Mixed-ligand Complexes of Palladium(II). Part 2.† Diaqua(ethylenediamine)palladium(II) Complexes of L-Asparagine and L-Glutamine

By **Meng-Chay Lim**, Chemistry Department, University of Malaya, Kuala Lumpur, Malaysia

The reactions of $[Pd(en)(OH_2)_2]^{2+}$ (en = ethylenediamine) with L-asparagine monohydrate and L-glutamine in 0.5 mol dm^{-3} $K[NO_3]$ have been studied by potentiometric titrations. The results obtained can be explained by equilibria (i) and (ii) where $L^- = H_2NCOCH_2CH(NH_2)CO_2^-$ or $H_2NCOCH_2CH_2CH(NH_2)CO_2^-$, and log K_1 and

$$[Pd(en)(OH_2)_2]^{2+} + L^- \overset{K_1}{\rightleftharpoons} [Pd(en)L]^+ \quad (i)$$

$$[Pd(en)L]^+ \overset{K_a'}{\rightleftharpoons} [Pd(en)L'] + H^+ \quad (ii)$$

pK_a' are 10.46 and 6.46 for asparagine and 10.76 and 9.03 for glutamine respectively. The mode of co-ordination of the two ligands in their protonated and deprotonated complexes is discussed on the basis of these parameters.

THE naturally occurring amino-acids L-asparagine (Asn) and L-glutamine (Gln) are potentially tridentate ligands towards metal ions, with three donor sites on the terminal amino- and carboxyl as well as the amide groups on the side chain of the molecules. Martin and his co-workers [1] showed that titrations of a solution containing copper(II) ions and Asn with base resulted in the formation of two types of complex: at pH <11 the amino-acid acts as a bidentate ligand with the amide group not involved in co-ordination; at pH >11, however, deprotonation of the amide group occurs and the ligand presumably becomes tridentate in the complex. This is supported by comparing the circular dichroism of the solution of copper asparaginate at appropriate pH with those of a number of related ligands. Unfortunately, at high pH, where deprotonation of the amide group takes place, considerable precipitation of copper hydroxide occurs which renders impossible the determination of the accurate pK_a' of the amide group from the complex. In the case of copper peptide complexes, such pK_a' values often serve as valuable guides in deducing the mode of co-ordination of the ligands. No comparable study has been reported for Gln. Similarly the deprotonation of the amide group in Asn has also not been reported for other metal ions.

Recently,[2] in a study of the reactions of palladium analogues of anti-tumour platinum complexes with biologically significant material, it was shown that diaqua(ethylenediamine)palladium(II) forms very stable complexes with glycylglycine (Gly-Gly) and glycinamide [Gly(NH_2)] and promotes the ready deprotonations of the amide groups at very low pH. In view of the remarkable resemblance of the side chains of Asn and Gln to Gly(NH_2), it is interesting to investigate the mode of co-ordination of these two ligands to the same palladium species. The results of a potentiometric study are now reported.

EXPERIMENTAL

Materials.—The preparation of crystalline $[PdCl_2(en)]$, and $[Pd(en)(OH_2)_2][NO_3]_2$ (en = ethylenediamine) in solution therefrom has been reported previously.[3,4] L-Asparagine monohydrate and L-glutamine were AnalaR grade materials from B.D.H. and were used without further purification. All the other chemicals used were of AnalaR grade quality.

Potentiometric Titrations.—(a) $[Pd(en)(OH_2)_2][NO_3]_2$ + *ligands.* The potentiometric titrations were carried out on solutions containing 1 : 1 molar ratios of $[Pd(en)(OH_2)_2][NO_3]_2$ and the respective ligands at a constant ionic strength of 0.5 mol dm^{-3} $K[NO_3]$ at 25 °C. The apparatus and procedure were similar to those reported previously.[2] Equilibrium was established rapidly as evidenced by the steady e.m.f. readings during titrations up to 1 equivalent of base added per ligand in both the asparagine (Asn) and glutamine (Gln) systems. Beyond the first equivalent of base, however, the e.m.f. readings changed instantaneously in the direction of high pH on addition of base and then decreased gradually to steady values. In the case of Asn the establishment of equilibrium at each titration point in this region required *ca.* 10 min, while in the case of Gln a somewhat longer time was required.

(b) *Free ligands.* The pK_A and pK_B of the free ligands, *i.e.* the dissociation constants of the carboxyl and the amino-groups respectively, were determined under the same conditions of ionic strength and temperature, by titrating weighed samples of the ligands with standard HNO_3 and Na[OH] respectively.

RESULTS AND DISCUSSION

The ionisations of the free ligands may be represented as in (1) where $L^- = H_2NCOCH_2CH(NH_2)CO_2^-$ (AsnO)

$$[H_2L]^+ \overset{K_A}{\rightleftharpoons} H^+ + HL \overset{K_B}{\rightleftharpoons} H^+ + L^- \quad (1)$$

† Part 1 is ref. 2.

[1] E. W. Wilson, jun., M. H. Kasperian, and R. B. Martin, *J. Amer. Chem. Soc.*, 1970, **92**, 5365.

[2] M- C. Lim, *J.C.S. Dalton*, 1977, 15.

[3] H. D. K. Drew, F. W. Pinkard, G. H. Preston, and A. W. Wardlow, *J. Chem. Soc.*, 1932, 1895.

[4] M- C. Lim and R. B. Martin, *J. Inorg. Nuclear Chem.*, 1976, **38**, 1911.

or $H_2NCOCH_2CH_2CH(NH_2)CO_2^-$ (GlnO). The values of pK_A and pK_B are summarised in Table 1 together with values reported in the literature.[5-12]

Typical titration curves for $[Pd(en)(OH_2)_2][NO_3]_2$ with Asn and Gln are shown in the Figure. A titration curve for $[Pd(en)(OH_2)_2][NO_3]_2$ with $Gly(NH_2)$ obtained under the same conditions is also included for comparison. It is seen that, unlike the case of $Gly(NH_2)$ where the titration curve shows only one sharp inflexion point at 2 equivalents of base per ligand, for both Asn and Gln

TABLE 1

Dissociation constants of L-asparagine and L-glutamine in 0.5 mol dm^{-3} $K[NO_3]$ at 25 °C

Species	pK_A	pK_B	Experimental conditions	Ref.
Asparagine	2.26 ±0.01	8.79 ±0.01	0.5 mol dm^{-3} $K[NO_3]$, 25 °C	This work
		8.71	0.15 mol dm^{-3}, 25 °C	5
	2.09	8.79	1.0 mol dm^{-3} $Na[ClO_4]$, 20 °C	6
	2.14	8.85	0.1 mol dm^{-3}, 20 °C	7
		8.84	0.15 mol dm^{-3} $K[NO_3]$, 22.15 °C	8
		9.13	*ca.* 0, 15 °C	9
		8.88	1.0 mol dm^{-3} $K[NO_3]$, 30 °C	10
	2.14	8.72	0.1 mol dm^{-3} $K[NO_3]$, 25 °C	11
		9.04	0.6 mol dm^{-3}, 25 °C	12
Glutamine	2.29 ±0.01	9.09 ±0.01	0.5 mol dm^{-3} $K[NO_3]$, 25 °C	This work
		9.34	*ca.* 0, 15 °C	9
	2.17	9.01	0.1 mol dm^{-3} $K[NO_3]$, 25 °C	11

the titration curves show two buffer regions separated by a sharp inflexion at 1 equivalent of base per ligand.

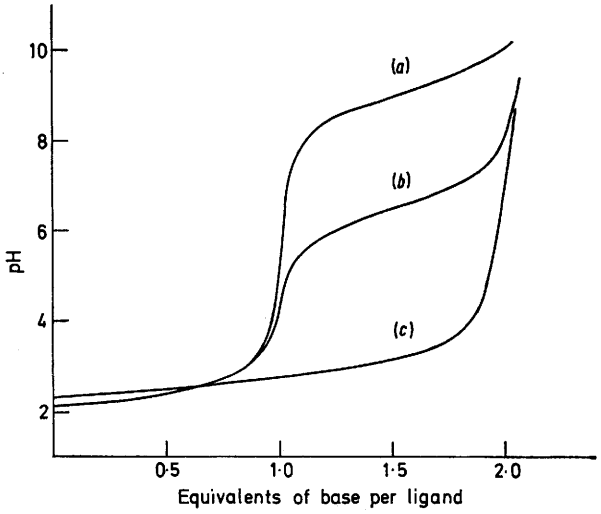
Equilibria (2) and (3) account satisfactorily for all

$$[Pd(en)(OH_2)_2]^{2+} + L^- \overset{K_1}{\rightleftharpoons} [Pd(en)L]^+ \quad (2)$$

$$[Pd(en)L]^+ \overset{K_a'}{\rightleftharpoons} [Pd(en)L'] + H^+ \quad (3)$$

the systems in the Figure, where L^- = glycinamide, asparaginate, or glutamate. One major difference between the $Gly(NH_2)$ system and those of Asn and Gln is that equilibria (2) and (3) occur simultaneously for the former whereas for the latter (2) and (3) occur in two distinct stages. In other words, the formation of $[Pd(en)L]^+$ is essentially complete before deprotonation of the amide groups begins. For this reason the evaluation of log K_1 and pK_a' becomes much simpler for Asn and Gln. All the experimental points below 1 equivalent of added base were ascribed to step (2) and those between 1 and 2 equivalents of base were used for evaluating K_a'. The calculations were made with the aid of an IBM 1130 computer. Titration results are available as Supplementary Publication No. SUP 22058 (3 pp.); * log K_1 and pK_a' values for the Asn and Gln systems are summarised in Table 2.

It is seen from Table 2 that both amino-acids form very stable complexes with $[Pd(en)(OH_2)_2]^{2+}$, log K_1 for both systems being greater than those reported for their



Titration curves of $[Pd(en)(OH_2)_2][NO_3]_2$ + glutamine (*a*), asparagine (*b*), and glycinamide (*c*) with sodium hydroxide

copper(II) complexes.[13] There is, however, very little difference in stability between the two palladium complexes. The pK_B values show that Gln is slightly more basic than Asn and this probably accounts for the slightly higher value of log K_1 for the glutamine complexes. Since two positions of the palladium ion are blocked by nitrogen ligands, and in view of the preference of palladium for square-planar configuration in its complexes, it is unlikely that either ligand is tridentate in its complex. Assuming that these amino-acids are both bidentate in their palladium complexes where the Pd^{II} assumes its usual planar configuration, one can envisage two different ways in which the amino-acids

TABLE 2

Stability and dissociation constants of $[Pd(en)L]^+$ for L-asparagine and L-glutamine in 0.5 mol dm^{-3} $K[NO_3]$ and 25 °C

	Log K_1	pK_a'
Asparagine	10.46 ± 0.01	6.46 ± 0.01
Glutamine	10.76 ± 0.01	9.03 ± 0.02

can bind to the palladium. The ligands may co-ordinate through the terminal amino- and carboxyl groups with the amide group in the side chain remaining free. The ligands would then behave like a simple amino-acid, *e.g.* alanine. Alternatively, they can also co-ordinate through the terminal amino-group and the carbonyl oxygen of the amide group, as the glycinamide analogues.

* For details see Notices to Authors No. 7, *J.C.S. Dalton*, 1976, Index issue (items less than 10 pp. are supplied as full-size copies).

[5] N. C. Li, E. Doody, and J. M. White, *J. Amer. Chem. Soc.*, 1958, **80**, 5901.
[6] D. D. Perrin, *J. Chem. Soc.*, 1958, 3125.
[7] A. Albert, *Biochem. J.*, 1950, **49**, 531.
[8] C. Tanford and W. S. Shore, *J. Amer. Chem. Soc.*, 1953, **75**, 816.
[9] D. J. Perkins, *Biochem. J.*, 1953, **55**, 649.
[10] G. N. Rao and R. S. Subrahmanya, *Proc. Indian Acad. Sci.*, 1964, **60**, 165, 185.
[11] J. H. Ritsma, G. A. Wiegers, and F. Jellinek, *Rec. Trav. chim.*, 1965, **84**, 1577.
[12] Yu. M. Azizov, A. Kh. Miftakhova, and V. F. Toropova, *Russ. J. Org. Chem.*, 1967, **12**, 345.
[13] 'Stability Constants of Metal–Ion Complexes,' *Special Publ.*, The Chemical Society, London, 1964, no. 17.

A third possibility involving the carboxyl and the amide group can be safely ruled out in view of the great affinity of palladium for nitrogen-donor centres. For the first two modes of co-ordination there is really no conclusive evidence as yet to exclude one or the other of the possibilities. Unfortunately, there are no available data regarding the co-ordination of $[Pd(en)(OH_2)_2]^{2+}$ with simple amino-acids which can serve as reference. The fact that the log K_1 values of the two systems are so similar indicates that the ligands probably co-ordinate as simple amino-acids without involvement of the side chain since in this way both complexes have the same co-ordinating centres and both form five-membered chelate rings. The second mode of co-ordination would mean that a six-membered ring would be formed in the asparagine complex and a seven-membered ring in the glutamine complex. The latter would probably be more strained and less favoured and a smaller log K_1 value would be expected. The observed log K_1 value for the Gln system is in fact slightly greater than that for the Asn system.

The pK_a' values of the two complexes strongly support the above argument. The pK_a' of the complex of Asn is much smaller than that of Gln. As with glycinamide, it is most likely that in the deprotonated complexes the ligands are co-ordinated to the metal by the amino-group and the deprotonated amide nitrogen. The affinity of palladium for nitrogen-donor centres provides the driving force for the deprotonation. The higher pK_a' values for the Gln system shows that the seven-membered chelate ring formed in the complex is less stable than the six-membered ring in the Asn system. The slow attainment of equilibrium during titration probably reflects the difficulty in forming the seven-membered ring.

It is interesting to note that complexes of the first-row transition metals with seven-membered chelate rings are relatively rare. This is probably the reason why deprotonations of glutamine complexes have not been observed with such ions. For palladium on the other hand, complexes involving seven-membered and larger chelate rings are apparently quite common. Shaw and his co-workers [14] showed that it is relatively easy to prepare complexes of palladium of the type *trans*-$[\{MCl_2[Bu^t_2P(CH_2)_nPBu^t_2]\}_x]$ where n can be as large as 12. In view of this and the great affinity of palladium for nitrogen centres it is not surprising that glutamine forms a complex containing a seven-membered chelate ring with $[Pd(en)(OH_2)_2]^{2+}$ on deprotonation of the amide group.

The relative magnitudes of the pK_a' values of the palladium complexes of Asn and Gln have interesting biological implications. Under normal physiological conditions (pH *ca.* 7.4) the two amino-acids would co-ordinate with $[Pd(en)(OH_2)_2]^{2+}$ in entirely different fashions: whereas asparaginate would be present entirely in the deprotonated form, glutaminate would exist solely in the protonated form. This means that even though $[Pd(en)(OH_2)_2]^{2+}$ can catalyse the deprotonation of the amide groups from both Asn and Gln, its catalytic action would be very specific under physiological conditions, being confined exclusively to asparagine. The slight difference in the side chains of the two amino-acids thus produces dramatic differences in their behaviour towards the palladium species.

I thank the University of Malaya for a Vote-F grant.

[7/053 *Received*, 11*th January*, 1977]

[14] A. Pryde, B. L. Shaw, and B. Weeks, *J.C.S. Dalton*, 1976, 322.