Some Complexes of Palladium(II) with C-phenylglycine and Its Derivatives. Cyclopalladation of N,N-dimethyl-C-phenylglycine Ethyl Ester

ALEXANDER D. RYABOV, VLADIMIR A. POLYAKOV and ANATOLY K. YATSIMIRSKY

Department of Chemistry, Moscow State University, 117234, Moscow, U.S.S.R.

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The reaction of both D-C-phenylglycine and its methyl ester with palladium(II) acetate in acetic acid solvent gives the acetato-bridged dimer $[PdL(OAc)_2]_2$ *and the monomeric complex* $[PdL_2(OAc)_2]$. *On the basis of IR and* ^1H *NMR measurements it is suggested that the ligands are bonded to the metal in a monodentate fashion, amine nitrogen being a donor group. N,N-Dimethyl-C-phenylglycine ethyl ester reacts with Pd(II) acetate in acetic acid or chloroform and* Li_2PdCl_4 *in aqueous dioxane in the presence of sodium acetate to afford the cyclopalladated species* $[Pd\{Me_2NCH(CO_2Et)C_6H_4\}X]_2$, *where X = OAc or Cl. The assignment of the ortho-metallated compounds has been made on the basis of* ^1H *NMR data. Some characteristic reactions of these cyclopalladated complexes are presented.*

Introduction

As a rule palladium(II) forms chelate complexes with amino acids, their derivatives, and peptides [1]. Usually N and O donors of amino and deprotonated carboxylic groups are therewith involved in coordination [2]. In sulfur-containing amino acids and related compounds binding with the metal occurs through S and N sites [3]. There are a number of examples of N,N coordination in imidazole-containing amino acids [4]. Several other combinations of donor sites are known, namely S,O [5], N and the O atom of the carbonyl ester group [6]. Fairly often polydentate coordination takes place, especially in the case of peptides [7], which are often losing amide hydrogen on binding with palladium(II) [7].

Recent advances in the chemistry of cyclopalladated compounds [8] prompted us to prepare novel C,N chelated palladium(II) complexes of aromatic amino acids, having an aromatic C–Pd bond, which could be stabilized by coordination of Pd(II) with a nitrogen donor. This type of palladium complex has not been reported previously. The complexes are of interest for at least two reasons. Firstly, they may be useful intermediates in ortho-functionalization of aromatic fragments [9] and, secondly, these species with their strong sigma donor phenyl ligand may possess a biological, particularly carcinogenic, activity [10], since some examples of anti-tumor Pd(II) complexes have recently been reported [10, 11]. With this in mind we started with C-phenylglycine as a model compound. Its ortho-palladation would lead, if nitrogen is a donor site, to a five-membered palladocycle, which is more readily available than a six-membered one, as is expected in the case of widespread phenylalanine or tyrosine. The only known example of a related compound recently reported [12], is the platinum(II) complex [Pt(phe-2C,N)(phe-N)Cl] with ortho-metallated α-phenylalanine.

This paper reports the preparation and characterization of a series of palladium(II) complexes of C-phenylglycine (α-aminophenylacetic acid), its methyl ester, and N,N-dimethyl-C-phenylglycine ethyl ester. Palladation of the latter resulted in the formation of an ortho-metallated C,N chelate. A preliminary communication has been published elsewhere [13].

Results and Discussion

*C-Phenylglycine**

The addition of an approximately stoichiometric amount of C-phenylglycine to a solution of Pd(II) acetate in acetic acid (HOAc) solvent at *ca.* 50 °C leads to the rapid dissolution of this poorly soluble amino acid. The colour of the solution turns yellow. In a few minutes a white complex $[Pd(PhglyH)_2(OAc)_2]$ precipitates, while the dimeric species $[Pd(PhglyH)(OAc)_2]_2$ remains in the solution and can be isolated by column chromatography. Thus, this reaction proceeds according to

$$\text{`Pd(OAc)}_2\text{'} + \text{PhglyH} \xrightarrow{\text{HOAc}} \underset{(I)}{[Pd(PhglyH)_2(OAc)_2]} + \underset{(II)}{[Pd(PhglyH)(OAc)_2]_2}$$

*Abbreviations used: PhglyH, C-phenylglycine; PhglyMe, C-phenylglycine methyl ester.

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The relative yields of complexes *I* and *II* depend on the ratio [PhglyH]/[$Pd(OAc)_2$]. When the ratio is *ca.* 2, the 2:1 adduct *I* is the main product, but when the ratio is 1 or less the dimeric species *II* is predominant and usually no precipitation of *I* is observed.

Complex *I* has low solubility in all common solvents and this prevents its study by NMR. Only the most intense proton NMR resonances of *I* in d_6-DMSO could be assigned reliably. The methyl group of the terminal acetato ligand appears as a singlet at δ 1.90, revealing the presence of the only isomer, which is probably trans. Complexes of the type [$PdL_2(OAc)_2$], where L is different amines and phosphines, have been reported by Wilkinson and co-workers [14]. We suppose that *I* also belongs to this family of compounds, palladium(II) being bonded to the amino acid through amine nitrogen. Two IR absorptions at 3150 and 3075 cm^{-1} can be attributed to the coordinated NH_2 group [15]. The analysis of the IR spectrum in the carboxylic group region is complicated by the presence in *I* of two types of carboxylic groups. Nevertheless, some conclusions can be made by comparing our results with those obtained by Wilkinson [14]. A very strong band at 1600 cm^{-1} and a weaker band at 1370 or 1325 cm^{-1} suggest the presence of terminal acetates of trans configuration [14]. An absorption at 1670 cm^{-1}, which is intermediate between the absorptions of the zwitterionic (1610) and hydrochloride (1735) forms of PhglyH, may be assigned to the protonated noncoordinated -COOH group of the ligand. This suggestion is in line with ν(CO) at 1670 and 1650 cm^{-1} for the free carboxylic group in the related complex [Pd(acac)(PPh_3)(CH_2COOH)] [16].

We believe that the same coordination mode of the amino acid and Pd(II) occurs in the case of the binuclear complex *II*. This type of coordination for both *I* and *II* seems reasonable, since the reaction medium is acetic acid, and one can not expect the formation of N,O chelates with deprotonated carboxylato function. Dimer *II* is moderately soluble in MeOH and DMSO and its ^1H NMR spectrum has been recorded in the latter solvent. It reveals two unequivalent acetates at δ 1.80 and 1.88, attributable to bridging and terminal acetates, respectively [17, 18]. Firstly, the [$PdL(OAc)_2]_2$ type compounds have been prepared by Wilkinson [19], L being PAr_3 and $AsAr_3$. More recently analogous amine complexes have been synthesized [17, 18]. The spectroscopic features of *II* resemble well those reported for other amine complexes [17, 18]. The IR spectrum of the glass-like compound *II* is less informative compared with that of *I*. The presence of broad bands at 1550 and 1405 cm^{-1}, as well as at 1630 and 1360 or 1320 cm^{-1} indicates the presence of both bridging and terminal acetates, respectively [14, 19].

The dimeric structure of *II* is also supported by molecular weight determination. The value of 640 which was found is somewhat lower than the expected 751, but this is likely due to a low stability of the complex in MeOH solution, where it disproportionates to give *I* and Pd(II) acetate. The low stability of this type of complex has been noticed previously [18]. Pyridine cleaves acetato bridges of *II* to afford the monomer [Pd(PhglyH)(Py)($OAc)_2$], and this is also in accord with the recent observations of Nielson [18].

C-Phenylglycine Methyl Ester

This compound behaves quite similarly to PhglyH. Depending on the reaction conditions one can obtain either a 2:1 adduct [$Pd(PhglyMe)_2(OAc)_2$] (*III*) or a binuclear complex [$Pd(PhglyMe)(OAc)_2]_2$ (*IV*). Undoubtedly, PhglyMe is bonded to Pd(II) through the nitrogen of the amino group, and in the case of *III* this is supported by two absorptions at 3150 and 3050 cm^{-1} [15]. Contrary to *I*, in the ^1H NMR spectrum of *III* the acetate methyl appears as two singlets at δ 1.75 and 1.68 of approximately equal intensity. This may be due to the presence of *cis* and *trans* isomers of *III*. In the binuclear complex *IV*, bridging and terminal acetates resonate at δ 1.95 and 1.80, respectively.

The carbonyl stretching frequency in free and complexed PhglyMe is observed at *ca.* 1740 cm^{-1}, showing that the carbonyl oxygen is not involved in coordination. The similarity of the complexes obtained from either PhglyH or PhglyMe suggests that in both cases we have isolated monodentate Pd(II) complexes with a palladium–nitrogen bond. No palladation of the aromatic C–H bond occurs and, as a result, a desirable C,N chelate is not formed. These results support earlier observations [8] that the formation of five-membered palladocycles with primary and secondary nitrogen donors is an exception rather than a rule. These species are in fact formed only in certain cases [20, 21] and our failure to obtain palladocycles from PhglyH and PhglyMe is well understood in the light of these works.

It has been well documented by now [8] that five-membered palladocycles are much easier to obtain when a donor atom is tertiary nitrogen. Thus, N,N-dialkylated phenylglycine ester as well as the N-acylated derivative have been prepared.

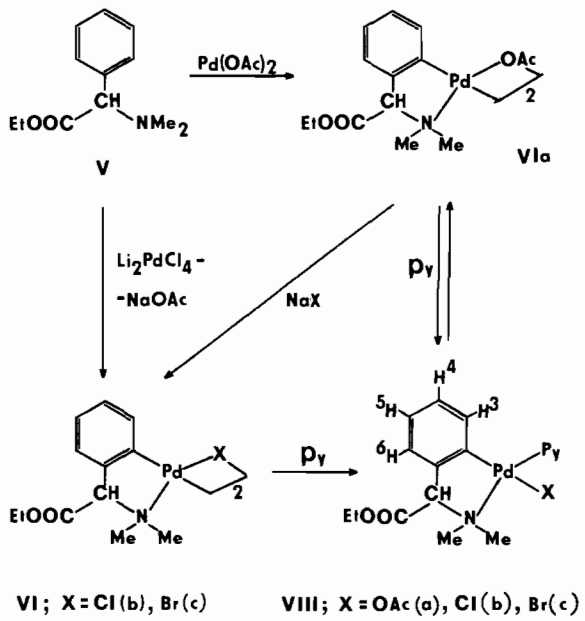
N-Acetyl-C-phenylglycine Methyl Ester

We attempted to obtain complexes of this compound with Pd(II) acetate under various conditions, *e.g.* in HOAc solvent at 50 °C and under reflux, as well as in refluxing toluene. But all efforts to isolate complexes of any definite composition proved unsuccessful. Nor did Li_2PdCl_4 react with the acylated amino acid ester in aqueous dioxane in the presence of NaOAc, and only the starting materials were recovered.

N,N-Dimethyl-C-phenylglycine Ethyl Ester (V)

The reaction of this compound with Pd(II) acetate in HOAc or $CHCl_3$ leads to the formation of the expected complex *VIa* with a Pd–C bond, see Scheme. The similar chloro-bridged dimer *VIb* can be obtained by reacting Li_2PdCl_4 with *V* in aqueous dioxane in the present of NaOAc. Alternatively, chloro-, as well as bromo-bridged dimers, may be produced from *VIa* in aqueous methanol in the presence of NaCl or NaBr, respectively.

The IR spectrum of *VIa* has two intense bands of bridging acetates [22] at 1580 and 1420 cm^{-1}. The dimeric structure of *VIa* and *VIb* is supported by molecular weight measurements. Spectral changes in the region of deformation vibrations of aromatic C–H bonds of *VIa–c* compared to *V* indicate the presence of a 1,2-substituted ring in the complexes [23]. Two bands at 730 and 700 cm^{-1} of *V* disappear on palladation, and a new band at 745 cm^{-1} is observed in the case of *VIb* and *VIc*. The acetato-bridged dimer *VIa* has a similar band at 750 cm^{-1} and an additional one at 680 cm^{-1}, which can be assigned to δ deformation vibration of the acetato ligand [15]. The stretching frequency of the ester carbonyl in *VI* is not altered compared with that in free *V*. This indicates that carbonyl oxygen is not involved in coordination, ruling out a possible structure *VII* with a six-membered palladocycle, similar to recently reported complexes [24].



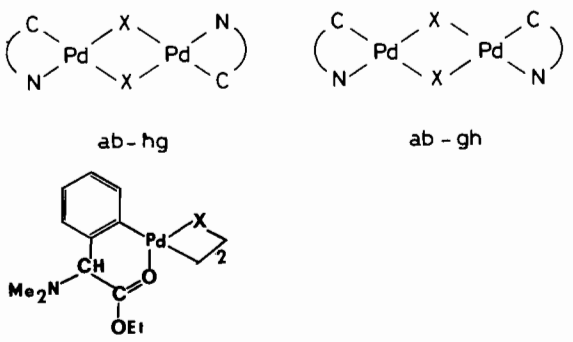
^1H NMR data of *V–VIII* are included in Table I. A downfield shift of N–CH proton in *VIa* compared with free *V* suggests that nitrogen is coordinated to the metal [8]. Its appearance as a singlet indicates that the N–CH fragment has an equivalent configuration in the dimeric molecule. Signals at δ 2.07, 2.15, and 2.97 refer to the acetato ligand and two diastereotopic [25] N-methyl groups. A similar spectrum has been previously observed for the related compound di-μ-acetatobis[N,N-dimethylbenzylamine-2C,N] dipalladium(II) [26, 27]. However, in the latter works no special attention has been drawn to the proper assignment of these signals.

A sharp singlet of acetic methyl reveals that both acetates are equivalent and *VIa* has a ab-hg type configuration. A signal at δ 2.97 refers to one of the diastereotopic methyls, since bridging acetates never resonate in a field lower than 2.4 ppm [28]. To ascribe signals at δ 2.07 and 2.15 we studied the

TABLE I. ^1H NMR Spectra of Cyclopalladated Compounds.[a]

Compound	Aromatic protons	CH_2	CH_3	N-CH	N-CH_3	OAc
		Et				
V[c]	7.30m[b]	4.06q	1.14t	3.86s	2.20s	
VIa	6.72m[b]	4.17q	1.26t	4.36s	2.15s 2.97s	2.07s
VIb	6.95m[b]	4.30q	1.34t	4.44s	2.85s 2.96s	
VIc	6.94m[b]	4.30q	1.35t	4.44s	2.87s 2.97s	
VIIIa[d]	6.06–6.96m	4.28q	1.32t	4.44s	2.80s 2.97s	1.94s
VIIIb	5.76–6.98m	4.27q	1.31t	4.39s	2.93s 2.96s	
VIIIc	6.00–7.30m	4.25q	1.28t	4.37s	2.95s	

[a]$CDCl_3$, δ scale, 28 °C; s - singlet, t - triplet, q - quartet, m - multiplet. [b]Position of a weight integral line. [c]CCl_4 solvent. [d]Exists only in solution.



VII

temperature dependence of the *VIa* spectrum in d_8-toluene solvent in a range from $-90°$ to $+90$ °C. At $-90°$ the methyl resonances appear at δ 2.00, 2.01, and 2.74; at $-20°$ at δ 2.02, 2.14, and 2.78, but at $+90°$ they are observed at 2.01, 2.20, and 2.84. It is seen that in the temperature range of 180° the position of one signal remains unchanged, while the others migrate to a lower field from δ 2.00 to 2.20 and from δ 2.74 to 2.84. It is well known [28e, 29] that dimeric acetato-bridged five-membered cyclometallated palladium(II) complexes have a folded 'boat' type structure, palladocycle being planar, as evident from X-ray structure determinations. Dihedral angles reported are 24 [28e], 25.7, and 25.9° [29]. In such a folded structure, as is seen from the study of molecular models of *VIa*, N-CH_3 groups of the complex are shielded by phenyl rings, α-protons being shielded to a greater extent compared with β-protons, Fig. 1. Evidently, the effect is greater the more the molecule is folded and the lower is the dihedral angle. On the contrary, unfolding of the

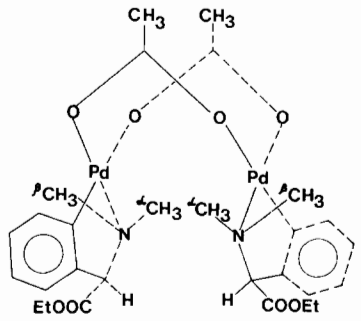


Fig. 1. The probable structure of the cyclopalladated chloro-bridged dimer *VIa*.

molecule should lead to a decrease of the shielding and concomitant downfield shift of methyl resonances. On the other hand this unfolding should have no effect on the chemical shift of acetate. Thus, the signal, which is not altered by the temperature, and those migrating with it should be assigned to the OAc-ligand and two N-CH_3 groups, respectively. Note that the signal of the stronger shielded αCH_3-group migrates up to 20 Hz, while the βCH_3-group shifts up to 10 Hz, *i.e.* the former is more sensitive, as expected, to the unfolding of *VIa*. The strong chemical nonequivalence of N-CH_3 groups ($\Delta = 0.82$ ppm) depends on at least two factors: (a) folded conformation of the acetato-bridged complex and (b) hindered rotation across the C–N bond [30] due to the coordination of nitrogen to the metal. In fact, on going to complexes *VIb* and *VIc*, which can be assumed to be planar [8], the Δ values are lower and equal to 0.11 and 0.10 ppm, respectively. A cleavage of acetato-bridges with pyridine to give *VIIIa* also decreases Δ markedly to 0.17 ppm. There is no shielding of the N-CH_3 groups by the phenyl ring in this case.

Recently, the ^{1}H NMR study of monomeric cyclopalladated complexes, obtained from the respective dimers reacting with d_5-Py, has been proved useful for the determination of the structure of these compounds [31, 32]. We applied the method to complexes *VIa* and *VIb*. The low-field part of the 250 MHz ^{1}H NMR spectrum of *VIIIb* is shown in Fig. 2.

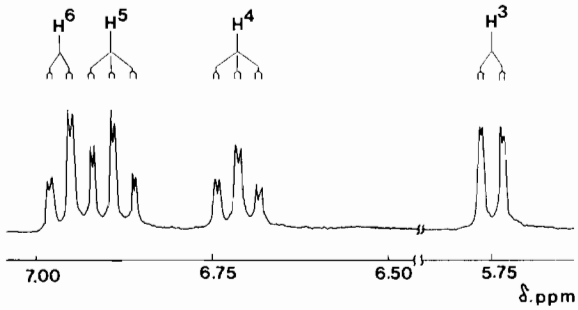


Fig. 2. The low-field region of the 250 MHz ^{1}H NMR spectrum of *VIIIb* in $CDCl_3$.

The signals of all four aromatic protons are well resolved here. The double doublet in the highest field (δ 5.76) undoubtedly refers to the H^3 proton, which is so strongly shifted due to anisotropic shielding from the pyridine ring [31]. The signal of the H^4 proton appears at δ 6.70, since it may also be affected by the Py ligand. Two remaining signals centered at δ 6.91 and 6.98 refer to H^5 and H^6 protons, respectively. A similar situation is found for *VIIIa*. The H^3–H^6 proton resonances are centered at δ 6.06 (dd), 6.73 (ddd), 6.90 (ddd), and 6.96 (dd), respectively. These findings show convincingly that the complexes in question do contain a palladium–carbon bond, which is stabilized by coordination with the N donor to form a C,N chelate.

It is interesting to note that we were unable to isolate *VIIIa* as a solid by addition of hexane to benzene or chloroform solution of the compound. The acetato-bridged dimer *VIa* precipitated instead. On the contrary, the monomer *VIIIb* can easily be obtained by this procedure. In $CDCl_3$ solution diastereotopic methyl groups of *VIIIb* begin to coalesce

in the presence of d_5-Py, the coalescence temperature being 45 °C at [Py] = 2.5 M.

Experimental

Electronic spectra were recorded on a Hitachi-356 spectrophotometer in EtOH. IR spectra were recorded on a Jasco-200 spectrophotometer in KBr pellets. ^{1}H NMR spectra were obtained on Tesla BS-497 (100 MHz) and Bruker WM-250 spectrophotometers with Me_4Si as an internal standard. Melting points were determined with a VEB Analytic Dresden PHMK apparatus and are uncorrected. Molecular weight determinations were made osmometrically.

Reagents

Palladium(II) chloride was a Reakhim reagent. Palladium(II) acetate was prepared as described [14]. D-C-Phenylglycine was purchased from Sigma. Its methyl ester and N-acetyl-C-phenylglycine methyl ester were prepared according to ref. [33]. N,N-Dimethyl-C-phenylglycine ethyl ester was prepared as follows. To a solution of phenylacetic acid ethyl ester (Koch-Light) (42 g, 0.26 mol) in 100 ml of CCl_4, bromine (20.8 g, 0.13 mol) was added dropwise, and the reaction mixture was heated and exposed to the light (600 W lamp). After the reaction was completed CCl_4 was removed and the residue was distilled *in vacuo* (145 °C, 15 mm Hg). 30.9 g of $C_6H_5CHBrCOOEt$ was obtained. To 12.2 g (0.05 g mol) of the latter 10 ml of 33% aqueous dimethylamine and 5 g of K_2CO_3 were added and the resulting mixture was heated on a water bath for 3 h. The solution was filtered off and the residue was washed with benzene. The organic fractions were combined and developed with 50 ml of 3% HCl. The aqueous fraction was neutralized with 5 N NaOH up to pH *ca.* 7, extracted with 100 ml of benzene, and dried over $MgSO_4$. Distillation *in vacuo* gave 5 g of N,N-dimethyl-C-phenylglycine ethyl ester.

Interaction of PhglyH with Palladium(II) Acetate. Diacetatobis(C-phenylglycine-N)palladium(II) (I) and Di-μ-acetatodiacetatobis(C-phenylglycine-N)dipalladium(II) (II)

Since it is known [2] that $PdCl_4^{2-}$ forms N,O chelates with amino acids, Pd(II) acetate was used in this study. To a solution of Pd(II) acetate in acetic acid (40 ml) at *ca.* 60 °C PhglyH (0.245 g, 1.62 mmol) was added. The intense colour of the starting solution faded on dissolution of the amino acid and after several minutes *I* precipitated. The latter was filtered after 20 min, washed with HOAc and $CHCl_3$. The yield was 31.2% (based on PhglyH). The filtrate was evaporated *in vacuo*, the residue dissolved in 2 ml of $CHCl_3$, and put onto a silica gel column. Traces of Pd(II) acetate were eluted first with $CHCl_3$ and then *II* was eluted with methanol. Evaporation of the solvent *in vacuo* gave the orange glass-like compound in a 23.2% yield. Analytical and physical data of the compounds are summarized in Table II. When PhglyH and Pd(II) were reacted in a ratio of 2:1 the monomer *I* was obtained in a 64% yield.

Complexes of PhglyMe. Diacetatobis(C-phenylglycine Methyl Ester-N)palladium(II) (III) and di-μ-acetatodiacetatobis(C-phenylglycine Methyl Ester-N)dipalladium(II) (IV)

Pd(II) acetate (0.16 g, 0.72 mmol) and ester (0.131 g, 0.79 mmol) were dissolved in 25 ml of acetic acid. The solution was kept at *ca.* 50 °C for 30 min. The solvent was removed *in vacuo*, the residue dissolved in 2 ml of $CHCl_3$, and column chromatographed as in the case of *II*. The yield of *IV* was 39%. Complex *III* was prepared by mixing palladium salt and ester in a ratio of 1:2 in benzene and precipitating the compound twice with hexane. Yield 38%.

Di-μ-acetatobis(N,N-dimethyl-C-phenylglycine Ethyl Ester-2C',N)dipalladium(II) (VIa)

To a solution of Pd(II) acetate (0.205 g, 0.92 mmol) in 30 ml of acetic acid 0.193 g (0.92 mmol) of *V* was added. The reaction mixture was kept at 55 °C for 15 min and then for 48 h at room temperature. The solvent was removed *in vacuo* and the oily residue was column-chromatographed on a SiO_2 column ($CHCl_3$ eluent). The first coloured band was separated, concentrated, and hexane added, yielding 0.164 g of *VIa* (48%). A crystalline product could be obtained on recrystallization from benzene–heptane. The complex may also be prepared by reacting Pd(II) acetate and *V* in $CHCl_3$. $\lambda_{max} = 330$ nm, $\epsilon_{max} = 1160\ M^{-1}\ cm^{-1}$.

Di-μ-chlorobis(N,N-dimethyl-C-phenylglycine Ethyl Ester-2C',N)dipalladium(II) (VIb)

To a solution of Li_2PdCl_4 (0.304 g, 1.16 mmol) and NaOAc (0.095 g, 1.16 mmol) in 80% aqueous dioxane at room temperature, *V* (0.24 g, 1.16 mmol) was added. After 5 min a reduction of Pd(II) became evident and after 10 min the reaction mixture was strongly diluted with water. The products were extracted with chloroform. The organic layer was dried over $MgSO_4$, concentrated, and column-chromatographed on silica gel ($CHCl_3$ eluent). Yield 21%. $\lambda_{max} = 338$ nm, $\epsilon_{max} = 1660\ M^{-1}\ cm^{-1}$. This compound was also prepared by metathetical reaction. Complex *VIa* (0.10 g, 0.13 mmol) was dissolved in 7 ml of MeOH and 5 ml of 0.1 *M* aqueous solution of NaCl was added. The precipitated *VIb* was filtered and dried *in vacuo* to give *VIb* in a 96% yield. The bromo-bridged compound *VIc* was prepared similarly.

TABLE II. Analytical and Physical Data for Palladium(II) Complexes.

Compound	Molecular formula	Anal. Found (Calcd.) (%)			Colour	M.p., °C
		C	H	N		
I	$C_{21}H_{26}N_2O_8Pd$	45.3 (45.6)	4.2 (4.6)	5.8 (5.3)	white	280–285
II	$[C_{12}H_{15}NO_6Pd]_2$[b]	38.9 (38.4)	3.9 (4.0)	3.9 (3.7)	orange	dec. > 205[a]
III	$C_{22}H_{28}N_2O_8Pd$	49.3 (47.6)	6.0 (5.1)	5.1 (5.3)	white-yellow	dec. > 280
IV	$[C_{13}H_{17}NO_6Pd]_2$	40.8 (40.1)	4.6 (4.4)		orange	dec. > 205[a]
VIa	$[C_{14}H_{19}NO_4Pd]_2$[c]	45.2 (45.2)	5.3 (5.1)	4.5 (3.8)	yellow	184–186
VIb	$[C_{12}H_{16}NO_2ClPd]_2$[d]	41.4 (41.4)	4.7 (4.6)	4.0 (4.0)	yellow	197–198
VIc	$[C_{12}H_{16}NO_2BrPd]_2$	37.4 (36.7)	4.7 (4.1)	3.6 (3.6)	yellow	197
VIIIb	$C_{17}H_{21}N_2O_2ClPd$	48.3 (47.8)	5.0 (5.0)	6.6 (6.6)	white	144–146

[a]These glass-like compounds began to soften at *ca.* 120 °C; mol weight found (calcd.): [b]620(751), [c]755(744), [d]640(696).

Chloro(N,N-dimethyl-C-phenylglycine Ethyl Ester-2C',N)pyridinepalladium(II) (VIIIb)

Complex *VIb* (0.076 g, 0.106 mmol) was suspended in 3 ml of benzene and pyridine (0.02 ml, 0.25 mmol) was added, resulting in complete dissolution of the material. Hexane was added to precipitate *VIIIb*, which was filtered and dried *in vacuo*. Yield 96%.

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