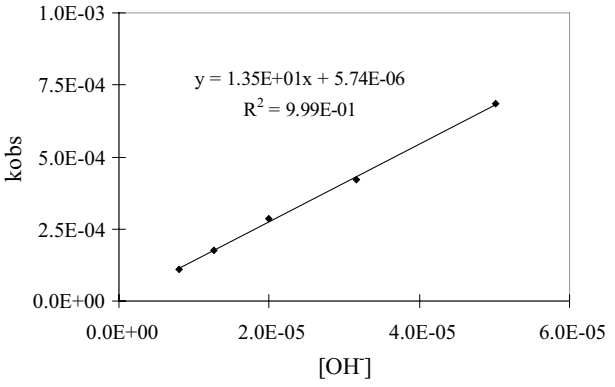


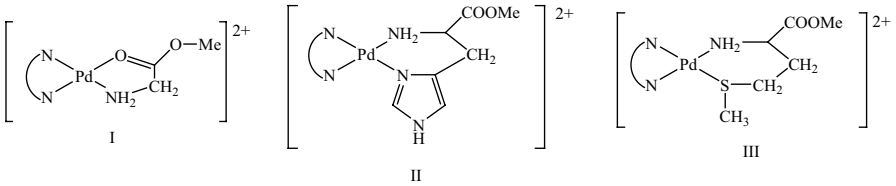
Fig. 4 Plot of k_{obs} (s^{-1}) vs. [OH^-] (M) for hydrolysis of the $[Pd(AEMP)(HisOMe)]^{2+}$ complex at 25 °C

Table 1 Kinetic hydrolysis data for $[Pd(AEMP)(ester)]^{2+}$ at 25 °C and 0.1 M ionic strength

Ester	k_{OH} (M^{-1} s^{-1})	k_{H_2O} (M^{-1} s^{-1})	$k_{OH}^{(ester)a}$ (M^{-1} s^{-1})	$k_{OH}/k_{OH}^{(ester)}$
Glycine methyl ester	$(1.47 \pm 0.08) \times 10^5$	$(1.6 \pm 0.2) \times 10^{-5}$	1.28	1.15×10^5
Methionine methyl ester	16.7 ± 1.2	$(1.3 \pm 0.2) \times 10^{-7}$	0.767	21.8
Histidine methyl ester	13.5 ± 0.3	$(1.0 \pm 0.1) \times 10^{-7}$	0.62	17.6

[a]Data from Refs.[51, 52]

have shown that the formation of such complexes with pendant ester groups lead only to relatively small acceleration rates, i.e. one would have obtained much higher catalysis ratios if the ester carbonyl was directly bound to Pd(II).



In order to differentiate between these mechanisms, activation parameters for the hydrolysis of the coordinated methyl histidine ester were determined using the Eyring plot [55] of ($\ln k_{OH}/T$) versus 1/T, according to Eq. 6). The data for the glycine methyl ester complex are reported in Table S3 (Supporting Information) and displayed graphically in Fig. 5.

$$\ln(k_{OH}/T) = (\ln(k/h) + \Delta S^{\neq}/R) - \Delta H^{\neq}/RT \quad (6)$$

$\Delta H^{\neq}$ and $\Delta S^{\neq}$ are the activation parameters for enthalpy and entropy changes on going to the transition state.

The values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated to be $\Delta H^{\neq} = 34.2 \pm 0.2$ kJ mol^{-1} and $\Delta S^{\neq} = -31.7 \pm 0.7$ J K^{-1} mol^{-1}. For the base of hydrolysis of the 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} [56].

The higher rate for base hydrolysis of the coordinated ester in the complex [Pd(AEMP)GlyOMe]$^{2+}$ is therefore due to contributions from a decrease in $\Delta H^{\neq}$ and an increase in $\Delta S^{\neq}$. The increase in $\Delta S^{\neq}$ is due to desolvation between the ground and transition states and confirms the mechanism involving nucleophilic attack by external OH^- on the carbonyl of the complexed ester group as in path A shown in Fig. 7.

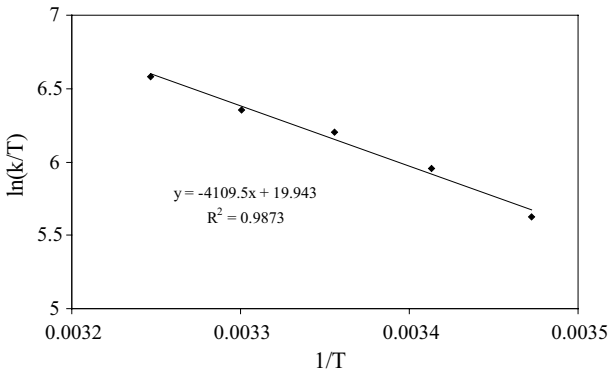


Fig. 5 Effect of temperature on the hydrolysis of the [Pd(AEMP)glycine methyl ester]$^{2+}$

DFT calculations

We started our DFT work by calculating the structure of [Pd(AEMP)Cl_2] since its crystal structure was reported in an earlier publication [32]. The DFT optimized structure of [Pd(AEMP)Cl_2] in the gas phase shown in Fig. 6a is in good agreement with the published X-ray structure. Subsequently, we calculated the structure of the $[Pd(AEMP)(H_2O)_2]^{2+}$ cation shown in Fig. 6b for which no crystal data is available. The structures are very similar in both cases.

The first order dependence on the OH^- concentration can be accounted for by two mechanisms [29, 52, 56]. In order to simulate the possible reaction mechanism for the hydrolysis of all three investigated α-amino acid esters catalyzed by $[Pd(AEMP)(H_2O)_2]^{2+}$ in the presence of OH^-, and the obtained experimental results, DFT (B3LYP(CPCM)/def2svp//B3LYP/def2svp + ZPE(B3LYP/def2svp)) calculations were performed and the calculated energies are summarized in Fig. 7.

In the first step of the reaction, $[Pd(AEMP)(H_2O)_2]^{2+}$ reacts rapidly with the three selected amino esters to form the mono-substituted product as shown in Fig. 7. The energy values relative to the energy of the first formed species for all three α-amino acid esters are included in the schemes. These energies are taken from the CPCM single point calculations in water as solvent for the previously optimized structures in the gas phase. In case of the GlyOMe ester, the aliphatic nitrogen atom coordinates rapidly to the metal center. In case of the HisOMe ester, the first coordination goes via a nitrogen atom of the imidazole histidine residue which was found to be 1.69 kcal/mol lower in energy relative to the coordination of the aliphatic nitrogen atom. In the case of MetOMe, the first coordination step proceeds via a sulfur atom from the methionine residue to the Pd(II) center, which is understandable, considering the fact that both species are soft Lewis acids.

Pathway A involves first a fast ring-closure reaction to displace the weakly coordinated water molecule, followed by base hydrolysis of the ester. In the case of GlyOMe, the carbonyl group of the ester coordinates to the metal, whereas in the other

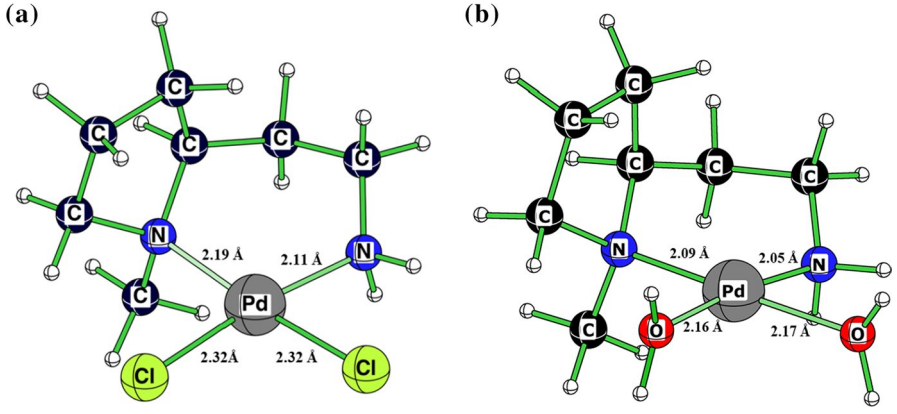


Fig. 6 DFT (B3LYP/def2svp) optimized structures of the complexes [Pd(AEMP)Cl_2] and $[Pd(AEMP)(H_2O)_2]^{2+}$ showing the bond lengths around the metal center

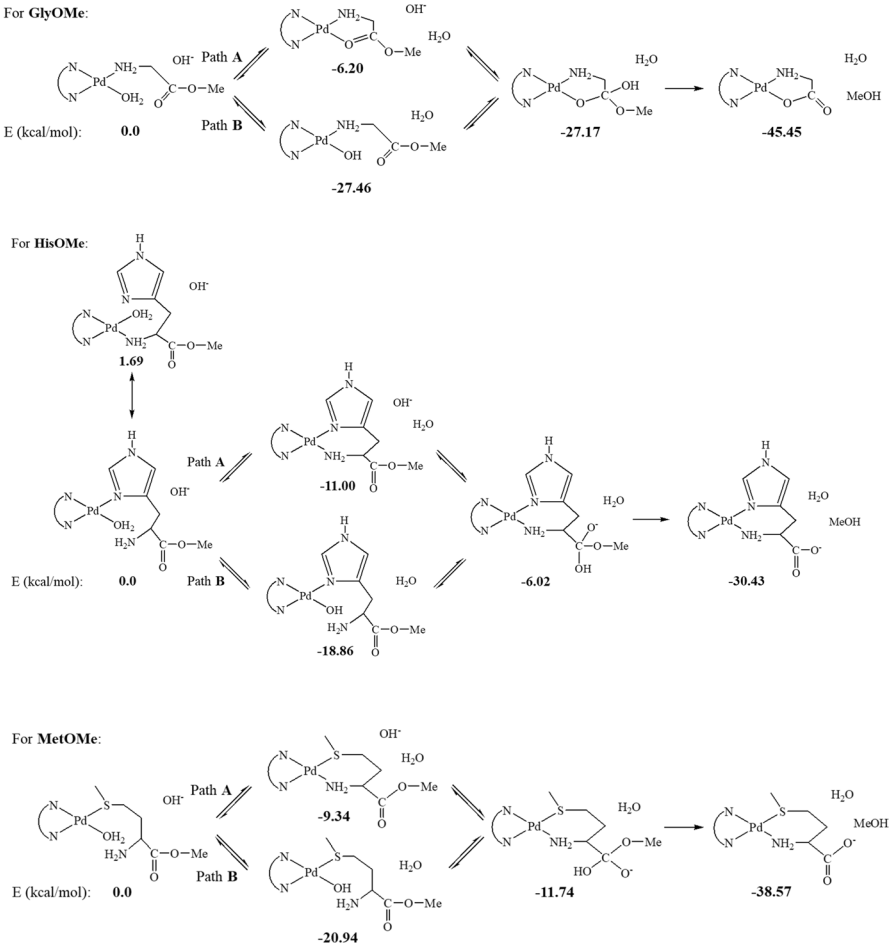


Fig. 7 Possible reaction pathways for the base hydrolysis of all three investigated α-amino acid esters catalyzed by $[Pd(AEMP)(H_2O)_2]^{2+}$ in the presence of OH^- (Energy: B3LYP(CPCM)/def2svp//B3LYP/def2svp + ZPE(B3LYP/def2svp))

two cases the aliphatic nitrogen atom is involved in the ring-closure process. The next step is the rate-determining attack by OH^-.

The alternative path B involves rapid formation of a Pd–OH complex, followed by an intra-molecular attack by OH^-. This path cannot be correct since the Pd–OH bond is known to be extremely strong such that in the case of all three α-amino acid esters an intermediate is formed that is much more stable than the species formed in path A. Therefore, path A seems to be the more logic option from a chemical point of view. This is also in agreement with the experimental data since the reaction shows a linear dependence on the OH^- concentration with a significant intercept in the case of the glycine methyl ester, which can be ascribed to the parallel water reaction path.

Conclusions

The present investigation draws a more general picture of biological applications of Pd(II) complexes as outlined in the Introduction. The reaction of the diaqua species $Pd(AEMP)(H_2O)_2^{2+}$ with amino acid esters leads to the formation of the hydroxo-complex and the complex with a chelated ester. The concentration of each species depends on the pH of the medium and the stability constant of the complex. The hydrolysis of the glycine methyl ester is catalyzed significantly by $[Pd(AEMP)(H_2O)_2]^{2+}$ with a catalytic ratio of 1.15×10^5. This is due to the binding of the Pd(II) complex directly to the carbonyl group of the ester which accounts for the enormous catalytic effect. However, the catalytic effect of the complex on the histidine- and methionine-methyl esters is not strong with catalytic ratios of 17.6 and 21.8 for the mentioned esters, respectively, due to the extended distance of the carbonyl group away from the metal center. The mechanism of hydrolysis was discussed in detail. A mechanism involving the direct interaction of OH^- with the carbonyl carbon atom was suggested. The activation parameters were determined for the hydrolysis of the coordinated glycine methyl ester. The values were compared to those of the free ester and the proposed mechanism was supported. DFT calculations allowed the optimization of the structure of the glycine-, histidine- and methionine-methyl ester complexes before, during and after hydrolysis. The calculations throw light on the mechanism of the base hydrolysis process.

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