Hydrolysis of α-Amino-acid Esters in Mixed-ligand Complexes with Ethylenediaminepalladium(II)

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α-Amino-acid esters react with $[Pd(en)(OH_2)_2]^{2+}$ (en = ethylenediamine) according to the equilibrium (i). The

$$[Pd(en)(OH_2)_2]^{2+} + \overset{+}{N}H_3CH(R)CO_2R' \overset{K}{\rightleftharpoons} [Pd(en)\{NH_2CH(R)CO_2R'\}]^{2+} + H_3O^+ + H_2O \quad (i)$$

kinetics of hydrolysis of $[Pd(en)L]^{2+}$ [L = $NH_2CH(R)CO_2R'$] have been studied by pH-stat and rate constants obtained for the kinetic processes (ii) and (iii) where A^- = $NH_2CH(R)CO_2^-$ and L = ethyl glycinate (gly-OEt),

$$[Pd(en)L]^{2+} + H_2O \xrightarrow{k_{H_2O}} [Pd(en)A]^+ + R'OH + H^+ \quad (ii)$$

$$[Pd(en)L]^{2+} + OH^- \xrightarrow{k_{OH}} [Pd(en)A]^+ + R'OH \quad (iii)$$

methyl glycinate (gly-OMe), ethyl α-alaninate (α-ala-OEt), ethyl β-phenylalaninate (phe-OEt), ethyl picolinate (pic-OEt), ethyl cysteinate (cys-OEt), and methyl histidinate (his-OMe). For the first five esters substantial rate accelerations are observed for base hydrolysis (factors of 4×10^4 for gly-OEt to 1.4×10^7 for pic-OEt). The effects with cys-OEt and his-OMe are much less marked, as the mixed-ligand complexes with these ligands do not involve alkoxycarbonyl donors. Possible mechanisms for these reactions are considered, and it is suggested that the reaction may involve kinetically important ion pairing between the complex and the incoming nucleophile prior to nucleophilic attack on the ester ligand.

LIM [1-3] has studied the reactions of a number of α-amino-acids HA with $[Pd(en)(OH_2)_2]^{2+}$ (en = ethylenediamine) in aqueous solution and has determined equilibrium constants for the equilibrium (1) for a large

$$[Pd(en)(OH_2)_2]^{2+} + A^- \rightleftharpoons [Pd(en)(A)]^+ + 2H_2O \quad (1)$$

variety of α-amino-acids. Lim [4] has also shown that methyl glycinate reacts with $[Pd(en)(OH_2)_2]^{2+}$ according to equilibrium (2) with $\log K = 7.12$ at 25 °C and $I = 0.5$ mol dm^{-3} ($K[NO_3]$). The resulting mixed-ligand com-

$$[Pd(en)(OH_2)_2]^{2+} + L \overset{K}{\rightleftharpoons} [Pd(en)L]^{2+} + 2H_2O \quad (2)$$

plex $[Pd(en)L]^{2+}$ undergoes ready hydrolysis by water and hydroxide ion with $k_{H_2O} = 3.8 \times 10^{-6}$ dm^3 mol^{-1} s^{-1} and $k_{OH} = 1.06 \times 10^4$ dm^3 mol^{-1} s^{-1} at 25 °C and $I = 0.5$ mol dm^{-3}.

It is of considerable interest to extend these investigations to a variety of other α-amino-acid esters. Much work has been published [5] on the hydrolysis of such ligands in the co-ordination sphere of metal centres such as cobalt(III), copper(II), and nickel(II). However, little information is available on the palladium(II) systems.

EXPERIMENTAL

The complex $[Pd(en)Cl_2]$ was synthesised as previously described.[6] The diaquo-complex $[Pd(en)(OH_2)_2][NO_3]_2$ was prepared in solution by stirring the chloro-complex with 2 equivalents of $Ag[NO_3]$ overnight. The solution was filtered and made up to the requisite volume in a standard flask. The L-α-amino-acid ester hydrochlorides were purchased from Fluka and converted into the corresponding hydronitrates $\{[NH_3CH(R)CO_2R'][NO_3]\}$ by stirring with an equivalent of $Ag[NO_3]$, filtering off the precipitated AgCl, and making up to the desired volume in a standard flask. For the L-cysteine ester hydrochloride it was necessary to prepare the hydronitrate salt by passage through an ion-exchange resin (Amberlite IRA-400 in the nitrate form).

Only freshly prepared solutions were used in the kinetic studies. Ethyl picolinate (ethyl pyridine-2-carboxylate) was obtained from Koch-Light. All other chemicals were AnalaR grade.

Kinetic Measurements.—Hydrolysis kinetics were monitored using a pH-stat. The equipment and general experimental technique employed have been outlined elsewhere.[7] It was necessary to avoid any contamination of the palladium solutions with chloride ion. Leakage of chloride ion from the calomel electrode was avoided by use of a $K[NO_3]$ salt bridge. The typical conditions employed in the kinetic measurements were 2×10^{-4} mol dm^{-3} $[Pd(en)(OH_2)_2]^{2+}$ and 2×10^{-4} mol dm^{-3} amino-acid ester hydronitrate. The ionic strength of the medium was adjusted to 0.1 mol dm^{-3} using $K[NO_3]$. Rate constants ($k_{obs.}$) were calculated from linear plots of $\log (V_\infty - V_t)$ *versus* time, where V_∞ is the final volume of base consumed (which was always close to the theoretical volume) and V_t is the volume consumed at time t. Values of the hydroxide-ion concentration were obtained from the pH using a value of $pK_w = 13.997$ and an activity coefficient of 0.772.

The base hydrolysis of ethyl picolinate was monitored spectrophotometrically at 266 nm ($\lambda_{max.}$ for the ester). Usually, 10 μl of a dilute solution of the ester in methanol were added to an absorption cell which contained the requisite concentration of K[OH] adjusted to $I = 0.1$ mol dm^{-3}. The absorbance change was monitored on a Gilford 2400 instrument. Plots of $\log (A_t - A_\infty)$ *versus* time were linear and values of $k_{obs.}$ were obtained from such plots.

RESULTS AND DISCUSSION

The reaction of the various α-amino-acid esters with $[Pd(en)(OH_2)_2]^{2+}$ can be summarised by equilibrium (3). The equilibrium constant K is sufficiently large that in

the range pH 5—6, at a 1 : 1 ratio of palladium complex to α-amino-acid ester, formation of the mixed-ligand

$$[Pd(en)(OH_2)_2]^{2+} + \dot{N}H_3CH(R)CO_2R' \overset{K}{\rightleftharpoons} [Pd(en)\{NH_2CH(R)CO_2R'\}]^{2+} + H_3O^+ + H_2O \quad (3)$$

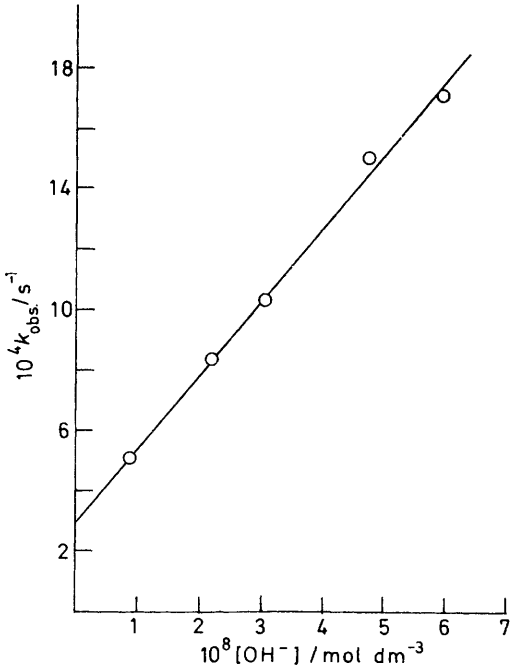
complex is essentially complete. Thus 1 mol of base is consumed per mol of palladium in the pH-stat measurements. (The hydrolysis of the unco-ordinated α-amino-acid ester is extremely slow in this pH range.) Formation of the mixed-ligand complex with ethyl picolinate was essentially complete at pH 3.0 (the pK_{NH} value of ethyl picolinate is 0.9,[8] compared with *ca.* 7.5 for the other esters [5]).

TABLE 1

Kinetics of hydrolysis of $[Pd(en)L]^{2+}$ complexes at 25 °C and I = 0.1 mol dm^{-3}

		10^6[OH$^-$]/ mol dm^{-3}	$10^4k_{obs.}$/s^{-1}
Ethyl glycinate	pH		
	5.83	0.88	5.10
	6.23	2.22	8.43
	6.37	3.06	10.37
	6.56	4.74	14.48
	6.66	5.96	17.58
		10^6[OH$^-$]/	
Methyl glycinate	pH	mol dm^{-3}	$10^4k_{obs.}$/s^{-1}
	5.07	1.53	3.65
	5.21	2.12	4.03
	5.68	6.24	6.48
	5.79	8.04	8.10
	5.83	8.82	7.97
		10^6[OH$^-$]/	
Ethyl α-alaninate	pH	mol dm^{-3}	$10^4k_{obs.}$/s^{-1}
	5.22	2.16	10.23
	5.40	3.27	10.27
	5.56	4.73	12.77
	5.89	10.13	14.97
		10^6[OH$^-$]/	
Ethyl L-β-phenylalaninate	pH	mol dm^{-3}	$10^4k_{obs.}$/s^{-1}
	5.21	2.12	8.25
	5.34	2.85	9.53
	5.57	4.84	10.65
	5.75	7.33	14.20
	5.93	11.10	20.73
	6.04	14.30	21.50
		10^{11}[OH$^-$]/	
Ethyl picolinate	pH	mol dm^{-3}	$10^4k_{obs.}$/s^{-1}
	3.08	1.57	12.08
	3.35	2.92	13.33
	3.54	4.52	14.40
	3.65	5.83	15.45
	3.74	7.17	16.02
	3.87	9.67	17.65
	4.01	13.35	19.88
		10^5[OH$^-$]/	
Ethyl L-cysteinate	pH	mol dm^{-3}	$10^4k_{obs.}$/s^{-1}
	9.37	3.06	3.07
	9.51	4.22	3.75
	9.92	10.90	5.57
	10.08	15.70	6.33
		10^5[OH$^-$]/	
Methyl L-histidinate	pH	mol dm^{-3}	$10^4k_{obs.}$/s^{-1}
	9.71	6.69	12.77
	9.80	8.23	12.28
	9.91	10.60	18.68
	10.10	16.42	23.03
	10.21	21.15	26.78
	10.35	29.20	42.60

Plots of log $(V_\infty - V_t)$, where V_∞ is the final volume of base consumed and V_t is the volume of base consumed at time t, were linear in all cases. Values of $k_{obs.}$ (the observed first-order rate constant at constant pH) were obtained from these plots and are summarised in Table 1. Plots of $k_{obs.}$ *versus* the hydroxide-ion concentration were linear with a positive intercept (Figure). The rate



Plot of $k_{obs.}$ *versus* the hydroxide-ion concentration for the hydrolysis of $[Pd(en)(NH_2CH_2CO_2Et)]^{2+}$ at 25 °C and I = 0.1 mol dm^{-3} ($K[NO_3]$)

expression is therefore of the form $k_{obs.} = k_0 + k_{OH}[OH^-]$. The k_0 term arises due to water attack on the mixed-ligand complex. Values of $k_{H_2O} = k_0/55.5$, where 55.5 mol dm^{-3} is the molar concentration of water, were determined from the intercept, and values of k_{OH} from the slope of these plots.

These rate constants are listed in Table 2. Also included in Table 2 are values of the rate constants k_{OH}^{ester} which have been previously reported [5,7] for the hydrolytic reaction (4). The appropriate rate constant for the base hydrolysis of ethyl picolinate was deter-

TABLE 2

Hydrolysis data (k/dm^3 mol^{-1} s^{-1}) at 25 °C and I = 0.1 mol dm^{-3} ($K[NO_3]$)

Ester	k_{OH}	k_{H_2O}	k_{OH}^{ester}
gly-OEt	2.45×10^4	5.3×10^{-6}	0.64
gly-OMe	6.25×10^4	4.9×10^{-6}	1.28
α-ala-OEt	6.15×10^4	1.6×10^{-5}	0.55 [a]
phe-OEt	11.75×10^4	1.04×10^{-5}	0.24
cys-OEt	4.20	5.17×10^{-6}	0.04 [b]
his-OMe	12.76	5.48×10^{-6}	0.62
pic-OEt	6.47×10^6	2.05×10^{-5}	0.46

[a] Estimated from the value for the methyl ester where k_{OH} = 1.11 dm^3 mol^{-1} s^{-1}. (Methyl esters normally undergo base hydrolysis at about twice the rate of ethyl esters.) All the base-hydrolysis data for the unprotonated esters are taken from ref. 5. [b] For $-SCH_2CH(NH_2)CO_2Et$.

mined spectrophotometrically as 0.45 ± 0.04 dm^3 mol^{-1} s^{-1} at 25 °C and I = 0.1 mol dm^{-3} (KCl), Table 3. This

$$NH_2CH(R)CO_2R' + OH^- \xrightarrow{k_{OH}^{ester}} NH_2CH(R)CO_2^- + R'OH \quad (4)$$

value compares reasonably well with the 0.54 dm^3 mol^{-1} s^{-1} reported by Ågren and Van der Veen [8] at an unspecified ionic strength. In addition, this paper does not state the method used to determine the hydroxide-ion concentrations, and the authors may have employed hydroxide-ion activities.

For the α-amino-acid esters gly-OEt, gly-OMe, α-ala-OEt, phe-OEt, and ethyl picolinate the rate accelerations k_{OH}/k_{OH}^{ester} are quite substantial, falling in the

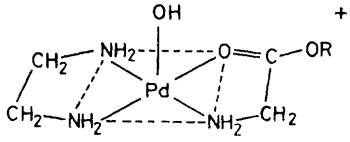
TABLE 3

Base hydrolysis of ethyl picolinate at 25 °C and I = 0.1 mol dm^{-3}

10^3[OH$^-$]/ mol dm^{-3}	$10^2 k_{obs.}$/s^{-1}	$k_{obs.}$[OH$^-$]$^{-1}$/ dm^3 mol^{-1} s^{-1}
2.00	4.85	0.40
4.00	10.65	0.44
5.00	14.63	0.49
6.00	17.55	0.49

k_{OH} = 0.45 ± 0.05 dm^3 mol^{-1} s^{-1}.

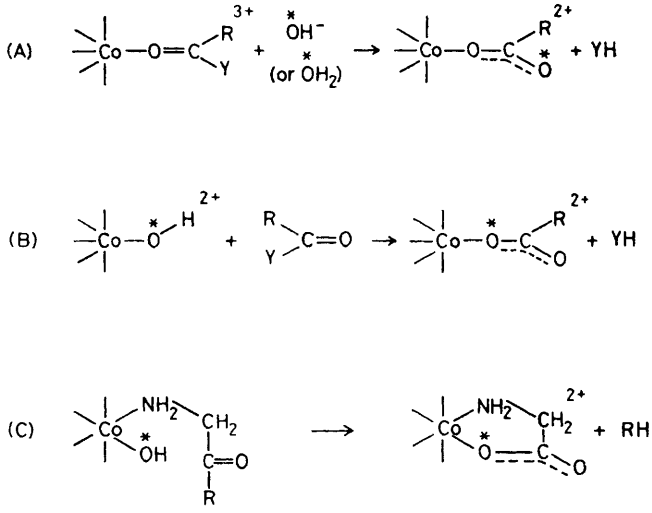
range 4 × 10^4 (gly-OEt) to 1.4 × 10^7 for ethyl picolinate. The value of k_{OH} obtained for gly-OEt (2.45 × 10^4 dm^3 mol^{-1} s^{-1}) is in reasonable agreement with Lim's value [4] of 1.06 × 10^4 dm^3 mol^{-1} s^{-1} at I = 0.5 mol dm^{-3} (K[NO$_3$]). Similar agreement is observed in the k_{H_2O} values where Lim [4] reports k_{H_2O} = 3.8 × 10^{-6} dm^3 mol^{-1} s^{-1} which may be compared with our value of 5.3 × 10^{-6} dm^3 mol^{-1} s^{-1}. The rate accelerations of 4 × 10^4—1.4 × 10^7 are consistent with the formulation of the mixed-ligand complex as in (I) in which there is a direct interaction



(I)

between Pd^{II} and the alkoxycarbonyl group of the ester. Metal ions and metal complexes have been found to accelerate the hydrolysis of esters, amides, and peptides.[5] In these studies kinetically inert metal centres such as cobalt(III) have been used to differentiate between the direct polarisation mechanism (A) and the alternative 'metal-hydroxide' mechanism (B), Scheme. Mechanism (A) provides rate enhancements of 10^4—10^6 for all substrates, independent of the leaving group.[9-14] Mechanism (B) is effective only with the more reactive species (CO_2, anhydrides, aldehydes, and esters with good leaving groups).[15] In addition, for the direct polarisation mechanism, the rate enhancement is due entirely to entropy factors, whereas, both $\Delta H^\ddagger$ and $\Delta S^\ddagger$ contribute in mechanism (B). For mechanism (A), nucleophilic attack by species other than OH$^-$ (*e.g.* NH_2R, ROH, H_2O) is also observed,[16,17] while only hydrolysis occurs with metal hydroxides [18] and general-acid or -base catalysis is not observed.

The intramolecular counterpart of mechanism (B), *i.e.* mechanism (C), does occur with amino-acid esters,[19,20] amides,[21] and nitriles [22] where five- or six-membered chelate rings can result on hydrolysis. Usually, substantial rate accelerations (as high as 10^{11}) occur in these reactions and $\Delta H^\ddagger$ factors become of great significance. Lim [4] has determined the activation parameters for the base hydrolysis of [Pd(en)(gly-OEt)]$^{2+}$ as $\Delta H^\ddagger$ = 16.3 kJ mol^{-1} and $\Delta S^\ddagger$ = −113.4 J K^{-1}



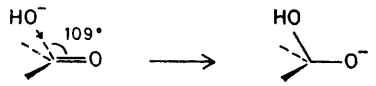
SCHEME Possible mechanisms for the hydrolysis of carbonyl substrates on cobalt(III) complexes

mol^{-1}. For the hydrolysis of unprotonated ethyl glycinate the corresponding values are [5] $\Delta H^\ddagger$ = 35.8 kJ mol^{-1} and $\Delta S^\ddagger$ = −133.9 J K^{-1} mol^{-1}. It is clear that in this case the rate acceleration of 4 × 10^4 arises primarily from $\Delta H^\ddagger$ with only a small contribution from $\Delta S^\ddagger$. On this basis we tentatively suggest that there may be some contribution from a species such as (I) in which there is an initial interaction between the incoming nucleophile and palladium(II).* This interaction may only involve the formation of a kinetically important ion pair, which should be favoured by the dipositive charge on the complex. Hydroxide ion is recognised to be a poor nucleophile towards Pt^{II} and Pd^{II} so that ion pairing seems to be more probable in this case. The effect of ion pairing would be to increase the 'effective concentration' of the nucleophile in the region of the substrate, as occurs in an intramolecular reaction where 'effective concentrations' usually lie [24] within the range 50—100 mol dm^{-3}.

Baldwin [25,26] has discussed the importance of the 'flight path' of the nucleophile at tetrahedral, trigonal, and digonal centres. For attack at an sp^2-hybridised centre the nucleophile should approach at an angle of

* A referee has pointed out that an intermediate analogous to (I) has been suggested by Nord [23] in the base hydrolysis of platinum(II)–bipyridyl complexes.

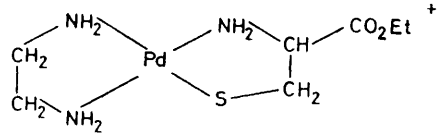
109° to the carbonyl bond as shown in (II). As a result, it appears unlikely that the formation of complex (I) would lead to attack by the ' co-ordinated hydroxide



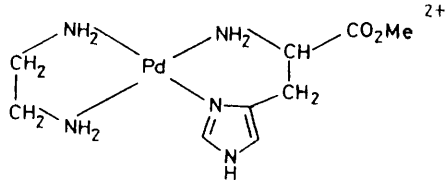
(II)

ion ' at the sp^2 centre, since the flight path of the nucleophile would be so unfavourable. It is presumably for this reason that no evidence has been obtained for the attack of ' co-ordinated hydroxide ' on *chelated* glycine esters in cobalt(III) chemistry.

The relatively small rate accelerations observed with ethyl cysteinate ($k_{OH}/k_{OH}^{ester} = 105$) and methyl histidinate ($k_{OH}/k_{OH}^{ester} = 20.6$) suggest that in these cases the alkoxycarbonyl group is not bonded to the ester. The ethyl cysteinate 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 with methyl histidinate, with the α-amino-group and the pyridine nitrogen of the imidazole ring acting as donors. Previous studies [27-30] have shown that formation of such complexes with non-bonded or pendant ester functions leads to only relatively small rate accelerations.



(III)



(IV)

For those esters where there is a direct interaction between the alkoxycarbonyl group and palladium(II), the values of k_{OH}/k_{H_2O} fall within the range 3.8×10^9—3.2×10^{11}. Such values for the relative nucleophilicity of hydroxide ion and water are quite comparable with those previously obtained for copper(II) complexes.[31] For cys-OEt and his-OMe the values are 0.8×10^6 and 2.3×10^6 respectively.

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