Amino Acid Complexes of Palladium(II). 2. Reactions of the Diaqua(ethylenediamine)palladium(II) Cation with *N*-Acetylglycine, Glycinamide, and *N*-Glycylglycine[1,2]

Trevor G. Appleton,* Danny R. Bedgood, Jr., and John R. Hall

Department of Chemistry, The University of Queensland, Brisbane, Qld, Australia 4072

Received December 14, 1993®

Multinuclear NMR (^{15}N, ^{13}C, ^{1}H) was used to study the reactions of $[Pd(en)(H_2O)_2]^{2+}$ (**1**) with ligands that model peptides. *N*-acetylglycine (H_2acgly) with **1** in strongly acidic solution (pH 1.2) gave $[Pd(en)(Hacgly\text{-}O)(H_2O)]^{+}$ and other complexes with acetylglycine bound only through carboxylate O. At higher pH (7–10) the chelate complex [Pd(en)(acgly-*N*,*O*)] predominated. With glycinamide ($N_{(1)}H_2CH_2C(O)N_{(2)}H_2$, Hglyam) at pH 4–10, $[Pd(en)(glyam\text{-}N_{(1)},N_{(2)})]^{+}$ was formed. At lower pH (1–3), this complex was in equilibrium with its protonated form, $[Pd(en)(Hglyam\text{-}N_{(1)},N_{(2)})]^{2+}$, and with $[Pd(en)(Hglyam\text{-}N_{(1)},O)]^{2+}$ and $[Pd(en)(Hglyam\text{-}N_{(1)})(H_2O)]^{2+}$. With *N*-glycylglycine ($^{+}N_{(1)}H_3CH_2C(O_{(1)})N_{(2)}HCH_2CO_2^{-}$, H_2digly), the $N_{(1)}N_{(2)}$-chelate complex $[Pd(en)(digly\text{-}N_{(1)}N_{(2)})]$ predominated under most conditions, but under strongly acidic conditions (pH 1), peaks were also present in NMR spectra which were assigned to $[Pd(en)(H_2digly\text{-}N_{(1)}O_{(1)})]^{2+}$. When **1** was present in initial excess, the free carboxylate group in the $N_{(1)}$,$N_{(2)}$-chelate complex bound to $Pd(en)(H_2O)^{2+}$. The dinuclear complex $[\{Pd(en)\}_2(digly)]^{2+}$, with one Pd atom bound to $N_{(1)}$ and $O_{(1)}$, and the second Pd atom bound to $N_{(2)}$ and carboxylate O, also formed.

Introduction

Following our use of ^{15}N NMR spectroscopy to study aspects of the chemistry of ammine complexes of palladium(II),[3] we used ^{15}N and ^{13}C NMR spectra to study the reactions of $[Pd(en)(H_2O)_2]^{2+}$ (**1**) (en = 1,2-diaminoethane) with the simple amino acids $^{+}NH_3(CH_2)_nCO_2^{-}$ (n = 1–3).[2] In this paper, we describe the extension of this work to the reactions of **1** with *N*-acetylglycine (H_2acgly) (a model for the O-terminal end of a peptide), glycinamide (Hglyam) (a model for the N-terminal end of a peptide), and *N*-glycylglycine (H_2digly), the simplest peptide. The structures of these molecules are shown in Figure 1, with the atom numbering scheme that will be used. A major aim in this work is to compare the chemistry of these palladium complexes with that of the corresponding diammineplatinum(II) complexes that we have recently reported,[4,5] with the aim of clarifying the kinetic and thermodynamic effects that determine the products of the reactions in both these systems.

Experimental Section

Starting Materials. Ethylenediamine highly enriched in ^{15}N (en-$^{15}N_2$) was prepared from labeled potassium phthalimide as previously described.[2] The amino acids and derivatives, H_2acgly, (H_2glyam)Cl, and H_2digly, were used as supplied by Sigma. (H_2glyam)(NO_3) was prepared from the chloride salt as previously described.[5] Samples of glycylglycine specifically labeled (a) with ^{15}N at $N_{(1)}$ and with ^{13}C at $C_{(4)}$ and (b) with ^{15}N at $N_{(2)}$ and with ^{13}C at $C_{(2)}$ were prepared from labeled glycine by the Drug Design and Development Centre (3D Centre) at the University of Queensland. Details of the NMR spectra of these labeled samples are given in the supplementary material. A solution containing *cis*-$[Pd(en)(H_2O)_2](NO_3)_2$ was prepared by dissolving solid $[Pd(ONO_2)_2(en)]$ in water, as previously described.[2] As discussed in our previous paper, solutions prepared in this way usually contained small amounts of $[Pd(en)_2]^{2+}$ as an impurity, and ^{15}N NMR spectra of solutions of **1** were usually broadened to some extent because of exchange between coordinated water and other weak O-donor ligands.

$CH_3C(O)NHCH_2CO_2H$	H_2acgly
$N_{(1)}H_2CH_2C(O)N_{(2)}H_2$	Hglyam
$^{+}N_{(1)}H_3C_{(1)}H_2C_{(2)}(O_{(1)})N_{(2)}HC_{(3)}H_2CO_2^{-}$	H_2digly

Figure 1. Ligands used in this work, with abbreviations and atom numbering.

NMR Spectra. The 20.2-MHz ^{15}N, 200-MHz ^{1}H, and 50.2-MHz ^{13}C NMR spectra were obtained with the use of a Bruker AC-200F spectrometer equipped with a 5-mm quad probe ($^{1}H/^{13}C/^{15}N/^{19}F$) as previously described.[2] ^{15}N peaks are referenced relative to the $^{15}NH_4^{+}$ signal ($\delta_N = 0$) from 5M $^{15}NH_4NO_3$ in 2 M HNO_3 in a coaxial capillary. The reference for ^{13}C spectra was internal dioxane ($\delta_C = 67.73$). ^{1}H spectra were obtained in $^{2}H_2O$, and are referenced relative to the methyl signal of 3-(trimethylsilyl)propanesulfonate (TSS) ($\delta_H = 0$). All shifts are positive to lower nuclear shielding. Spectra of nuclei other than ^{1}H were ^{1}H-decoupled.

Preparation of NMR Samples. For all experiments, approximately 0.08 g of $[Pd(ONO_2)_2(en)]$ (with either ^{14}N or ^{15}N present) was dissolved in 0.75 mL of water ($^{1}H_2O$ or D_2O as appropriate), and the amino acid (approximately 0.8 mol equiv) was added. The mixture was warmed briefly, to dissolve all solids, and NMR spectra were obtained from solutions in which the pH was adjusted to the desired pH value by addition of 1 M HNO_3 or KOH solutions (in $^{1}H_2O$) or D_2SO_4 or NaOD solutions in D_2O. Readings from a pH meter in D_2O were converted to pD values by addition of 0.4 to the reading.[6]

Results

^{15}N and ^{13}C (for carboxylate, amide, and peptide carbon atoms) NMR data are given in Table 1. Data from the methylene region of ^{13}C spectra are less useful in assigning structures, and overlap between peaks from ethylenediamine and other ligands can make assignments difficult. This region of the spectrum was therefore not routinely examined.

Reactions of $[Pd(en)(H_2O)_2]^{2+}$ (1) with *N*-Acetylglycine (Scheme 1). When *N*-acetylglycine (0.8 mol equiv) was added to a solution of $[Pd(en\text{-}^{15}N_2)(H_2O)_2]^{2+}$ (**1**), and the pH adjusted to 1.6, the ^{15}N NMR spectrum (Figure 2a) of the resultant solution

* Author to whom correspondence should be addressed.

® Abstract published in *Advance ACS Abstracts*, July 1, 1994.

(1) Presented in part at the Ninth National Conference of the Royal Australian Chemical Institute, Melbourne, Vic., Dec 6–11 1992; Inorganic Chemistry Division Abstract TI-60.

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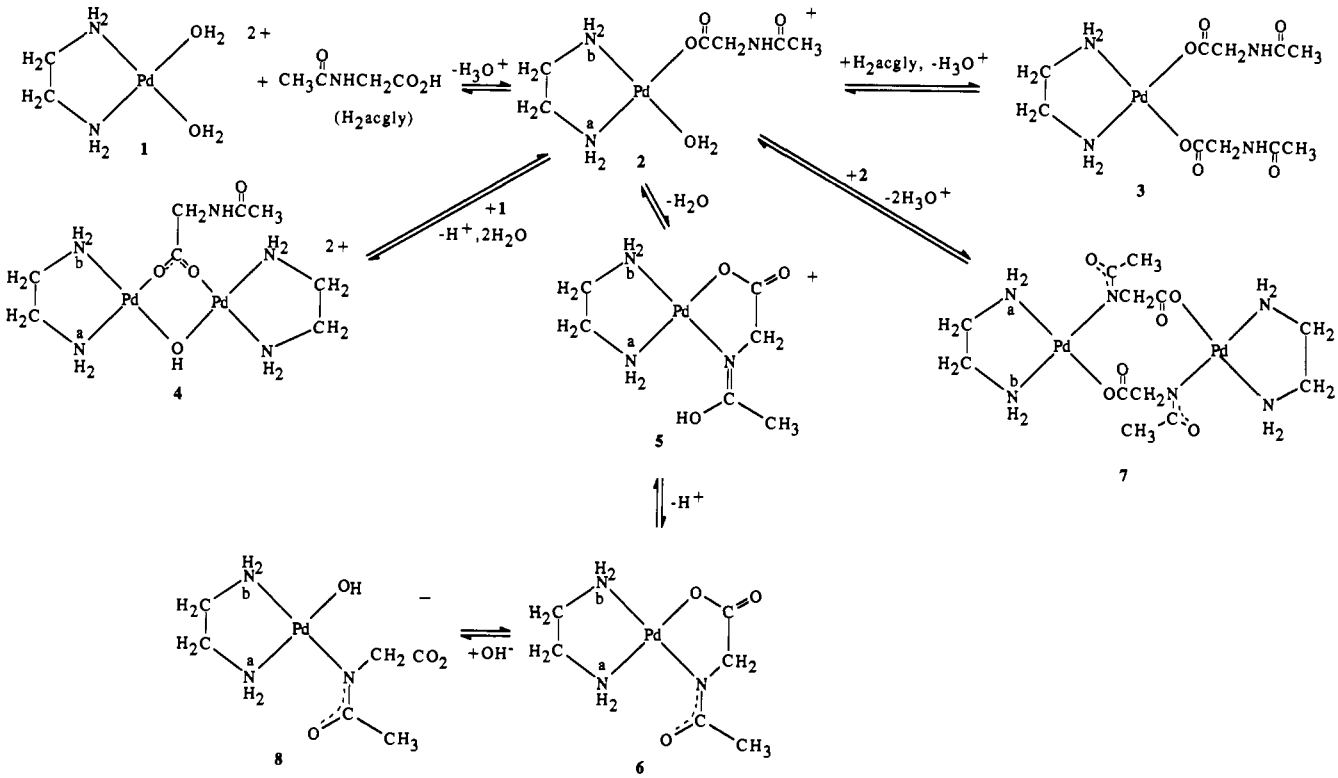
Table 1. NMR Data[a]

compound	pH	δ_N en ^{15}N	δ_N trans ligand	δ_N digly ^{15}N	δ_C CO_2^-	δ_C C—C(O)—N
$[Pd(en)(Hacgly\text{-}O)(H_2O)]^+$ (**2**)	4.1	a −26.2	O(Hacgly$^-$)		179.1	175.6
		b −29.5	H_2O			
$[Pd(en)(Hacgly\text{-}O)_2]$ (**3**)	4.1	−28.2	O(Hacgly$^-$)			
$[\{Pd(en)\}_2(\mu\text{-Hacgly})(\mu\text{-OH})]^{2+}$ (**4**)	4.1	a −26.5	O(Hacgly$^-$)			
		b −23.5	μ-OH$^-$			
$[Pd(en)(acgly\text{-}N,O)]$ (**6**)	10	a −29.5	O(acgly^{2-})		187.9	179.2
		b −19.0	N(acgly^{2-})			
$[\{Pd(en)(\mu\text{-acgly})\}_2]$ (**7**)	10	a −24.9	O(acgly^{2-})			
		b −19.7	N(acgly^{2-})			
$[Pd(en)(glyam\text{-}N_{(1)},N_{(2)})]^+$ (**9**)	10	a −20.2	$N_{(1)}$			186.9
		b −22.9	$N_{(2)}$			
$[Pd(en)(Hglyam\text{-}N_{(1)},N_{(2)})]^{2+}$ (**10**)	1.1	a −20.4	$N_{(1)}$			
		b −21.7	$N_{(2)}$			
$[Pd(en)(Hglyam\text{-}N_{(1)},O)]^{2+}$ (**11**)[b]	1.7	a −17.0	$N_{(1)}$			186.9[c]
		b −28.6	O(Hglyam)			
$[Pd(en)(Hglyam\text{-}N_{(1)})(H_2O)]^{2+}$ (**12**)[b]	1.7	a −17.0	$N_{(1)}$			
		b −27.0	H_2O			
$[Pd(en)(digly\text{-}N_{(1)},N_{(2)})]$ (**14**)	10	a −15.9	$N_{(1)}$	$N_{(1)}$ −44.2	179.7	182.9[d]
		b −20.4	$N_{(2)}$	$N_{(2)}$ −18.6		
$[Pd(en)(H_2digly\text{-}N_{(1)},O)]^{2+}$ (**16**)[b]	1.0	a −17.0	$N_{(1)}$	$N_{(1)}$ −37.8	173.2[e]	183.0[e,f]
		b −28.4	O(H_2digly)			
$[Pd(en)(H_2digly\text{-}N_{(1)})(H_2O)]^{2+}$ (**17**)[b]	1.0	a −17.0	$N_{(1)}$			
		b −27.0	H_2O			
$[\{Pd(en)\}(digly)\{Pd(en)(H_2O)\}]^{2+}$ (**18**)[b]	1.0	a −15.3	$N_{(1)}$			
		b −20.4	$N_{(2)}$			
		c −25.9	$O_{(2)}$			
		d −29.1	H_2O			
$[\{Pd(en)\}_2(digly)]^{2+}$ (**20**)	3.0	a −18.3	$N_{(1)}$	$N_{(1)}$ −38.9	186.5	187.2
		b −18.9	$N_{(2)}$			
		c −28.2	$O_{(2)}$[g]			
		d −28.7	$O_{(1)}$[g]			

[a] All compounds with ethylenediamine N atoms highly enriched in ^{15}N. Spectra in ^1H_2O, at 298 K unless otherwise noted. [b] ^{15}N NMR spectrum obtained at 277 K. [c] ^{13}C NMR spectrum run at 298K, at pH 1.1. Amide peak broad. [d] $J(C_{(2)}\text{–}N_{(2)})$ 10.8 Hz. [e] ^{13}C NMR spectrum run at 298 K. [f] Broad peak. [g] Assignments for N_c and N_d could be reversed.

Scheme 1



showed, in addition to the broad peak from **1** at −27.4 ppm, two broad peaks at −26.2 and −29.5 ppm. From our empirical knowledge of the dependence of δ_N for ethylenediamine nitrogen atoms on the ligand trans to nitrogen,[2] it is clear that both these chemical shifts correspond to nitrogen trans to oxygen. The peaks were sharper than those in spectra obtained under similar conditions from solutions of **1** with betaine ($^+(CH_3)_3NCH_2CO_2^-$, bet),[2] where the major species were proposed to be $[Pd(en)(bet\text{-}O)(H_2O)]^{2+}$ and $[Pd(en)(bet\text{-}O)_2]^{2+}$, with the exchange between coordinated carboxylate groups and water occurring at an intermediate rate on the NMR time scale. The peaks in the present spectrum were assigned to $[Pd(en\text{-}^{15}N_2)(Hacgly\text{-}O)$-

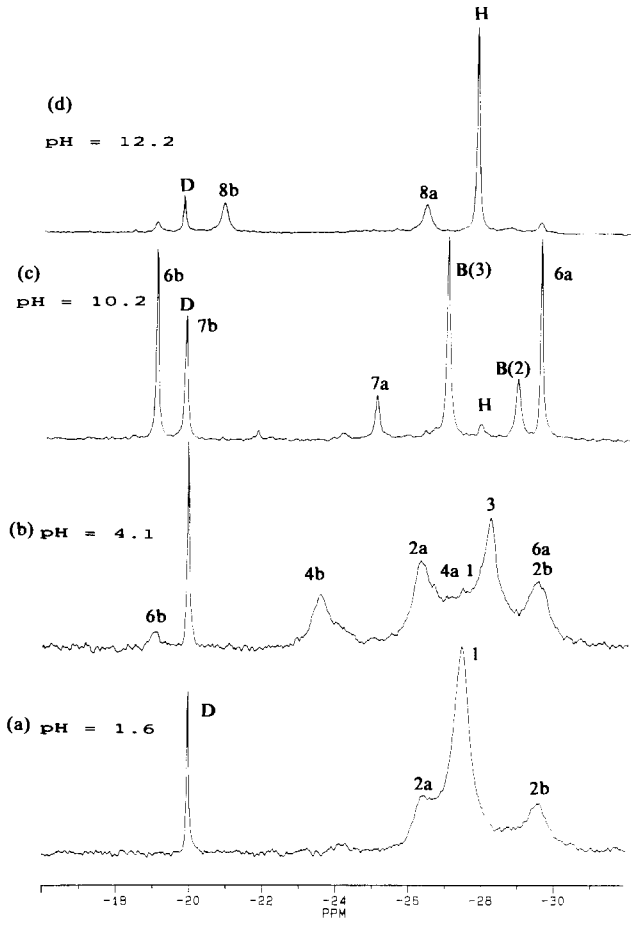


Figure 2. Effect of pH on the 20.2-MHz ^{15}N NMR spectrum at 298 K of a solution obtained by addition of 0.8 mol equiv of *N*-acetylglycine to $[Pd(en\text{-}^{15}N_2)(H_2O)_2](NO_3)_2$ in ^1H_2O. Peak labels correspond to those given in Scheme 1 and Table 1. Except for the following: **D**, $[Pd(en\text{-}^{15}N_2)_2]^{2+}$; **H**, $[Pd(en\text{-}^{15}N_2)(OH)_2]$; **B(2)**, $[\{Pd(en\text{-}^{15}N_2)(\mu\text{-}OH)\}_2]^{2+}$; **B(3)**, $[\{Pd(en\text{-}^{15}N_2)(\mu\text{-}OH)\}_3]^{3+}$.

$(H_2O)]^+$ (**2**). The greater sharpness of the lines compared with the betaine analogue presumably would be due to a slower exchange with water. This would reflect stronger Pd–carboxylate bonding, which, in turn, would be due to the net negative charge on the Hacgly$^-$ ligand. We have previously reported[4] NMR data for an analogous platinum complex, *cis*-$[Pt(^{15}NH_3)_2(Hacgly\text{-}O)(H_2O)]^+$, for which the characteristic dependence of J(Pt–N) on the trans ligand allowed the ammine N-atoms trans to Hacgly$^-$ and trans to H_2O to be assigned. The assignments of nitrogen nuclei in **2** (Table 1) were made on the basis of comparisons of relative nitrogen chemical shifts with these data.

At pH 4.1 (Figure 2b), the ^{15}N NMR peak due to **1** was much less intense. As well as the peaks from **2**, there was also a peak assigned to $[Pd(en)(Hacgly\text{-}O)_2]$ (**3**) which grew at the expense of those from **1** and **2** when more acetylglycine was added. The spectrum shown in Figure 2b also showed a broad peak at −23.5 ppm, and there was clearly another broad peak near −26.5 partly overlapping with peak **2a**. It is likely that these peaks were due to species containing bridging carboxylate. Reactions of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with $^+NH_3(CH_2)_nCO_2^-$ (n = 2, 3) near pH 4 gave $[\{Pt(NH_3)_2\}_2\{\mu\text{-}O_2C(CH_2)_nNH_3\}(\mu\text{-}OH)]^{3+}$, with the ammine nitrogen trans to bridging hydroxide relatively deshielded.[7] The peaks in our spectrum were therefore tentatively assigned to an analogous complex, $[\{Pd(en)\}_2(\mu\text{-}O,O'\text{-}Hacgly)(\mu\text{-}OH)]^{2+}$ (**4**). The spectrum also showed a weak, slightly broadened peak at −19.0 ppm. This shift corresponds to ethylenediamine ^{15}N trans to an N-donor ligand. When the pH was increased (see Figure 2c), this peak greatly increased in intensity, and sharpened. There was also a companion peak at −29.5 ppm, which initially overlapped with peak **2b**, corresponding to ethylenediamine ^{15}N trans to an O-donor. These peaks at higher pH (Figure 2c) were assigned to the N,O-chelate complex **6**. At pH 4.1, **6** would be in equilibrium with the protonated form, **5**, causing the observed peak broadening.

The ^{13}C NMR spectrum of a solution at pH 3.9 showed a peak due to carboxylate carbon in **2** at 179.2 ppm, shifted significantly from the peak for the free ligand at this pH (177.2 ppm). All of the other ^{13}C shifts for **2** were within 0.1 ppm of those for the free ligand (in the form Hacgly$^-$, with carboxylate deprotonated at this pH). At pH 1.2, the carboxylate group of the ligand is protonated (H_2acgly), which causes a shift in δ_C for the methylene group to 42.5 ppm, so that at this pH this peak was well separated from that for the methylene group in **2** (43.7 ppm), but the peaks for the acetyl methyl group and amide carbon remained coincident with those from the free ligand. A significant change in δ_C for the carbon atoms of the acetyl group would be expected if the compound contained a six-membered chelate ring with acetate O as well as carboxylate coordinated, rather than a coordinated water molecule, as postulated for **2**. These ^{13}C peaks were all sharp. A similar solution of $[Pd(en\text{-}^{14}N_2)(Dacgly\text{-}O)(D_2O)]^+$ (**2**) in D_2O at pD 1.1 showed in its ^1H NMR spectrum a peak due to free D_2acgly at 3.98 ppm and a well-resolved peak at 3.80 ppm assigned to **2**, but the acetyl methyl peaks were coincident at 2.04 ppm.

The peaks from the N,O-chelate complex **6** were dominant in the ^{15}N NMR spectrum between pH 7.0 and 10.5, and were quite sharp (line width < 2 Hz). Since $Pd(en)^{2+}$ was in excess, there were also peaks over this pH range due to $[\{Pd(en)(\mu\text{-}OH)\}_n]^{n+}$ (n = 3, peak B(3); n = 2, peak B(2)). The large increase in the amount of N,O-chelate complex present compared with complexes with acetylglycine O-bound when the pH was increased from 4 to 7 indicated that the protonated form **5** of the N,O-chelate complex was not very stable relative to the carboxylate complexes and that the pK_a for the deprotonation of **5** to give **6** is in the range 4–7 (probably near 6). As proposed for the diammineplatinum analogue,[4] and as usually observed for protonated peptide complexes,[8] the proton in **5** probably resides on the acetyl oxygen atom, but we have no direct evidence that this is the preferred tautomer in the palladium system.

The formulation of the major complex present at pH 10 as the N,O-chelate complex **6** was confirmed by the ^{13}C NMR spectrum, which showed a peak due to the carboxylate carbon atom at 187.9 ppm. This low shielding corresponds to carboxylate carbon in a five-membered chelate ring.[4,7,9]

There were additional minor peaks in ^{15}N spectra run between pH 7 and 10, including a peak at −24.8 ppm. Spectra run between pH 8 and 9 showed a companion peak at −19.6 ppm, whose shift was slightly dependent on pH, so that at pH 10.2 (Figure 2c) it coincided with peak D at −19.7 ppm from $[Pd(en\text{-}^{15}N_2)_2]^{2+}$. These two peaks were tentatively assigned to a dinuclear complex **7** with deprotonated acetylglycinate ligands bridging between palladium atoms (*cf.*, γ-aminobutyric acid analogues[2]). Isomer **7** might be expected to be preferred over the alternative structure with two acgly N atoms coordinated to the one metal for steric reasons, but other weak peaks present could be due to that isomer, or to other compounds containing bridging acetylglycinate.[10]

Over the pH range 7–10, these ^{15}N NMR spectra showed that there were significant quantities present of hydroxo complexes containing no coordinated acetylglycinate. ^{13}C NMR spectra of

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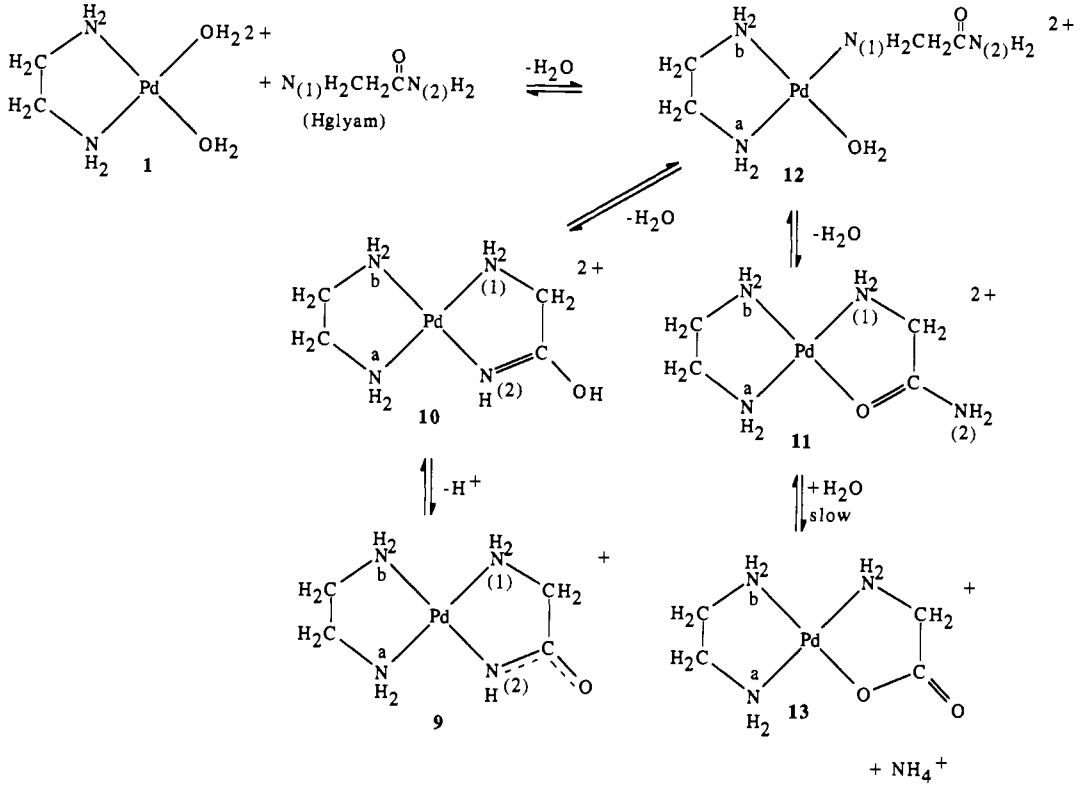
(8) Sigel, H.; Martin, R. B. *Chem. Rev.* **1982**, *82*, 185.

(9) Howarth, O. W.; Moore, P.; Winterton, M. J. *J. Chem. Soc., Dalton Trans.* **1974**, 2271.

(10) We considered the possibility that the peaks assigned to **7** might instead be an isomer of [Pd(en)(acgly-*N*,*O*)] related to **6** by restricted rotation about the C–N bond, similar to the isomers observed for N,S-chelate complexes of *N*-acetyl-*S*-methylcysteine,[11] but this possibility was not consistent with the variations in the spectra obtained between pH 10 and 12, discussed below.

(11) Appleton, T. G.; Bedgood, D. R.; Hall, J. R.; Prenzler, P. D. To be submitted for publication.

Scheme 2



the same solutions showed that there was also excess acetylglycine in these solutions. The free ligand was always in equilibrium with palladium starting complexes.

At pH 12.2, Figure 2d, the major peak in the ^{15}N NMR spectrum was H, due to [Pd(en-$^{15}N_2$)(OH)$_2$]. Most of the *N*-acetylglycine had therefore been displaced from palladium by hydroxide. The peaks from the N,O-chelate complex **6** were very weak. There were also new broad peaks due to a species with one ethylenediamine ^{15}N trans to an N-donor, and one trans to an O-donor. These peaks were assigned to [Pd(en-$^{15}N_2$)(acgly-*N*)(OH)]$^-$, **8**. An analogous ring-opening reaction to give [Pd(en)(gly-*N*)(OH)] was observed when the pH of a solution of [Pd(en)(gly-*N*,*O*)]$^+$ was increased from 10 to 12,[2] but the Pd–N bond was more stable there. At high pH, [Pt(NH$_3$)$_2$(acgly-*N*,*O*)] slowly underwent a ring-opening reaction to form *cis*-[Pt(NH$_3$)$_2$(acgly-*N*)(OH)]$^-$.[4]

Careful examination of ^{15}N NMR spectra run between pH 10 and 12 showed that the peaks assigned to the dinuclear complex **7** broadened and coalesced with those due to the hydroxo complex **8** as more alkali was added. The peaks assigned to the chelate complex **6** decreased in intensity, but remained relatively sharp.

There was no evidence for significant hydrolysis of the acetyl C–N bond under our experimental conditions.

Reactions of [Pd(en)(H$_2$O)$_2$]$^{2+}$ (1) with Glycinamide (Scheme 2). When approximately equimolar quantities of [Pd(en-$^{15}N_2$)(H$_2$O)$_2$](NO$_3$)$_2$ (**1**) and (H$_2$glyam)(NO$_3$) were mixed in aqueous solution and the pH of the solution was adjusted to 3.5 (Figure 3e), the ^{15}N NMR spectrum of the solution showed only two sharp singlets of equal intensity, at −20.2 and −22.9 ppm (apart from the weak peak D from [Pd(en-$^{15}N_2$)$_2$]$^{2+}$ impurity). These shifts both corresponded to ethylenediamine ^{15}N trans to nitrogen, so the complex present was formulated as [Pd(en-$^{15}N_2$)(glyam-$N_{(1)}N_{(2)}$)]$^+$ (**9**). There was no obvious basis for assigning each ^{15}N resonance to a particular nucleus. However, from comparison with the spectra of [Pd(en-$^{15}N_2$)(digly-$N_{(1)}N_{(2)}$)] (**14**) with digly N atoms selectively labeled with ^{15}N (see below), the lower-frequency peak in the spectrum of **9** could be assigned to ethylenediamine ^{15}N trans to the amide nitrogen, $N_{(2)}$. There was no change in the ^{15}N NMR spectrum when the pH was

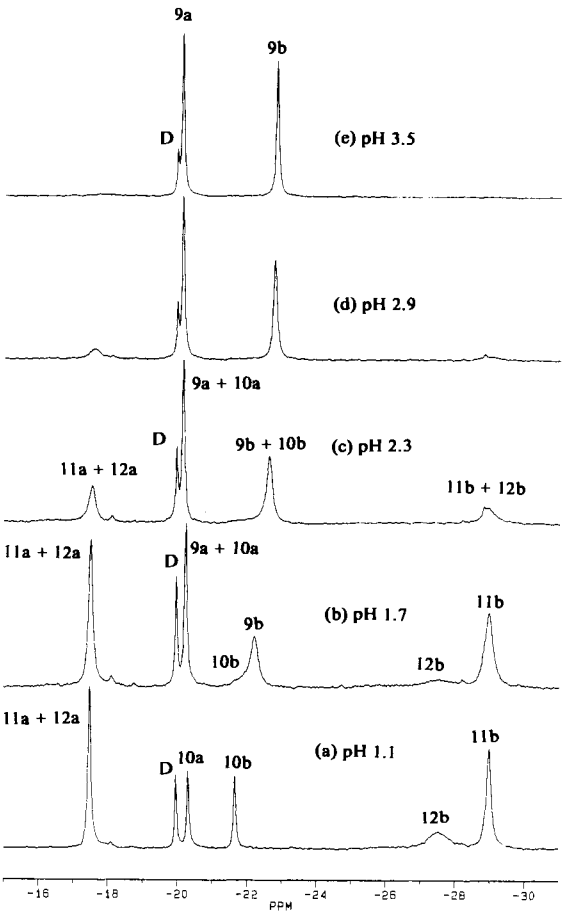


Figure 3. Effect of pH on the 20.2-MHz ^{15}N NMR spectrum at 298 K of a solution obtained by addition of an equimolar quantity of (H$_2$glyam)(NO$_3$) to [Pd(en-$^{15}N_2$)(H$_2$O)$_2$](NO$_3$)$_2$ in ^{1}H$_2$O. Peak labels correspond to those in Scheme 2 and Table 1, except for **D**, [Pd(en-$^{15}N_2$]$^{2+}$.

increased, up to pH 10, except that the peaks sharpened slightly. The ^{13}C NMR spectrum of this solution showed two doublets from the ethylenediamine methylene carbon atoms, a singlet at

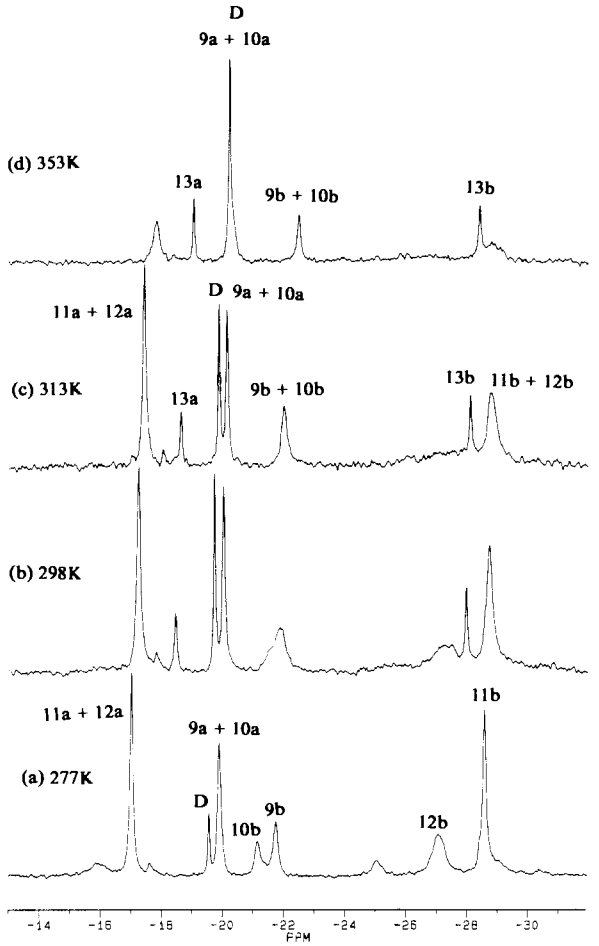


Figure 4. Variable-temperature 20.2-MHz ^{15}N NMR spectra of a solution obtained from addition of an equimolar quantity of $(H_2glyam)(NO_3)$ to $[Pd(en\text{-}^{15}N_2)(H_2O)_2](NO_3)_2$ in ^1H_2O, with the pH adjusted to 1.7. Peak labels correspond to those in Scheme 2 and Table 1, except for **D**, $[Pd(en\text{-}^{15}N_2)_2]^{2+}$.

48.5 ppm from the glycinamido methylene carbon, and a singlet at 186.9 ppm from the amide carbon. The low shielding of theamide carbon nucleus is consistent with the presence of the postulated five-membered chelate ring.[5] Addition of more glycinamide to these solutions had no effect beyond causing peaks from the free ligand to be present in the spectra.

When the pH of a solution containing **9** was decreased below 3.5, the changes in the ^{15}N NMR spectrum are illustrated in Figure 3 (spectra in Figures 3 and 4 are selected from a large number run at various pH and temperature values). The peaks due to the $N_{(1)},N_{(2)}$-chelate complex shifted and broadened down to pH 1.7 (Figure 3b). At pH 1.1 (Figure 3a), they were again quite sharp (although diminished in intensity). Careful examination of the shape of the peak near −22 ppm in the spectra at pH 2.3 and 1.7 showed an asymmetry consistent with a weaker peak at higher frequency just coalescing with the main peak. This was confirmed by variable-temperature ^{15}N NMR spectra at pH 1.7 (Figure 4). At 277 K (Figure 4a), the peak near −20 ppm remained relatively sharp, but that near −22 ppm had split into two peaks. The simplest way of explaining these changes in the spectra of the $N_{(1)},N_{(2)}$-chelate complex was in terms of an equilibrium between the deprotonated complex **9** and the protonated complex **10** (Scheme 2) which was slow enough on the NMR time scale at 277 K to allow separate peaks to be observed for N_b in **9** and **10**. The interconversion between **9** and **10** was still not fast enough at 298 K (Figure 4b) to cause complete averaging of the peaks. At higher temperatures (Figure 4c,d), as would be expected, the coalesced peak from **9b** plus **10b** sharpened (there was also clearly a significant effect of temperature on δ_N). These results show that the chemical shift of N_b trans to the amide nitrogen $N_{(2)}$ was much more sensitive to the protonation of **9** than the shift of N_a cis to $N_{(2)}$.

Once again, by analogy with protonated peptide complexes, we have proposed that the proton resides on the amide oxygen atom in **10**. At sufficiently high pH (>3.5), the complex was almost totally in the deprotonated form **9**, so that peak **9b** was sharp (Figure 3e). At low pH (1.1) (Figure 3a), the complex was almost totally in the protonated form **10**, so once again peak **10b** was sharp. For pH values near the pK_a for the deprotonation reaction, both forms would be present, giving separate peaks **9b** and **10b** at low temperature, and a broad peak for **9b** + **10b** at 298 K.

If the interpretation of the data given above is correct, the pK_a for the deprotonation of **10** must be close to 1.7 at 298 K. The chemical shift of the average signal, δ, at a given pH is related to the pK_a and the shifts of the acid form of the complex, δ_A, and the base form, δ_B, by eq 1.[12] Because peaks **9b** and **10b** were

$$pK_a = pH + \log\{(\delta - \delta_B)/(\delta_A - \delta)\} \quad (1)$$

incompletely averaged at 298 K, it was more appropriate to use the smaller pH dependence of the shift of the fully averaged peak from **9a** + **10a** to calculate pK_a at 298 K. Taking δ_A and δ_B as the chemical shifts at 298 K for this peak at pH 1.1 (−20.366 ppm) and pH 3.45 (−20.143 ppm) respectively, and δ as the shift for the peak at pH 1.68 (−20.275 ppm), the calculated value of pK_a was 1.5.

Also evident in Figure 3 was the growth of additional peaks, at the expense of those from **9** and **10**, when the pH of the solution was decreased below 3.5. Broad peaks near −18 ppm (corresponding to ethylenediamine ^{15}N trans to nitrogen) and −29 ppm (in the region corresponding to ethylenediamine trans to an O-donor) were visible in spectra run at pH 2.9 (Figure 3d) and 2.3 (Figure 3c). At pH 1.7 (Figure 3b) and 1.1 (Figure 3a), there was a relatively sharp peak near −29 ppm and a separate, broader peak near −27.5 ppm. In the low-temperature (277 K) spectrum of a solution at pH 1.7 (Figure 4a) both of these low-frequency peaks were sharper, and as the temperature was increased, they broadened and coalesced. These spectra may be explained in terms of interconversion between a $N_{(1)}$,O-chelate complex, **11**, and an aqua complex, **12**, in which glycinamide is bound through $N_{(1)}$ only, with the shifts for ethylenediamine ^{15}N atoms (N_b) trans to O different in the two complexes and shifts for the ethylenediamine ^{15}N atoms (N_a) trans to $N_{(1)}$ in the two complexes similar.

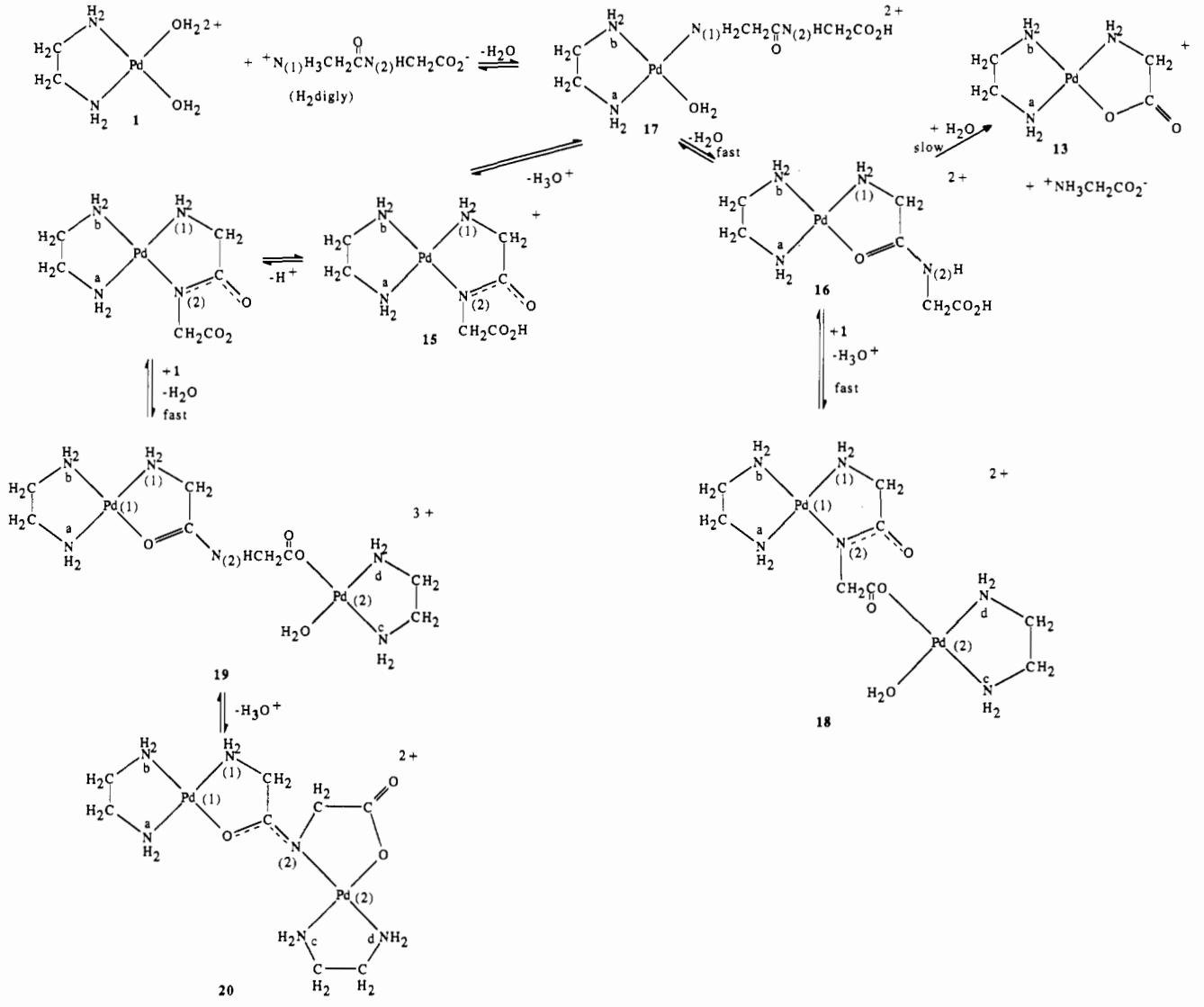
The spectrum at 277 K (Figure 4a) also showed two much weaker peaks near −16 and −25 ppm which appeared to coalesce with those from **12** at higher temperatures. The origin of these peaks was uncertain. It is possible that they could be due to a nitrato complex $[Pd(en)(Hglyam\text{-}N_{(1)})(ONO_2)]^+$ which was in rapid equilibrium with $[Pd(en)(Hglyam\text{-}N_{(1)})(H_2O)]^{2+}$ (**12**) at higher temperatures.

The ^{13}C NMR spectrum (298 K) of a solution at pH 1.1 showed a broad peak ($\Delta\nu_{1/2}$ 34 Hz) at 186.9 ppm. From the ^{15}N spectrum, the major species present under these conditions was $[Pd(en)(Hglyam\text{-}N_{(1)},O)]^{2+}$ (**11**), in equilibrium with a smaller amount of $[Pd(en)(Hglyam\text{-}N_{(1)})(H_2O)]^{2+}$ (**12**), and with $[Pd(en)(Hglyam\text{-}N_{(1)}N_{(2)})]^{2+}$ (**10**). The ^{13}C peak probably corresponded to overlapping peaks from the amide carbon atoms in the chelate rings of **11** and **10**. A peak from the nonchelate complex **12** would be expected to lower frequency but would also be expected to be broad, because of the interconversion with **11**. It was not observed.

The variable temperature spectra (Figure 4) showed that there was no rapid exchange between the $N_{(1)},N_{(2)}$-chelate complexes **9** + **10**, and **11** + **12**. Even at 378 K (not illustrated) the coalesced peaks from **9** + **10** remained sharp. At 353 K (Figure 4d) and above, however, the peak from **11a** + **12a** broadened. Since

(12) Edward, J. T.; Leane, J. B.; Wang, I. C. *Can. J. Chem.* **1962**, *40*, 1521.

Scheme 3



increased rate of interconversion between **11** and **12** could only sharpen this peak, the process responsible for this high-temperature broadening must involve breaking of the Pd–$N_{(1)}$ bond.

Hydrolysis of the amide C–N bond occurred slowly in strongly acid solutions (pH < 3) at 298 K to give $[Pd(en)(gly\text{-}N,O)]^+$ (**13**). The effect of this hydrolysis is evident in Figure 4. The low-temperature spectrum (Figure 4a) was run soon after the sample was prepared, but the sample was allowed to stand for 24 h before the high-temperature spectra were run. Peaks due to the glycinate complex **13** were present in the latter spectra (Figure 4b–d). Hydrolysis was more rapid at higher temperatures. The free ligand, in the absence of palladium, did not hydrolyse significantly under the same conditions.

Reactions of $[Pd(en)(H_2O)_2]^{2+}$ (1) with *N*-Glycylglycine (Scheme 3). Whether palladium complex or *N*-glycylglycine (H_2-digly) was in excess, the only peaks from a glycylglycinate complex observed in NMR spectra after the pH of the solution was adjusted to 10 were assigned to the $N_{(1)},N_{(2)}$-chelate complex, $[Pd(en)(digly\text{-}N_{(1)},N_{(2)})]$, **14**. With ^{15}N-enrichment only at ethylenediamine, the ^{15}N NMR spectrum showed two sharp peaks, at −15.8 and −20.3 ppm, corresponding to ethylenediamine ^{15}N nuclei trans to nonequivalent N-atoms. In the spectrum of a similar sample obtained from $^{15}N_{(1)},^{13}C_{(4)}$-labeled glycylglycine, the peak at −20.3 ppm remained a singlet, the peak at −15.8 ppm was split into a doublet (3.7 Hz), and a new doublet was present from digly $^{15}N_{(1)}$ at −44.2 ppm. Since ^{15}N–M–^{15}N coupling is observed only when nonequivalent ^{15}N atoms are mutually trans (M = Pd,[2] Pt,[5,13,14]), the peak at −15.8 ppm may be assigned as that trans to the digly terminal nitrogen, $N_{(1)}$. Confirmation of this assignment was provided by the ^{15}N NMR spectrum of the solution obtained with the $^{15}N_{(2)},^{13}C_{(2)}$-labeled glycylglycine. The peak at −15.8 ppm was a singlet, while that at −20.3 ppm was split into a doublet (5.0 Hz) by coupling with the trans peptide nitrogen $N_{(2)}$. The spectrum also showed a doublet of doublets (from coupling with trans ^{15}N and adjacent $^{13}C_{(2)}$) for the peptide N-atom, $N_{(2)}$ at −18.6 ppm.

At pH 10, the ^{13}C NMR spectrum of a solution prepared using unlabeled glycylglycine showed two peaks in the C=O region, at 182.9 and 179.7 ppm. Spectra run with the specifically-labeled digly ligands allowed unequivocal assignment of these peaks to $C_{(2)}$ (in the five-membered chelate ring) and $C_{(4)}$ (deprotonated free carboxylate) respectively. Thus, the ^{13}C spectrum obtained with the $^{15}N_{(1)}$, $^{13}C_{(4)}$-labeled digly showed a strong singlet at 179.7 ppm, and the spectrum obtained with $^{15}N_{(2)},^{13}C_{(2)}$-labeled digly showed a strong doublet at 182.9 ppm ($J(^{13}C_{(2)}–^{15}N_{(2)})$ 10.8 Hz).

The appearance of spectra obtained when the pH was decreased to 7.0 or below was very much dependent on the concentrations of the reactants. The simplest spectra were obtained for relatively dilute solutions with glycylglycine in excess (*e.g.*, digly:Pd = 1.6). Under these conditions, there were no significant changes in the spectra down to pH 2. When the pH was decreased to 0.9 (Figure 5), peaks from the ethylenediamine ^{15}N atoms of a $N_{(1)},N_{(2)}$-

(13) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 673.
(14) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 4685.

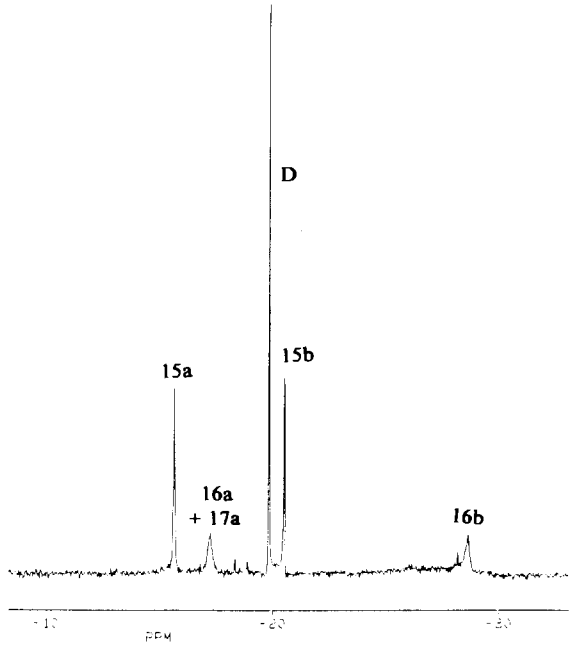


Figure 5. 20.2-MHz ^{15}N NMR spectrum of a solution obtained by addition of 1.6 mol equiv of *N*-glycylglycine to a solution of [Pd(en-$^{15}N_2$)(H_2O)$_2$](NO_3)$_2$ in ^1H_2O. The pH of the solution was adjusted to 0.9, after the solution had been allowed to stand for several hours at pH 10. The relatively high intensity of peak **D**, from [Pd(en-^{15}N)$_2$]$^{2+}$, was due to ligand redistribution reactions which occurred during standing (see text). Other peak labels are as in Scheme 3 and Table 1. The unlabeled, weak, sharp peaks are assigned to **20**.

chelate complex were still present, although they were no longer the only peaks in the spectrum. They were still sharp, and had moved only slightly from their shifts at pH 10. This may be contrasted with the analogous glycinamide complex discussed above, where protonation at amide oxygen caused both changes in δ_N and peak broadening. It was therefore likely that pK_a for the protonated coordinated peptide group in **14** was <0.9. The free carboxylate group in **14** would, however, be expected to be protonated at low pH, to give **15**. This protonation would have little effect on δ_N for the ethylenediamine N atoms.

The spectrum at pH 0.9 (Figure 5) also showed broad peaks at −17.3 and −28.7 ppm, with the latter apparently approaching coalescence with a weaker peak to higher frequency (−28.2 ppm). The peak at −17.3 ppm in spectra run using $^{15}N_{(1)}$,$^{13}C_{(4)}$-labeled digly was split into a doublet (4.0 Hz) from coupling with digly $N_{(1)}$, and there was a broadened doublet at −37.8 ppm from coordinated digly $N_{(1)}$. The peaks at −17.3 and −28.7 ppm were therefore assigned to N_a and N_b respectively of [Pd(en-$^{15}N_2$)(H_2digly-$N_{(1)}$,$O_{(1)}$)]$^{2+}$ (**16**). The weak broad peak at −28.2 ppm was assigned to N_b trans to H_2O in [Pd(en-$^{15}N_2$)(H_2digly-$N_{(1)}$)(H_2O)]$^{2+}$ (**17**) in equilibrium with **16**, with the interconversion at 298 K intermediate on the NMR time scale. The peaks from N_a (trans to digly $N_{(1)}$) in **16** and **17** would be similar, so that these peaks coalesced by 298 K. This behavior is analogous to that discussed above for glycinamide complexes.

With glycylglycine present in large excess, slow irreversible changes also occurred in the spectra, as the peak from [Pd(en-$^{15}N_2$)$_2$]$^{2+}$ (peak D) grew, and solids formed, presumably palladium(II) complexes of glycylglycinate not containing ethylenediamine. These changes were accelerated at higher temperatures. The effects of these processes are evident in Figure 5, which shows peak D much stronger than expected from the small amount initially present as an impurity in the solution of **1**.

When Pd(en)$^{2+}$ was in excess over glycylglycine, the spectra in acid solution were much more complex than when digly was in excess. The appearance of the spectra depended on the absolute concentrations of the reactants, as well as their ratio. The spectra were therefore interpreted in terms of the formation of dinuclear

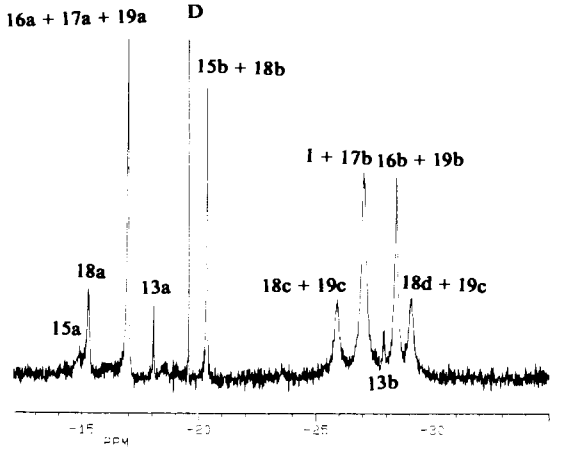


Figure 6. 20.2-MHz ^{15}N NMR spectrum at 277K of a solution obtained by addition of 0.5 mol equiv of *N*-glycylglycine to a solution of [Pd(en-$^{15}N_2$)(H_2O)$_2$](NO_3)$_2$ in ^1H_2O. Peak labels are as in Scheme 3 and Table 1, except for **D**, [Pd(en-$^{15}N_2$)$_2$]$^{2+}$.

complexes in which more than one Pd(en)$^{2+}$ unit binds to a glycylglycinate ligand. The free carboxylate group of **14** was able to react with **1** to give a dinuclear complex **18**. The most informative spectra were those obtained at low temperature. Figure 6 shows the ^{15}N NMR spectrum at 277 K of a solution at pH 1.0 obtained from H_2digly and excess **1**. The spectrum showed a peak from **1** and peaks assignable to ethylenediamine ^{15}N atoms trans to coordinated carboxylate (N_c) at −25.9 ppm and water (N_d) at −29.1 ppm (similar to the pattern observed for the betaine complex [Pd(en-$^{15}N_2$)(bet-*O*)(H_2O)]$^{2+}$,[2] or [Pd(en-$^{15}N_2$)(Hacgly-*O*)(H_2O)]$^+$ (**2**) (see above)). If these peaks were due to [Pd(en-$^{15}N_2$)(H_2digly-$O_{(2)}$)](H_2O)]$^{2+}$ in equilibrium with **1**, **15**, and **16**, they should have been observed also in spectra obtained from solutions with H_2digly in excess. The peaks from N_b trans to $N_{(2)}$ in **15** and **18** appear to be coincident (−20.4 ppm), but two peaks (−15.3, −14.9 ppm) were observed for N_a trans to $N_{(1)}$. By comparison of intensities with peaks from **18c** and **18d**, it appears that the stronger peak, at −15.3 ppm was due to N_a in the dinuclear complex **18**. The spectrum also showed peaks from [Pd(en-$^{15}N_2$)(H_2digly-$N_{(1)}$,$O_{(1)}$)]$^{2+}$ (**16**) (the weaker peak expected from N_b trans to H_2O in [Pd(en-$^{15}N_2$)(H_2digly-$N_{(1)}$)(H_2O)]$^{2+}$ (**17**) in equilibrium with **16** was obscured by the peak from **1**). If there was coordination of the carboxylate group of **16** or **17** to excess Pd(en)$^{2+}$ to form **19**, the peaks from the ^{15}N atoms bound to $Pd_{(2)}$ could well coincide with those from **18**. The ^{15}N atoms bound to $Pd_{(1)}$ in **19** might be expected to be very similar to those from **16**, as $Pd_{(2)}$ would be quite remote from $Pd_{(1)}$.

When the temperature was increased to 298 K, the reaction between excess **1** and the carboxylate groups of **14**/**15** and **16** + **17** became fast enough for the peaks from N_c and N_d in the different complexes to partly coalesce with that from **1**, and the peak from N_a in **15** + **18** was a broad, coalesced singlet. The peak from N_b in **15** + **18**, already one sharp peak at 277 K, remained sharp at higher temperatures.

There was slow hydrolysis to [Pd(en)(gly-*N*,*O*)]$^+$ (**13**) when acid solutions were allowed to stand (as with glycinamide, much faster than for free ligand under similar conditions).

Another dinuclear complex, which was present in larger proportions over the pH range 2–6 was [{Pd(en)}$_2$(digly)]$^{2+}$ (**20**), in which one Pd atom ($Pd_{(1)}$) was bound by digly terminal nitrogen $N_{(1)}$ and peptide oxygen $O_{(1)}$ and the other Pd atom ($Pd_{(2)}$) by peptide nitrogen $N_{(2)}$ and carboxylate oxygen, analogous to the platinum complex [{Pt(NH_3)$_2$}$_2$(digly)]$^{2+}$, which has been characterized by multinuclear NMR and X-ray crystallography.[5] The ^{15}N NMR spectrum of **18** with ^{15}N labels only on ethylenediamine showed four sharp peaks of equal intensity, two corresponding to nitrogen trans to N-donors, and two to nitrogen trans to O-donors (Table 1). Using specifically labeled glycylglycine in

a similar way to that detailed above for **14**, it was possible to assign the signals for ethylenediamine nitrogen trans to digly $N_{(1)}$ and $N_{(2)}$, and to assign the C=O signals, as in Table 1. As expected, the concentration of this species increased with increasing absolute concentration, but its peaks never dominated the spectra. This contrasts with the platinum analogue which became dominant in this pH range.[5]

Discussion

***N*-Acetylglycine Complexes.** Coordination of *N*-acetylglycine through carboxylate oxygen has long been recognized as the dominant coordination mode for this ligand.[8] The formation of $[Pd(en)(H_2acgly\text{-}O)(H_2O)]^{2+}$ (**2**) from reaction of **1** with *N*-acetylglycine under acid conditions is therefore not surprising. The platinum(II) complexes $[Pt(NH_3)_2(acgly\text{-}N,O)]$ and $[Pt(NH_3)_2(Hacgly\text{-}N,O)]^+$ were the first complexes reported in which this ligand forms a N,O-chelate ring.[4] In the palladium system, $[Pd(en)(acgly\text{-}N,O)]$ (**6**) formed readily when the pH of the solution was high enough to deprotonate the N-coordinated amide group. A major difference from the platinum system was the lack of a N,O-chelate complex with the acetyl oxygen atom protonated. This would appear to be a thermodynamic, rather than kinetic, difference between the two metal ions, as it is quite clear that the platinum complex with chelated protonated *N*-acetylglycine is present in equilibrium with other species in mildly acidic solution.[4] This difference may reflect a greater thermodynamic preference for M–N over M–O bonds for Pt(II) compared with Pd(II).

The acid dissociation constant (pK_a) for deprotonation of $[Pt(^{15}NH_3)_2(Hacgly\text{-}N,O)]^+$ was determined, from the variation in δ_N with pH, to be 2.6 ± 0.1.[4] For the palladium complex, it appears that pK_a is near 6. This substantial decrease in acidity of the coordinated amide group presumably reflects a weaker Pd–N interaction in **6** compared with the platinum analogue.

Glycinamide Complexes. With glycinamide, the dominant species under most conditions was the $N_{(1)}N_{(2)}$-chelate complex, **9**. This confirms the proposal by Lim,[15] based on a potentiometric study of the reaction of **1** with glycinamide, that a $N_{(1)},N_{(2)}$-chelate complex is formed with palladium(II), even under acidic conditions. Lim assumed that a $N_{(1)},N_{(2)}$-chelate complex with the coordinated amide group protonated, **10**, would not be stable and would be totally converted to a $N_{(1)}$,O-complex, **11**. On this basis, he estimated that the pK_a for deprotonation of **10** was 2.47. As we have shown, **10** does exist in equilibrium with **11**, and we were able to measure the pK_a for **10** from NMR spectra as 1.5, significantly lower than Lim's estimate.

The behavior of these palladium complexes contrasted with that observed for the diammineplatinum(II) system,[5] where no detectable complex was formed at pH 0.5, and at pH 5 the only glycinamide complex present was $[Pt(NH_3)_2(Hglyam\text{-}N_{(1)},O)]^{2+}$. No $N_{(1)},N_{(2)}$-chelate complex was ever observed with platinum.[5] Instead, hydrolysis occurred to $[Pt(NH_3)_2(gly\text{-}N,O)]^+$ and ammonia (rapid at pH 10, slow at pH 2–5). For a relatively "soft" metal ion, such as Pd(II) or Pt(II), a $N_{(1)},N_{(2)}$-chelate would be expected to be thermodynamically preferred over a $N_{(1)}$,O-chelate.[8] Thus, with tetraammineruthenium(II), the preferred complex is $[Ru(NH_3)_4(glyam\text{-}N_{(1)},N_{(2)})]^+$ (characterized by X-ray crystal structure determination[16]), while with ruthenium(III) $[Ru(NH_3)_4(Hglyam\text{-}N_{(1)},O)]^{3+}$ is preferred.[17] The thermodynamic preference for $N_{(1)},N_{(2)}$-chelation shown for the palladium complex is thus expected. This coordination mode would be thermodynamically preferred for platinum(II) as well, but is presumably not adopted because of kinetic barriers to isomerization from the $N_{(1)}$,O-complex. In this respect, Pt(II) is similar to the inert ion Co(III), for which $[Co(en)_2(Hglyam\text{-}N_{(1)},O)]^{3+}$ does not isomerize to the $N_{(1)},N_{(2)}$-chelate complex. At higher pH, there is rapid hydrolysis to $[Co(en)_2(gly\text{-}N,O)]^{2+}$.[18] Intramolecular amidolysis of glycine ethyl ester in $[Co(NH_3)_5(glyOEt\text{-}N)]^{3+}$ leads to $[Co(NH_3)_4(glyam\text{-}N_{(1)},N_{(2)})]^{2+}$, which, once formed, is stable toward hydrolysis of the amide group.[19] The lack of any detectable hydrolysis of the glycinamide ligand in the palladium system at 298 K is consistent with the statement by Sigel and Martin,[8] that "when coordinated to an amide oxygen, metal ions promote the hydrolysis of an amide bond. When substituting for a hydrogen at an amide nitrogen, metal ions inhibit the hydrolysis of amide bonds."

***N*-Glycylglycine Complexes.** When glycylglycine reacts with $[PdCl_4]^{2-}$ with the addition of the appropriate quantity of alkali, it forms $[PdCl(digly\text{-}N_{(1)},N_{(2)},O_{(2)})]^-$, with glycylglycinate coordinated tridentate, and the peptide group deprotonated.[8,20] In the (ethylenediamine)palladium(II) system, as long as ethylenediamine remains didentate, only two coordination sites are available. The coordination behavior of glycylglycine toward (ethylenediamine)palladium(II) is quite different from that with *cis*-diammineplatinum(II), where the available coordination sites are similarly restricted. The dominant palladium complex under most conditions is $[Pd(en)(digly\text{-}N_{(1)},N_{(2)})]$ (**14**), but an analogous $N_{(1)},N_{(2)}$-chelate complex was never observed in the reactions between *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and glycylglycine.[5] As with glycinamide, this is apparently due to a high kinetic barrier to rearrangement of a $N_{(1)},O_{(1)}$-chelate complex. $N_{(1)},N_{(2)}$-didentate coordination of glycylglycinate has been observed for many transition metals,[8,17] and a copper(II) complex has been characterized crystallographically.[21] The dominant diammineplatinum(II) complex under most conditions is the dinuclear compound $[\{Pt(NH_3)_2\}_2(digly)]^{2+}$. The analogous palladium complex, **20**, while present when $Pd(en)^{2+}$ was in excess, in mildly acidic solutions, was never present in such high proportions.

The pK_a for deprotonation of peptide oxygen in the $N_{(1)},N_{(2)}$-chelate complex appears to be quite low (<0.9). This is less than the value for deprotonation of peptide nitrogen in the complexes with glycylglycinate coordinated tridentate.[8,20]

Conclusions. Differences in thermodynamic preferences between Pd(II) and Pt(II) can sometimes affect the composition of an equilibrium mixture, as with *N*-acetylglycine in acid solution. More importantly, the large difference in lability of metal–ligand bonds does not always simply cause Pt(II) complexes analogous to Pd(II) ones to be formed more slowly, but can also cause the chemistry of the two metal ions to be quite different, as with glycinamide and *N*-glycylglycine. The behavior of palladium complexes should not be uncritically taken as a model for that of platinum analogues.

Acknowledgment. We thank the Australian Research Council for financial support and L. K. Lambert for assistance with some of the NMR spectra. We thank Dr. D. Fairlie of the 3D Centre at the University of Queensland for synthesis of the labeled glycylglycine samples.

Supplementary Material Available: Details of NMR spectra of specifically-labeled glycylglycine (1 page). Ordering information is given on any current masthead page.

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