The Palladium(II)-promoted Hydrolysis of Methyl and Isopropyl Glycylglycinate

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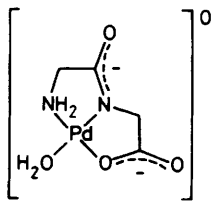
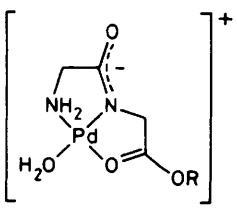
The palladium(II)-promoted hydrolysis of methyl glycylglycinate and isopropyl glycylglycinate has been studied at four temperatures (25, 30, 35, and 40 °C) at I = 0.1 mol dm^{-3} in the pH range 4—5. Under these conditions, and at a 1 : 1 metal to ligand ratio, the peptide esters act as tridentate ligands, donation occurring *via* the terminal amino-group, the deprotonated amide nitrogen, and the carbonyl group of the ester. Rate constants are reported for hydrolysis of the ester function by water and hydroxide ion, and activation parameters calculated. Base hydrolysis of the co-ordinated peptide esters is *ca.* 10^5 times faster than the unprotonated peptide esters. Mechanisms for the reactions are considered.

At pH 4 dipeptides form a tridentate chelate about palladium(II) consisting of two five-membered rings with amino, deprotonated amide, and carboxylato-oxygen donor atoms.[1,2] A representative structure involving glycylglycine is shown by (I). Peptide esters would be expected to form complexes of type (II), in which the amino, deprotonated amide, and alkoxycarbonyl groups act as donors. The formation of complexes such as (II), in which there is an interaction between the alkoxycarbonyl group of the ester and the metal ion, suggests that the hydrolysis of peptide esters should be susceptible to metal-ion catalysis. We have previously studied [3] the hydrolysis of copper(II) analogues of (II) and have shown that accelerated base hydrolysis rates were observed (*ca.* 10^3 times). The deprotonated complex is not susceptible to hydrolysis at the peptide bond; indeed this bond is greatly stabilised by co-ordination of the nitrogen atom to copper(II) as in (I).[4,5] The present paper discusses the kinetics and mechanism of the palladium(II)-promoted ester hydrolysis of methyl and isopropyl glycylglycinate.



(I)



(II) R = Me or Pr^i

Experimental

Glycylglycine was obtained from B.D.H. and used as received. Methyl glycylglycinate hydrochloride and isopropyl glycylglycinate hydrochloride were prepared using previously described procedures.[6] The methyl ester was recrystallised from methanol–diethyl ether (Found: C, 32.7; H, 6.1; N, 15.2. Calc. for $C_5H_{10}N_2O_3$·HCl: C, 32.9; H, 6.05; N, 15.3%). The isopropyl ester was recrystallised from refluxing propan-2-ol (Found: C, 39.8; H, 6.8; N, 13.1. Calc. for $C_7H_{14}N_2O_3$·HCl: C, 39.9; H, 7.15; N, 13.3%).

Kinetics and Measurements.—All kinetic measurements were carried out using a Radiometer TTT2 automatic titrator used as a pH-stat. A high-alkalinity glass electrode type G202B was used as indicator electrode and a saturated calomel electrode (s.c.e.) with diffusion filter, type K401, as reference electrode. The electrode system was standardised at 25 ± 0.1 °C using 0.05 mol dm^{-3} potassium hydrogenphthalate (pH 4.008) and 0.01 mol dm^{-3} disodium tetraborate (pH 9.185). At the other temperatures the recommended pH standards were employed.[7] The general technique employed in the kinetic measurements has been outlined previously.[8] All pH-stat studies were carried out at I = 0.1 mol dm^{-3} ($NaClO_4$) with methyl or isopropyl glycylglycinate hydrochloride (2.25 × 10^{-4} mol dm^{-3}) and $K_2[PdCl_4]$ (2.25 × 10^{-4} mol dm^{-3}). One mole of base was consumed per mole of the ester in the pH-stat measurements. Values of the hydroxide-ion concentration were obtained from the pH using a molar activity coefficient γ_1 of 0.772 [9] and a value of pK_w = 13.997 at 25 °C.[10] At the other temperatures the appropriate values are γ_1 = 0.770, pK_w = 13.833 (30 °C); γ_1 = 0.768, pK_w = 13.680 (35 °C); and γ_1 = 0.766, pK_w = 13.535 (40 °C).

For the potentiometric titrations the solutions used were 1 × 10^{-3} mol dm^{-3} in both $K_2[PdCl_4]$ and the ligand (methyl glycylglycinate hydrochloride or glycylglycine); I = 0.1 mol dm^{-3} ($NaClO_4$), θ_c = 25 °C. In this case pH measurements were made with a Radiometer PHM 64 Research pH-meter.

Results and Discussion

Potentiometric titration of a 1 : 1 molar mixture of $K_2[PdCl_4]$ with glycylglycine indicates the release of two protons, Figure 1(*a*), from the protonated amino-group and the peptide bond. Analogous behaviour is displayed by a 1 : 1 molar mixture of $K_2[PdCl_4]$ and methyl glycylglycinate, Figure 1(*b*). Hydrolysis of the ester ligand occurs in the pH range 4—5. One mole of base is consumed per mole of the ester on hydrolysis in the presence of one mol equiv. of $K_2[PdCl_4]$ in this pH range. Values of $k_{obs.}$ (the observed first-order rate constant at constant pH) for the hydrolysis of the ester are summarised in Table 1, at various temperatures. A plot of $k_{obs.}$ *versus* [OH$^-$] is linear with a positive intercept, Figure 2.

The kinetic data conform to the equation $k_{obs.} = k_0 + k_{OH}[OH^-]$, where k_0 can be assigned to a solvolytic pathway (water attack on the complex) and k_{OH} to base hydrolysis. Least-squares analysis of the data at 25 °C gives k_0 = 3.82 × 10^{-4} s^{-1} and k_{OH} = 1.55 × 10^5 dm^3 mol^{-1} s^{-1} at I = 0.1 mol dm^{-3}. Values of k_0 were converted to k_{H_2O} rate constants using the expression $k_{H_2O} = k_0/55.5$, where 55.5 mol dm^{-3} is the molar concentration of water, giving k_{H_2O} = 6.88 × 10^{-6} dm^3 mol^{-1} s^{-1} at 25 °C. The ratio k_{OH}/k_{H_2O} = 2.26 × 10^{10}, and is of the expected magnitude for the relative nucleophilicities of water and hydroxide ion in reactions of this type. The rate constants k_{OH} and k_{H_2O} at various temperatures are summarised in Table 2. The requisite activation parameters are $\Delta H^‡$ = 89.9 kJ mol^{-1}, $\Delta S_{298}^‡$ = −42 J K^{-1} mol^{-1} (for k_{H_2O}) and $\Delta H^‡$ = 78.7 kJ mol^{-1}, $\Delta S_{298}^‡$ = 118 J K^{-1} mol^{-1}

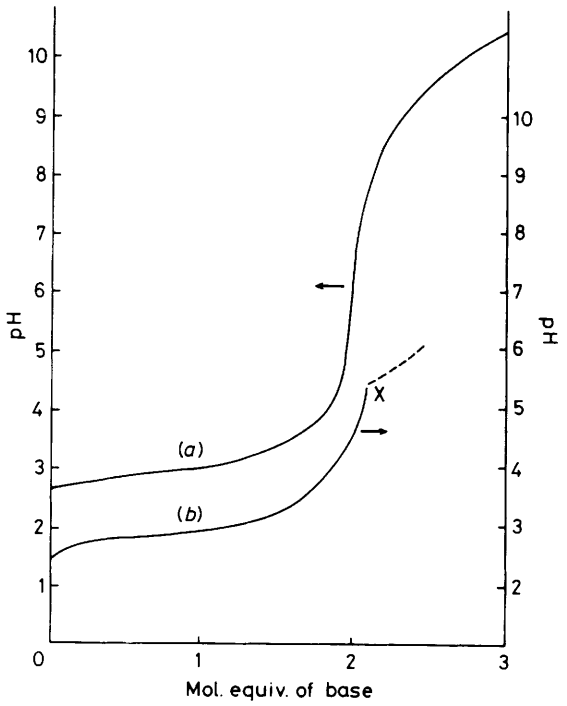


Figure 1. (*a*) Potentiometric titration of a 1 : 1 mixture (1×10^{-3} mol dm^{-3}) of $K_2[PdCl_4]$ and glycylglycine at 25 °C and $I = 0.1$ mol dm^{-3} ($NaClO_4$); (*b*) potentiometric titration of a 1 : 1 mixture (1×10^{-3} mol dm^{-3}) of $K_2[PdCl_4]$ and methyl glycylglycinate hydrochloride at 25 °C and $I = 0.1$ mol dm^{-3} ($NaClO_4$). The point × marks the onset of hydrolysis

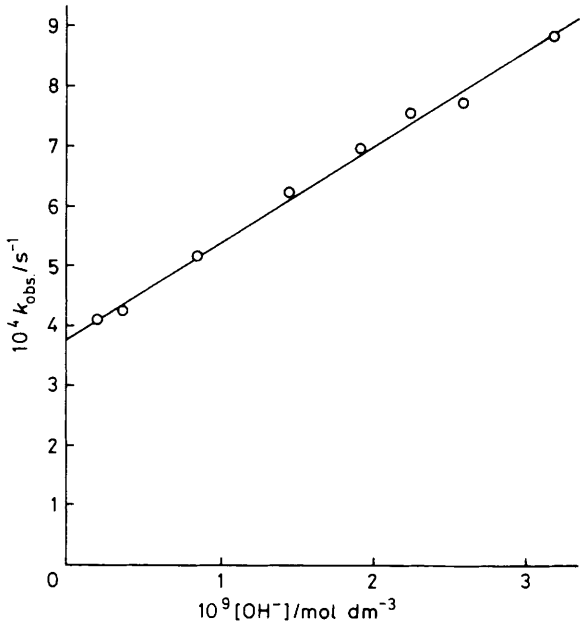


Figure 2. Plot of $k_{obs.}$ *versus* $[OH^-]$ for the hydrolysis of the 1 : 1 complex of methyl glycylglycinate with palladium(II) at 25 °C and $I = 0.1$ mol dm^{-3} ($NaClO_4$)

(for k_{OH}). Analogous measurements were carried out with isopropyl glycylglycinate and values of $k_{obs.}$ as a function of pH are summarised in Table 3. Values of the rate constants k_{H_2O} and k_{OH} at four temperatures are listed in Table 4. The

Table 1. Hydrolysis of the 1 : 1 complex of methyl glycylglycinate with palladium(II) at various temperatures and $I = 0.1$ mol dm^{-3} ($NaClO_4$)

pH	$10^{10}[OH^-]$/mol dm^{-3}	$10^4 k_{obs.}/s^{-1}$
$\theta_c = 25$ °C		
4.21	2.2	4.20
4.46	3.8	4.23
4.82	8.6	5.18
5.05	14.7	6.22
5.17	19.3	6.94
5.24	22.7	7.54
5.30	26.1	7.70
5.39	32.1	8.79
$\theta_c = 30$ °C		
4.10	2.40	7.40
4.38	4.58	8.13
4.46	5.50	8.22
4.75	10.73	9.62
4.90	15.15	10.72
5.16	27.57	13.04
$\theta_c = 35$ °C		
3.86	1.97	13.40
3.95	2.42	13.28
4.22	4.51	14.18
4.40	6.83	15.40
4.57	10.11	16.46
$\theta_c = 40$ °C		
3.89	2.96	25.11
4.00	3.81	25.72
4.10	4.80	26.57
4.26	6.93	27.90
4.40	10.49	30.66

Table 2. Values of k_{OH} for the hydrolysis of the 1 : 1 complex of methyl glycylglycinate with palladium(II) at various temperatures and $I = 0.1$ mol dm^{-3} ($NaClO_4$) *

θ_c/°C	$10^6 k_{H_2O}/dm^3\ mol^{-1}\ s^{-1}$	$10^{-5} k_{OH}/dm^3\ mol^{-1}\ s^{-1}$
25	6.88	1.55
30	12.73	2.23
35	22.45	4.02
40	41.36	7.30

* For k_{H_2O}: $\Delta H^{\ddagger} = 89.9$ kJ mol^{-1}, $\Delta S_{298}^{\ddagger} = -42$ J K^{-1} mol^{-1} [correlation coefficient (c.c.) = 0.9998]. For k_{OH}: $\Delta H^{\ddagger} = 78.7$ kJ mol^{-1}, $\Delta S_{298}^{\ddagger} = 118$ J K^{-1} mol^{-1} (c.c. = 0.992).

activation parameters for the isopropyl ester are $\Delta H^{\ddagger} = 91$ kJ mol^{-1}, $\Delta S_{298}^{\ddagger} = -40$ J K^{-1} mol^{-1} (for k_{H_2O}) and $\Delta H^{\ddagger} = 81.8$ kJ mol^{-1}, $\Delta S_{298}^{\ddagger} = 123$ J K^{-1} mol^{-1} (for k_{OH}). Base hydrolysis of the palladium(II) complex of the methyl ester is *ca.* twice as fast as that of the isopropyl ester. This leaving-group effect is also observed in the base hydrolysis of methyl- and isopropyl-glycinate.[11] The activation parameters for the two palladium complexes are very similar.

The hydrolysis of ethyl glycylglycinate has been studied by Meresaar and Ågren.[12] The various hydrolytic reactions are summarised in the Scheme, where E is the ester, A^- is glycylglycinate, and B is the ring-closed product piperazine-2,5-dione (produced by intramolecular attack by the free amino-function on the ethoxycarbonyl group). The abbreviations EH^+ and HA represent $H_3\overset{+}{N}CH_2CONHCH_2CO_2Et$ and $H_3\overset{+}{N}CH_2CONHCH_2CO_2^-$ respectively, and A^- is $H_2NCH_2CONHCH_2CO_2^-$. At 25 °C and $I = 1.0$ mol dm^{-3} the rate

Table 3. Hydrolysis of the 1 : 1 complex of isopropyl glycylglycinate with palladium(II) at various temperatures and I = 0.1 mol dm^{-3} ($NaClO_4$)

pH	10^9[OH$^-$]/mol dm^{-3}	$10^4 k_{obs.}$/s^{-1}
θ_c = 25 °C		
4.42	0.34	3.47
4.54	0.45	3.58
4.60	0.52	3.66
4.82	0.86	3.85
4.89	1.01	3.97
5.54	4.53	6.83
θ_c = 30 °C		
4.50	0.60	6.65
4.58	0.73	6.79
4.86	1.38	7.77
5.00	1.91	8.40
5.33	4.08	11.31
θ_c = 35 °C		
4.10	0.34	11.61
4.55	0.97	13.08
4.70	1.36	13.68
4.84	1.88	14.99
4.95	2.42	16.41
θ_c = 40 °C		
4.21	0.62	21.55
4.45	1.07	24.27
4.57	1.42	25.45
4.75	2.14	28.20
4.83	2.58	29.88

Table 4. Values of k_{OH} and k_{H_2O} for the hydrolysis of the 1 : 1 complex of isopropyl glycylglycinate with palladium(II) at various temperatures and I = 0.1 mol dm^{-3} ($NaClO_4$) *

θ_c/°C	$10^6 k_{H_2O}$/dm^3 mol^{-1} s^{-1}	$10^{-5} k_{OH}$/dm^3 mol^{-1} s^{-1}
25	5.76	0.80
30	10.55	1.34
35	19.43	2.27
40	35.02	4.11

* For k_{H_2O}: $\Delta H^{\ddagger}$ = 91.0 kJ mol^{-1}, $\Delta S_{298}^{\ddagger}$ = −40 J K^{-1} mol^{-1} (c.c. = 0.999). For k_{OH}: $\Delta H^{\ddagger}$ = 81.8 kJ mol^{-1}, $\Delta S_{298}^{\ddagger}$ = 123 J K^{-1} mol^{-1} (c.c. = 0.999).

$$EH^+ + OH^- \xrightarrow{k_1} HA + EtOH \quad (1)$$

$$E + OH^- \xrightarrow{k_2} A^- + EtOH \quad (2)$$

$$E + OH^- \xrightarrow{k_3} B + EtOH \quad (3)$$

$$E \xrightarrow{k_4} B + EtOH \quad (4)$$

Scheme.

constants are k_1 = 5.2 dm^3 mol^{-1} s^{-1} (approximate only), k_2 = 0.625 dm^3 mol^{-1} s^{-1}, and k_4 = 6.86 × 10^{-5} s^{-1}. Formation of the piperazinedione in basic solutions of methyl glycylglycinate is well established. Thus Nakon and Angelici [13] reported the appearance of a band at 1 625 cm^{-1} in basic solutions of methyl glycylglycinate which can be assigned to the amide carbonyl-stretching vibration of piperazine-2,5-dione. Metal ions prevent the formation of the piperazine-2,5-dione as they interact with the amino group, and so remove its nucleophilic character. Methyl esters normally base hydrolyse at *ca.* twice the rate of ethyl esters, *e.g.* for methyl glycinate k_{OH} = 1.28 dm^3 mol^{-1} s^{-1} while for ethyl glycinate k_{OH} = 0.64 dm^3 mol^{-1} s^{-1} (for the unprotonated species at 25 °C and I = 0.1 mol dm^{-3}).[11] Thus k_2 for methyl glycylglycinate will be *ca.* 1.25 dm^3 mol^{-1} s^{-1} at 25 °C. For the palladium(II) complex k_{OH} = 1.55 × 10^5 dm^3 mol^{-1} s^{-1} leading to an overall rate acceleration for base hydrolysis of *ca.* 10^5 times at 25 °C. A rate acceleration of this magnitude provides good evidence for the formation of a complex such as (II) in which there is a direct interaction between the alkoxycarbonyl group and palladium(II). This view is also supported by the activation parameters for the metal-promoted reactions. For base hydrolysis of unprotonated glycine methyl ester ($NH_2CH_2CO_2Me$) the activation parameters [11] are $\Delta H^{\ddagger}$ = 39.7 kJ mol^{-1} and $\Delta S_{298}^{\ddagger}$ = −117 J K^{-1} mol^{-1}. A large negative entropy of activation is expected in a bimolecular reaction of this type ($\Delta S^{\ddagger}$ values in the range −20 to −60 J K^{-1} mol^{-1}).[14] For the hydrolysis of methyl glycylglycinate a similarly large negative entropy of activation would be expected. Both metal-ion-promoted reactions have very similar activation parameters with $\Delta S_{298}^{\ddagger}$ = *ca.* +120 J K^{-1} mol^{-1}. In cobalt(III)[6,15-17] complexes it has been found that the direct polarisation mechanism involving attack of an 'external' nucleophile such as water or hydroxide ion on a 'co-ordinated' carbonyl group leads to rate accelerations of 10^5—10^6 for all substrates, independent of the leaving group. In addition, the rate enhancement is due entirely to entropy factors with no contribution from the $\Delta H^{\ddagger}$ term.[6] A similar situation appears to occur in these palladium(II) complexes. The metal ion effectively 'solvates' the developing negative charge on the carbonyl oxygen when nucleophilic attack occurs, thus reducing the solvation requirement (leading to a substantial negative entropy of activation) which occurs in the absence of the metal ion. The rate accelerations observed in the present work parallel those of 10^5—10^7 observed in the base hydrolysis of amino acid esters in mixed-ligand complexes with (2,2′-bipyridyl)palladium(II)[18] and (ethylenediamine)palladium(II).[19]

Acknowledgements

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