Metal Complexes of Biologically Important Ligands, CX [1].
Orthopalladation of N-(Diphenylmethylene) Schiff Bases from 
Peptide Esters - C,N versus C,N,O Coordination - Crystal Structure 
of ClPd[C₆H₄(C₆H₅)C≡N(Gly-L-Pro-L-Ala-OMe)-C,N,O] with cis/trans 
Peptide Bonds 

Andreas Böhm, Kurt Polborn [2], Wolfgang Beck* 
Institut für Anorganische Chemie der Ludwig-Maximilians-Universität, 
Meierstr. 1, D-80333 München, Germany 

Dedicated to Professor Jochen Ellermann on the occasion of his 65th birthday 
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N-(Diphenylmethylene) Peptide Esters, Orthopalladation, C,N,O Chelate, 
cis/trans Peptide Bonds 
The reaction of the N-(diphenylmethylene) Schiff base from glycyl-L-prolyl-L-alanine methyl ester 1 with tetrachloropalladate in the presence of sodium acetate affords the orthopalladated bicyclic C,N,O chelate 2. Complex 2 was characterized by X-ray diffraction. Remarkably, the unit cell contains two independent molecules, the cis isomer 2a and the trans isomer 2b (referring to the peptide bond). 2 reacts with PPh₃ by substitution of the carbonyl oxygen atom to give the C,N chelate 3.

Cyclopalladated compounds have been investigated extensively in the last few decades [3]. They show various interesting properties and have applications e.g. in organometallic synthesis [4], as catalysts [5] or as substances with liquid crystalline properties [6]. Orthopalladated complexes mostly consist of a palladacycle with a donor atom and a carbon atom as ligands [3]. Bicyclic and tricyclic complexes were obtained by palladation of ligands with one [7], two [8] or three [9] donor atoms and a large series of cyclopalladated Schiff bases have been synthesized [10]. Recently, we reported on the synthesis and reactivity of a series of orthopalladated complexes of N-(diphenylmethylene) Schiff bases from α-amino acid and peptide esters [11]. Comparable complexes were described by Grigg et al. and used as precursors for the synthesis of metal-1,3-dipoles [12]. By cyclopalladation of Schiff bases labelling [13] of peptides at the amino terminus seems to be possible [11].

Results and Discussion 
The reaction of tetrachloropalladate with N-(diphenylmethylene) Schiff bases of peptide esters in the presence of sodium acetate afforded dimeric chloro bridged orthopalladated complexes [11]. Now we found that with the corresponding Schiff base of glycyl-L-prolyl-L-alanine methyl ester 1 the monomeric C,N,O chelate 2 is obtained, which could be characterized by X-ray diffraction. 2 reacts with PPh₃ by substitution of the carbonyl oxygen atom to give the C,N chelate 3. 
The IR spectra of 2 and 3 show the carbonyl bands of the ester group at 1742 cm⁻¹ and of the free peptide amide groups at 1665 cm⁻¹. By coordination the absorptions of the C≡N group of 2 and 3 and of the coordinated carbonyl group of 2 are shifted to the arene wavelength region and cannot be assigned unambiguously. The ¹H NMR spectra of 2 and 3 show characteristic signals of the palladated phenyl group. They are separated from the other arene resonances and appear shifted to high field in the range of 6 7.1-6.4 as observed for other orthopalladated complexes [14]. For peptide bonds the existence of cis/trans conformers is well known. In general the trans isomer strongly dominates, but in the case of peptides containing a secondary amino acid (e.g. proline) the amount of the cis isomer can increase significantly [15]. The cis/trans isomers of proline containing peptides and proteins play an important role in biological systems and are e.g. involved in the folding process of proteins [15].

* Reprint requests to Prof. W. Beck.

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In the NMR spectra of 1 - 3 two sets of signals for the cis/trans isomers are observed (in the formulas only the trans-isomer is shown for 1 - 3), for each compound one with the strongest resonances could be assigned unambiguously. The ratio of the isomers could be determined by integration of suitable signals (e.g. the resonances of the methyl group of the alanine fragment) in the $^1$H NMR spectra ($cis/trans$ (CDCl$_3$) : 15/85 (1), 17/83 (2), 9/91 (3)). 

For 2 a broadening of the signals in the $^1$H NMR spectrum is observed. Presumably, in solution there exists an equilibrium between the mononuclear C,N,O chelate 2 and its corresponding dinuclear chloro bridged C,N chelate. This assumption is supported by the fact that sharp $^1$H NMR signals are observed for 3 where such an equilibrium is not possible. From these new results we assume that the chloro bridged orthopalladated complexes of Schiff bases of peptide esters we described recently [11] are also in equilibrium with their corresponding C,N,O chelates in solution, comparable with 2.

Molecular structure of 2 in the Crystal [16]

Suitable crystals were obtained by layering a solution of 2 (CH$_2$Cl$_2$/CDCl$_3$) with pentane. Interestingly, the unit cell contains two independent molecules, the cis isomer 2a (Fig. 1) and the trans isomer 2b (Fig. 2) ($cis/trans$ referring to the peptide bonds O1-C15-N2 and O1A-C15A-N2A). The planes C16N2C19 and O1C15C14 form an angle of 9.9(4)$^\circ$ in the cis-isomer and of 1.1(8)$^\circ$ in the trans-compound.

The palladium atom has a distorted square planar environment. The significant deviation of the C-Pd-Cl unit from linearity of about 18$^\circ$ is caused by the fusion of the two neighbouring five membered chelate rings. By coordination of the amide oxygen atom to the palladium atom the distances C15-O1 (126.5(6) pm) and C15A-O1A (124.7(6) pm) are lengthened compared with the distances C20-O2 (120.4(7) pm) and C20A-O2A (120.8(7) pm) of the free amide group.

As expected, the absolute configurations of the chiral $\alpha$-carbon atoms were determined as $Sc_{19}$, $Sc_{21}$ and $Sc_{19A}$, $Sc_{21A}$. In the crystal the molecules of 2 are connected through intermolecular hydrogen bridges between CO and NH groups (N3AH3A1-O4A 225 pm).

Experimental Section

All reactions were carried out in dry solvents under argon. - NMR: Jeol EX 400 or Jeol GSX 270, using the solvent as internal standard. - IR: Nicolet 520 FT-IR. - The Schiff base 1 was synthesized from benzophenonimine and glycyl-L-prolyl-L-alanine methyl ester according to a literature procedure [17].
Fig. 1. Molecular structure of 2a in the crystal. Selected bond lengths [pm] and angles [:] Pdl-C7 196.3(5), Pdl-N1 197.3(4), Pdl-C11 230.1(2), O1-C15 126.5(6), O2-C20 120.4(7), N1-C1 129.5(6), N2-C15 131.5(7), N3-C20 132.4(8), C7-Pdl-N1 82.1(2), C7-Pdl-O1 161.6(2), N1-Pdl-O1 79.9(2), C7-Pdl-C11 98.4(2), N1-Pd1-C11 173.4(12), O1-Pd1-C11 99.89(11), O1-C15-N2 120.5(5), O2-C20-N3 124.2(6).

1: Colourless powder. - IR (KBr): $\nu = 3303 \text{ cm}^{-1}$ m (NH), 1746 s (CO$_2$CH$_3$), 1641 vs, br (Amide I, C=N), 1599 w, 1576 w, 1543 m (C=C, Amide II). - $^1$H NMR (400 MHz, CDC$_3$): $\delta = 7.78-7.17$ (m, 11 H, Ph, NH), 4.60 (dd, $^2J = 8.3$ Hz, $^3J = 1.9$ Hz, 1 H, aCH), 4.45 (eq, 1 H, aCH), 4.25 (d, $^2J = 16.1$ Hz, 1 H, aCH), 4.15 (d, $^2J = 15.3$ Hz, 1 H, aCH), 3.68 (s, 3 H, OCH$_3$), 3.55-3.46 (m, 2 H, NCH$_2$), 2.35-1.79 (4 H, 2 CH$_2$), 1.35 (d, $^3J = 7.1$ Hz, 3 H, CH$_3$). - $^{13}$C NMR (100.5 MHz, CDC$_3$): $\delta = 173.20$, 171.62, 170.96, 170.26 (C=N, CO$_2$CH$_3$, 2 NCO), 139.28-127.79 (Ph), 59.91 (aC), 57.32 (aC), 52.37 (OCH$_3$), 48.30, 47.36 (NCH$_2$), 27.36 (CH$_2$), 25.13 (CH$_2$), 17.99 (CH$_3$).

C$_{24}$H$_{27}$N$_3$O$_4$Pd (421.53)
Calcd C 68.38, H 6.47, N 9.96 %, Found C 68.29, H 6.07, N 9.59 %.

2: To a solution of Na$_2$PdCl$_4$ (294 mg, 1 mmol) in methanol (20 ml) complex 1 (422 mg, 1 mmol) and sodium acetate (82 mg, 1 mmol) were added. After stirring for 24 h at room temperature the solution was filtered and concentrated to ca. 1 ml. After addition of pentane (50 ml) the resulting precipitate was centrifuged off, washed with pentane and dried in vacuo at 60 °C. Light yellow powder. - IR (KBr): $\nu = 3303 \text{ cm}^{-1}$ m (NH), 1746 s (CO$_2$CH$_3$), 1641 vs, br (Amide I, C=N, C=C, Amide II). - $^1$H NMR (270 MHz, CDC$_3$): $\delta = 7.57 - 7.26$ (m, 7 H, Ph, NH), 7.06- 6.87 (m, 2 H, C$_6$H$_4$), 0.54 (d, $^2J = 12.9$ Hz, 2 H, C$_6$H$_4$), 4.57-4.38 (m, 4 H, aCH$_2$, 2 aCH), 3.71 (s, 3 H, OCH$_3$), 3.43 (br, 2 H, NCH$_2$), 2.28-1.77 (m, 4 H, 2 CH$_2$), 1.57 (d, $^3J = 5.9$ Hz, 3 H, CH$_3$).

C$_{24}$H$_{26}$ClN$_3$O$_4$Pd (562.39)
Calcd C 51.26, H 4.67, N 7.47 %, Found C 50.44, H 4.70, N 7.20 %.

3: To a solution of 2 (281 mg, 0.5 mmol) in CH$_2$Cl$_2$ (20 ml) PPh$_3$ (131 mg, 0.5 mmol) was added. After stirring for 2 h at room temperature the solution was filtered and concentrated to ca. 1 ml. After addition of pentane (50 ml) the resulting precipitate was centrifuged off, washed with pentane and dried in vacuo at 60 °C. Light yellow powder. - IR (KBr): $\nu = 3323 \text{ cm}^{-1}$ m (NH), 1741 m (CO$_2$CH$_3$), 1665 vs (Amide I), 1613 w, 1597 w, 1573 m, 1554 w, 1530 m (C=C, C=N, Amide II), 1436 s (PPh$_3$). - $^1$H NMR (400 MHz, CDC$_3$): $\delta = 7.78-7.31$ (m, 21 H, Ph, NH), 6.73-6.41 (m, 4 H, C$_6$H$_4$), 5.09 (d, $^2J = 12.9$ Hz, 1 H, aCH), 4.53 (dd, $^2J = 7.8$ Hz, $^3J = 2.1$ Hz, 1 H, aCH), 4.21 (br, 1 H, aCH$_2$), 4.06 (eq, 1 H, aCH), 3.77 (br, 1 H, NCH$_2$), 3.59 (s, 3 H, OCH$_3$), 3.23 (dd, $^3J = 8.4$ Hz, $^2J = 16.0$ Hz, 1 H, NCH$_2$), 2.31-1.77 (4 H, 2 CH$_2$), 1.17 (d, $^3J = 7.0$ Hz, 3 H, CH$_3$). - $^{13}$C NMR
(100.5 MHz, CDCl₃): δ = 187.41 (C=N), 172.82, 171.44, 167.44 (CO₂CH₃, 2 NCO), 158.45 (Pd-C), 150.87–123.72 (Ph), 60.47 (qC), 56.30 (aC), 52.04 (OCH₃), 48.31, 46.48 (NCH₂, aC), 28.99 (CH₂), 24.19 (CH₂), 17.19 (CH₃). -

³¹P NMR (109.4 MHz, CDCl₃): δ = 44.09.

C₄₂H₂₄Cl₂N₃O₄Pd (824.71)
Calcd C 61.17, H 5.02, N 5.09 %, Found C 60.76, H 5.00, N 4.92 %.

X-ray structure determination of 2 [16]
C₄₂H₂₄Cl₂N₃O₄Pd x CH₂Cl₂, M = 647.25, T = 293(2) K, NONIUS CAD4 diffractometer, crystal size 0.57x0.53x0.40 mm³, orthorhombic, P2₁2₁2₁, a = 9.381 (3), b = 24.707 (9), c = 25.07 (1) Å, ß = 90.00 (3), V = 5811 (4) Å³, Z = 8, two independent molecules, 1 CH₂Cl₂ disordered, split, d(calc.) = 1.480 g/cm³, µ(Mo-Kα) = 0.948 mm⁻¹, F(000) = 2624, 2972 reflections collected, 9692 independent reflections [R(int) = 0.024], semiempirical absorption correction from ψ-scans, max./min. transmission 0.9995/0.8889, data/parameters = 9692/710, GOOF = 1.088, R₁ = 0.039, wR² = 0.098 [I>2σ(I)], R₁ = 0.051, wR² = 0.107 (all data), absolute structure parameter = -0.01(3), largest diff. peak/hole 0.764/-0.325 e Å⁻³ [16].

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[16] Further details of the crystal structure determination are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ (UK) on quoting the depository number CCDC-102168.