Cyclotetrapeptide Complexes of Nickel(II) and Palladium(II) by Template Synthesis from Dipeptide Esters with Functionalized Side Chains − Crystal Structure of [(*cyclo*-Gly-β-Ala-Gly-β-Ala-4H$^+$)Cu](PPN)$_2$[‡]

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Dedicated to Professor Dieter Seebach on the occasion of his 65th birthday

Keywords: Peptides / Nickel / Palladium / Copper

The cyclocondensations of dipeptide esters [Gly-L-Asp(OMe)$_2$, Gly-L-Glu(OMe)$_2$, L-AspOMe-β-AlaOMe, β-Ala-L-Lys(ω-*N*-Boc,OMe), β-Ala-L-Orn(ω-*N*-Boc,OMe)] at nickel(II), palladium(II), and copper(II) templates give dianionic square-planar complexes of deprotonated cyclotetrapeptides that contain functional groups in the side chains. The complexes with 14- or 16-membered rings were isolated as [Ph$_3$PNPPh$_3$]$^+$ salts. Hydrolysis of {[*cyclo*-Gly-Asp(OMe)-Gly-Asp(OMe)-4H$^+$]Pd}$^{2-}$ affords the tetraanionic complex [{*cyclo*-Gly-Asp(O$^-$)-Gly-Asp(O$^-$)-4H$^+$}Pd]$^{4-}$(Li$^+$)$_2$(PNP$^+$)$_2$. The crystal structure of [(*cyclo*-Gly-β-Ala-Gly-β-Ala-4H$^+$)Cu](PPN)$_2$ is also reported.

Introduction

Biologically active natural cyclic tetrapeptides[2] are promising candidates for new anticancer agents.[3] Seebach et al. have pioneered studies on the synthesis, structure, and biological activity of *cyclo*-β-tetrapeptides.[2,4] Although some cyclotetrapeptides are difficult to synthesize,[2,4,5,6] our facile route from non-activated peptide esters on metal centres[7,8] involves the cyclocondensation of dipeptide esters at metal templates (Cu^{2+}, Ni^{2+}, Pd^{2+}) and requires neither a protecting nor an activating group or a coupling agent. Also, high dilution of the reaction mixture is not necessary. With half sandwich tripeptide ester ruthenium complexes cyclization to cyclotripeptides has been observed.[9] Current interest in the metal complexes of cyclic peptides includes the functionalization of biomolecules,[10] complexes with marine natural products,[11] their structure,[12] in "molecular engineering",[13] as selective ligands,[14] as models for metal enzymes,[8,11,12,15] and as precursors for polyazamacrocyclic complexes.[1,16] Cyclopeptide complexes may be suitable diagnostic and therapeutic tools.[17] For example, linear peptides have been cyclized using conventional methods and their metal complexes may find use for scintigraphy and radiotherapy.[18] These applications seem to require water-soluble complexes and, therefore, we aimed to synthesize cyclotetrapeptide complexes that contain functional groups in the ligands. Seebach and co-workers have reported a series of linear and cyclic β-oligopeptides with functionalized polar side chains derived from serine, aspartic and glutamic acids.[19] We also report here the crystal structure of [Cu(*cyclo*-Gly-β-Ala-Gly-β-Ala-4H$^+$)](PPN)$_2$.

Results and Discussion

1. Cyclotetrapeptide Complexes with Aspartic and Glutamic Acid Units

The hydrochlorides of dipeptide dimethyl esters from aspartic acid and glycine react with Na_2PdCl_4 and $NiCl_2$ in the presence of NaOMe to give the dianionic complexes **1** and **2**, which have been isolated as their PPN$^+$ salts (**1a**, **2**) [PPN$^+$ = bis(triphenylphosphoranylidene)ammonium] in good yields. Similarly, [Gly-L-Glu(OMe)$_2$] and Na_2PdCl_4 gave the cyclotetrapeptide complex **3**. The dipeptide of β-alanine and aspartic acid affords complexes **4** and **5**.

Condensation of [Gly-L-Asp(OMe)$_2$] and [L-Asp(OMe)-β-AlaOMe] at the metal centre could lead to either 12- or 14-membered chelate rings. The less strained C_2-symmetric 14-membered ring is probably formed; a 12-membered chelate from Gly-L-AlaOMe was obtained only in low yield.[7] Recently it was demonstrated that 13-membered cyclic tetrapeptides are easier to synthesize from linear tetrapeptides, and are more stable and conformationally more homogeneous, than are 14-membered rings, which have unfavorable strain.[20]

[‡] Metal Complexes of Biologically Important Ligands, CLIII. Part CLII: Ref.[1]

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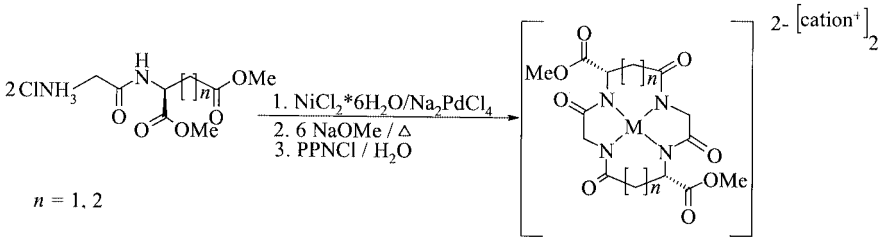
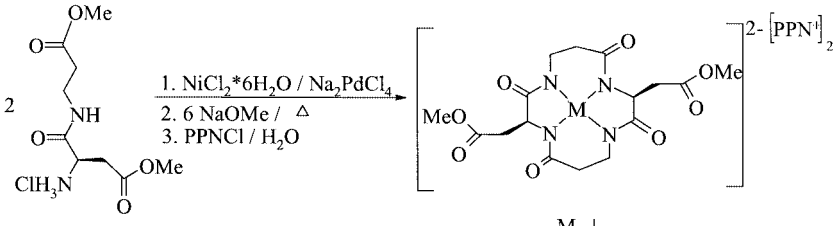


1a: $n = 1$, M = Pd^{2+}, cation = PPN^+
1b: $n = 1$, M = Pd^{2+}, cation = Na^+
2: $n = 1$, M = Ni^{2+}, cation = PPN^+
3: $n = 2$, M = Pd^{2+}, cation = PPN^+



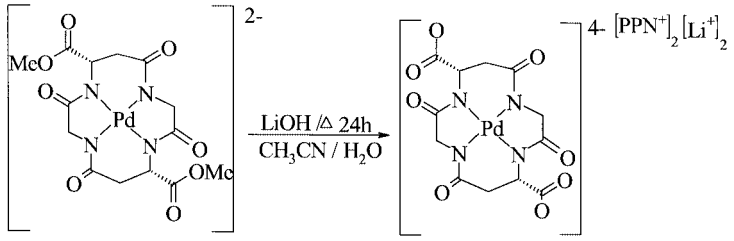
M	
Ni^{2+}	**4**
Pd^{2+}	**5**

The ester groups of complex **1** were hydrolyzed to give the tetraanionic palladium complex in **6**. For possible use in diagnostics and radiotherapy [17,18] the water-soluble sodium salts **1b** and **7** were prepared by the addition of water to a mixture of H-Gly-Asp(OMe)$_2$, NaOMe, and metal salt. The structures of complexes **1b** and **7** were verified by 2D NMR techniques. In one preparation of **7** the sodium compound $Na(OH_2)_4[O_2CCH_2CHC(O)NHCH_2C(O)NH]_2$ was obtained, as a by-product containing the (3,6-dioxopiperazine-2-yl)acetate anion, from [Gly-L-Asp(OMe)$_2$] by cyclocondensation of the amino group of the glycine component and the α-CO_2Me group of the aspartic acid component in the dipeptide. This product was characterized by X-ray crystallography [21] after recrystallization from water.

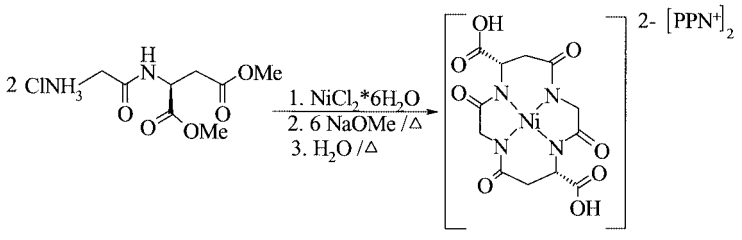
The mass spectra (FAB) show peaks for [M^{2-} + H^+] (m/z = 475 (**1**), 427 (**2**), 455 (**4**), 503 (**3**, **5**). An ESI spectrum of **6** exhibits peaks, among others, at m/z = 447 [M^{4-} + $3H^+$], 984 [M^{4-} + PPN^+ + $2H^+$] and 453 [M^{4-} + Li^+ + $2H^+$].

In the IR spectra characteristic signals appear for the ester groups (**1**: 1735 cm^{-1}; **4**, **5**: 1725 cm^{-1}) and for the carboxylate group in **6** at 1677 and 1665 cm^{-1}.

Two amide I absorptions of **1**−**5** appear at 1590 and 1570 cm^{-1}.



1 **6**



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The nickel complex **2** undergoes stepwise and selective hydroxylation at the α-carbon atom of the glycine units with oxygen in air.[8] This reaction is related to the copper enzyme peptidylglycine α-hydroxylating monooxygenase (PHM), which catalyzes the stereospecific hydroxylation of the α-C atom of the terminal glycine unit of a peptide.[22]

The ^{1}H NMR spectra (Tables 1 and 2) of compound **1** show only one signal for the two COOMe groups of the cyclotetrapeptide, while for **2**−**5** there are two singlets in a 1:1 ratio. Concomitantly, the glycine-containing complexes **2** and **3** show two AB sets for the glycine CH_2 protons, whereas **1**, and the hydrolyzed carboxylate derivatives **6** and **7**, have only one such set. Therefore compounds **1**, **6**, and **7** have a C_2 symmetry, while **2**−**5** have only C_1 symmetry, but for all compounds there exsists only one conformation of the cyclotetrapeptide unit. [Some weaker signals (< 10% intensities compared with the main signals) in all spectra indicate other, minor, cyclopeptide conformations.] Careful analysis of the AB parts of the glycine moieties of **1**−**3** and **6**, **7** (using the program WinDNMR) shows that the two CH_2 protons generally have quite different environments ($\Delta\delta > 0.20$ ppm), except for both glycine chelates in **3** and one in **2** (Table 1).

Table 1. ^{1}H NMR data (glycyl protons) of **1**−**3**, **6**, **7**

Compound	δ ($H_{A/B}$) [ppm]	J_{AB} [Hz]	Δδ (H_A/H_B)
1a	4.085/ 3.837	−19	0.248
2	3.725/ 3.477	−19	0.248
	3.588/ 3.534	−19	0.054
3	3.961/ 3.873	−19	0.088
	3.890/ 3.741	−19	0.149
6	4.120/ 3.863	−18	0.257
7	4.052/ 3.835	−18	0.217

Table 2. ^{1}H NMR data (aspartyl protons) of **1**, **2**, **6**, **7**

Compound	δ (H_A)	δ (H_B)	δ (H_X)	J_{AB}	J_{AX}	J_{BX}
1a	2.692	2.528	4.427	−15.7	4.7	4.6
2	2.696	2.639	4.014	−14	6	6
	2.454	2.489	4.122	−16.3	6	3
6	2.730	2.507	4.359	−15	4	4
7	2.673	2.692	4.136	−17	10.3	1.7

The ^{13}C NMR spectra of all compounds confirm the given interpretations, although good-quality spectra could not always be obtained.

2. Cyclopeptide Complexes with Lysine and Ornithine Units

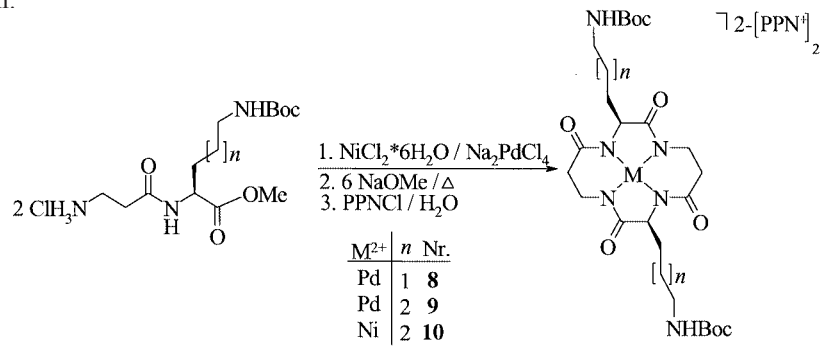
The dipeptide esters β-Ala-L-Lys(ω-NBoc)OMe and β-Ala-L-Orn(ω-NBoc)OMe afforded, with Na_2PdCl_4 or $NiCl_2$, compounds **8**−**10**. Treatment of **9** with a solution of hydrogen chloride in methanol furnished the free cyclopeptide **11**, which was easily separated due to its low solubility in methanol. Finally, the Boc protecting group can be cleaved by trifluoroacetic acid.

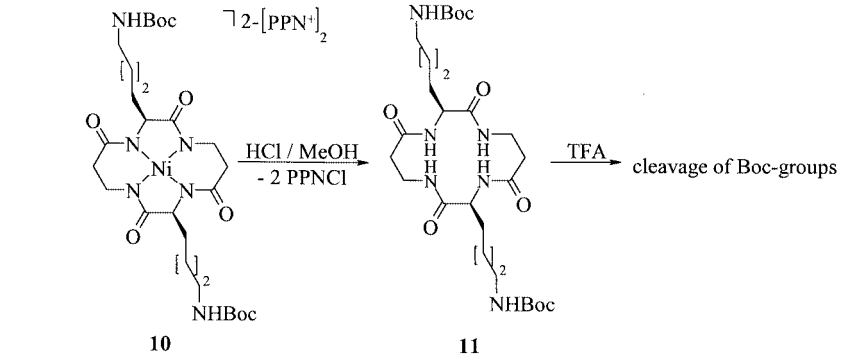
3. Crystal and Molecular Structure of [(*cyclo*-Gly-β-Ala-Gly-β-Ala-4H$^+$)Cu(PPN)$_2$ (12)

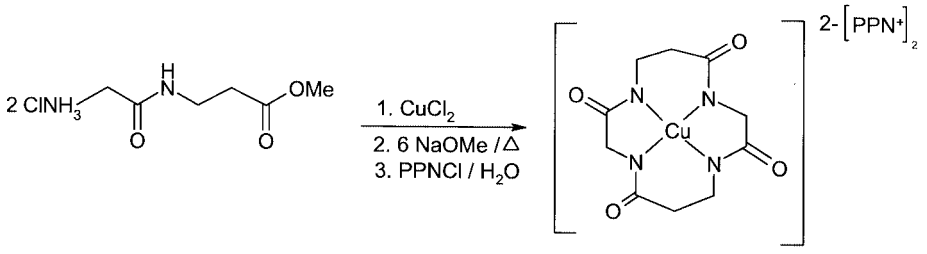
The crystal structure of the palladium complex [Pd(*cyclo*-Gly-β-Ala-Gly-β-Ala-4H$^+$)](PPN)$_2$ has been reported.[7] Crystals of the copper complex **12**, formed from Gly-β-Ala-OMe at the Cu^{2+} ion,[7] were obtained from acetonitrile solution, but as they quickly became opaque when taken out of the mother liquor the structure was determined at 266 K. Even so, the crystals decayed slowly, approximately 12% over the course of the measurement. The structure refinement yielded an average composition of the crystal as **12**·MeOH·2MeCN·6H_2O, with the methanol solvent disordered over two positions and two of the water molecules disordered over three positions.

The program VOID revealed that without the solvents the crystal structure contains large voids, making up for nearly 25% of the cell volume. The structure can be described as a sheet structure with alternating cation and anion layers parallel to the *ab* plane. Within the anion sheets, the anions are connected to a one-dimensional polymer in the (0 1 0) direction via a complex system of hydrogen bonds involving the amide oxygens and the water and methanol OH functions. A side view of the undulating sheets thus formed is given in Figure 1. The acetonitrile molecules are situated between the PPN cations, with their molecular axes almost parallel to the *z*-direction and their methyl groups pointing towards the neighbouring anion layers, excluding any hydrogen bond interactions of the nitrile nitrogens with the anion H-bond system.

The molecular structure (Figure 2) requires only a few comments on the complex anion. Due to crystal decomposition and other common difficulties in describing structures containing so many water molecules, the geometrical parameters have rather high standard deviations. Nonetheless, the copper ion clearly has a square-planar coordination with the four deprotonated amide nitrogens [the σ(plane)







12

parameter is 0.123 Å, with Cu1 0.032(6) Å out of that plane]. There are no further ligands attached to the copper, and no intermolecular contacts within 4.0 Å of the copper. The average copper−nitrogen distance of 1.928 Å is normal for a deprotonated amide nitrogen, and the long C−O and short C−N distances of the amide group suggest a strong contribution of the O−C=N form. Table 3 gives the important geometrical parameters of **12** along with those of other copper complexes of 1,4,8,11-tetraazacyclotetradecanes with 0, 1, and 2 oxo groups in the ligand backbone and the corresponding parameters of the Pd^{II} analogue of **12**.[7]

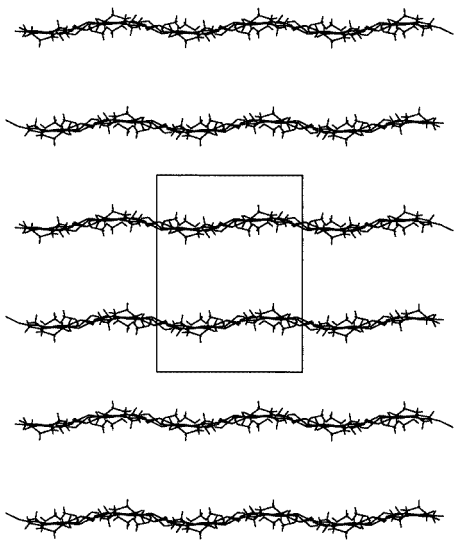


Figure 1. Packing of the anion sheets in the crystal of **12**

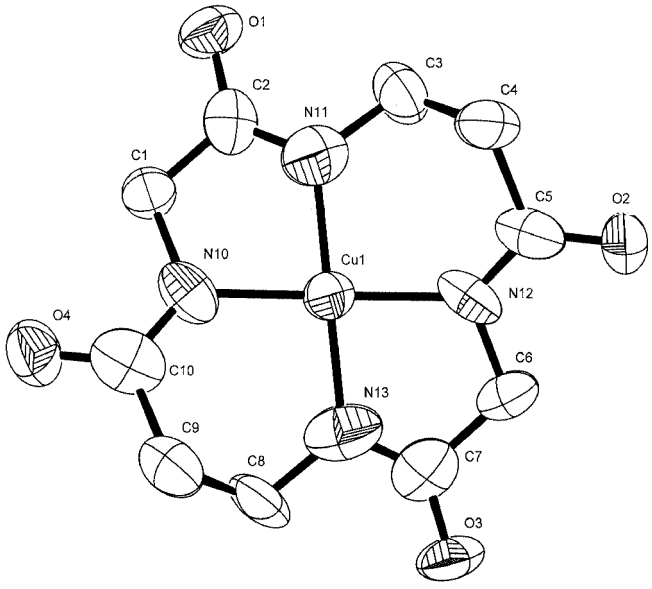
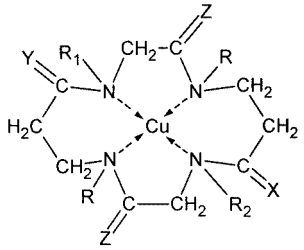


Figure 2. Molecular structures of the dianion of **12** in the crystal

Conclusion

Cyclotetrapeptides containing functional groups are accessible from the corresponding dipeptide esters by template synthesis at nickel(II) and palladium(II) centres. This is a very facile method in comparison to conventional procedures.

Table 3. Geometrical parameters of tetraazacyclotetradecanes



	R	R^1	R^2	X	Y	Z	Cu−NR[a]	Cu−N⁻	α, γ[a]	β, δ	C−O	C−N
[A]	H	H	H	H_2	H_2	H_2	2.012	–	85.7	94.3	–	1.49
[B]	H	H	⊖	O	H_2	H_2	2.017	1.960	85.6	94.2	1.286	1.299
[C]	CH_2py	⊖	⊖	O	O	H_2	2.054	1.962	84.6	95.5	1.280	1.314
12	⊖	⊖	⊖	O	O	O	–	1.93	83.5	96.6	1.294	1.252
[D]	⊖	⊖	⊖	O	O	O	–	–	83.0	97.0	1.280	1.291

[a] The angles α and γ correspond to the five-membered chelate rings, while β and δ are the bite angles in the six-membered chelates. The distances [Å] and angles [°] are average values. A: M. Studer, A. Riesen, T. A. Kaden, *Helv. Chim. Acta* **1984**, *72*, 1253. B: L. Siegfried, M. Neuburger, M. Zehnder, T. A. Kaden, *Chem. Commun.* **1994**, 951. C: A. E. Goeta, J. A. K. Howard, D. Maffeo, H. Paschmann, J. A. G. Williams, D. S. Yufit, *J. Chem. Soc.*, *Dalton Trans.* **2000**, 1873. D: Ref.[7]

Experimental Section

General Method for the Preparation of 1−10 (except for 1b, 6, 7): A methanolic sodium methoxide solution (6 mmol) was added dropwise to a mixture of the dipeptide ester hydrochloride (2 mmol) and metal salt (Na_2PdCl_4 or $NiCl_2{\cdot}6H_2O$, 1 mmol) dissolved in methanol (40 mL). The resultant solution was then heated to 65 °C for 24 h, after which [PPN]Cl (2 mmol) was added. Upon addition of water, the products **1−9** were obtained as crystalline solids.

{*cyclo*-[(Gly-L-Asp(OMe)-Gly-L-Asp(OMe)-4H$^+$]Pd}(PPN)$_2$ (1a): Colorless crystalline needles, yield: 1004 mg (58%). $C_{86}H_{76}N_6O_8P_4Pd{\cdot}10H_2O$ (1730.42): calcd. C 59.64, H 6.47, N 4.85; found C 59.61, H 5.54, N 4.76. ^{1}H NMR (CD_3OD, 400 MHz, ppm): δ = 3.634 (OCH_3). ^{13}C NMR (CD_3OD, 100 MHz, ppm): δ = 44.0, 52.4, 55.7, 57.9, 170.8, 174.3, 181.0. MS (FAB−): *m*/*z* = 475 [M^{2-} + H^+], 1012 [M^{2-} + PPN^+], 415 [M^{2-} + H^+ − ($HCOOCH_3$)]. IR (KBr): ν(OH) 3436 vs (H_2O), ν(C=O) 1735 s (COOMe), 1578vs, 1557 vs (amide-I).

{*cyclo*-[(Gly-L-Asp(OMe)-Gly-L-Asp(OMe)-4H$^+$]Pd}Na$_2$ (1b): A solution of NaOMe (6 mmol) in methanol (1.5 mL) was added dropwise to a solution of H-Gly-Asp(OMe)$_2$ (508 mg, 2 mmol) and Na_2PdCl_4 (284 mg, 0.97 mmol) in methanol (40 mL) − whereby the light yellow solution became colorless. The reaction mixture was then boiled under reflux for 48 h (60 °C). After removal of the solvent in vacuo the residue was dissolved in water (5 mL) and purified by HPLC (stationary C-18 reversed phase, mobile phase 100% of water). Colorless needles, yield: 402 mg (66%). $C_{14}H_{16}N_4Na_2O_8Pd{\cdot}6H_2O$ (628.52): calcd. C 26.73, H 4.46, N 8.91; found C 26.38, H 4.33, N 8.83. IR (KBr, cm^{-1}): ν(OH) 3436 vs (H_2O), ν(C=O), 1726 s (COOMe), 1598 vs, 1552 vs (amide-I). ^{1}H NMR (CD_3OD, 400 MHz, ppm): δ = 3.694 (OCH_3). ^{13}C NMR (100 MHz, CD_3OD, ppm): δ = 43.1, 52.6, 55.8, 57.7, 171.1, 174.7, 181.4. MS (FAB−/mNBA): *m*/*z* = 475 [M^{2-} + H^+], 497 [M^{2-} + Na^+].

{*cyclo*-[Gly-L-Asp(OMe)-Gly-L-Asp(OMe)-4H$^+$]Ni}(PPN)$_2$ (2): Yellow crystalline needles, yield: 950 mg (59%). $C_{86}H_{76}N_6NiO_8P_4{\cdot}6H_2O$ (1610.71): calcd. C 64.07, H 5.46, N 5.22; found C 63.91, H 5.49, N 5.15. ICP-AES (Ni, 231.60) calcd. Ni 3.64; Ni 4.16. ^{1}H NMR (CD_3OD; 400 MHz, ppm): δ = 3.667, 3.663 (OCH_3). ^{13}C NMR (CD_3OD, 100 MHz, ppm): δ = 38.7, 42.1, 52.0, 52.4, 53.0, 54.5, 57.5, 61.3, 171.7, 173.4, 174.7, 178.9; 180.1, 181.9. MS (FAB−): *m*/*z* = 427 [M^{2-} + H^+], 964 [M^{2-} + PPN^+], 367 [M^{2-} + H^+ − (HCOOMe)]. IR (KBr, cm^{-1}): ν(OH) 3428 vs (H_2O), ν(C=O) 1730s (COOMe), 1592 vs, 1581 vs, 1567 vs (amide-I).

{*cyclo*-[Gly-L-Glu(OMe)-Gly-L-Glu(OMe)-4H$^+$]Pd}(PPN)$_2$ (3): Colorless crystalline needles, yield: 1073 mg (61%). $C_{88}H_{80}N_6O_8P_4Pd{\cdot}10H_2O$ (1758.42): calcd. C 60.05, H 5.69, N 4.78; found C 60.18, H 5.69, N 4.74. ICP-AES (Pd, 340.46) calcd. Pd 6.05; Pd 6.24. ^{1}H NMR (CD_3OD, 400 MHz, ppm): δ = 3.613, 3.597 (OCH_3); δ (glutamyl res.) = 4.14 m/4.04 m (2 × H_X), 2.64 m/2.47 m/ 2.30 m/ 2.14 m/ 2.00 m/ 1.86 m (2 × H_{ABCD}). ^{13}C NMR (CD_3OD, 100 MHz, ppm): δ = 28.0, 30.0, 31.5, 34.3, 51.8, 51.9, 53.1, 59.4, 60.9, 65.3, 175.9, 176.4, 179.3, 179.8, 181.6, 184.4. MS (FAB−): *m*/*z* = 503 [M^{2-} + H^+], 443 [M^{2-} + H^+ − HCOOMe]. IR (KBr, cm^{-1}): ν(OH) 3436 vs (H_2O), ν(C=O) 1726 s (COOMe), 1590 vs, 1568 vs, 1557 vs (amide-I).

{*cyclo*-[β-Ala-L-Asp(OMe)-β-Ala-L-Asp(OMe)-4H$^+$]Ni}(PPN)$_2$ (4): Yellow crystalline needles, yield: 1193 mg (72%). $C_{88}H_{80}N_6NiO_8P_4{\cdot}7H_2O$ (1656.69): calcd. C 63.74, H 5.67, N 5.07; found C 64.08, H 5.57, N 4.43. ^{1}H NMR (CD_3OD, 400 MHz, ppm): δ = 3.814, 3.785; (OCH_3) 4.20 m, 3.25−3.15 m, 2.80−2.60 m, 2.43−2.07 m, 1.98−1.92m (2 × H_{ABX} + 2 × H_{ABCD}). ^{13}C NMR (CD_3OD, 100 MHz, ppm): δ = 39.3, 39.4, 39.5, 39.8, 40.0, 40.4, 51.9, 52.0, 62.4, 62.5, 173.96, 174.00, 176.2, 176.3, 180.0, 180.6. MS (FAB−): *m*/*z* = 455 [M^{2-} + H^+]; 381 [M^{2-} + H^+ − (CH_3COOCH_3)]. IR (KBr, cm^{-1}): ν(OH) 3429 vs (H_2O), ν(C=O) 1727 s (COOMe), 1580vs, 1548 vs (amide-I).

{*cyclo*-[β-Ala-L-Asp(OMe)-β-Ala-L-Asp(OMe)-4H$^+$]Pd}(PPN)$_2$ (5): Colorless crystalline needles, yield: 1091 mg (64%). $C_{88}H_{80}N_6O_8P_4Pd{\cdot}7H_2O$ (1704.42): calcd. C 61.96, H 5.52, N 3.29; found C 62.39, H 5.80, N 4.15. ^{1}H NMR (CD_3OD, 400 MHz,

ppm): δ = 3.701, 3.687 (OCH_3); 5.12 m, 4.97 m, 4.57−4.47 m, 3.65 m, 3.54−3.47 m, 2.92−2.45 m, 2.42−2.07 m. MS (FAB−): *m*/*z* = 503 [$M^{2-} + H^+$], 429 [$M^{2-} + H^+ - (CH_3COOCH_3)$], 1040 [$M^{2-} + PPN^+$]. IR (KBr, cm^{-1}): (OH) 3414 vs (H_2O), ν(C=O) 1723 s (COOMe), 1590 vs, 1568 vs, (amide-I).

{*cyclo*-[Gly-L-Asp-Gly-L-Asp-6H$^+$]Pd}Li$_2$(PPN)$_2$ (6): A mixture of **1a** (173 mg, 0.1 mmol) and LiOH (10 mg, 0.4 mmol) were dissolved in CH_3CN (10 mL). After the addition of H_2O (2 mL) the mixture was heated to 65 °C for 24 h. Colorless crystalline needles of **6** were then obtained following the addition of water. Yield: 115 mg (67%). $C_{84}H_{70}Li_2N_4O_8PdP_4 \cdot 10H_2O$ (1714.42): MS (ESI−): *m*/*z* = 447 [$M^{4-} + 3H^+$], 453 [$M^{4-} + Li^+ + 2H^+$], 984 [$M^{4-} + PPN^+ + 2H^+$], 1074 [$M^{4-} + PPN^+ + 5\ H_2O + 2H^+$], 1521 [$M^{4-} + 2\ PPN^+ + H^+$], 1611 [$M^{4-} + 5\ H_2O + 2\ PPN^+ + H^+$], 1701 [$M^{4-} + 10\ H_2O + 2\ PPN^+ + H^+$]. IR (KBr, cm^{-1}): ν(OH) 3377 vs (H_2O), ν(C=O) 1677 s, 1665 s (COOLi), 1570 vs (amide-I), 1438 s, 1415 cm^{-1} (COOLi).

{*cyclo*-[Gly-L-Asp-Gly-L-Asp-4H$^+$]Ni}Na$_2$ (7): A solution of NaOMe (6 mmol) in methanol (1.5 mL) was added dropwise to a solution of H-Gly-Asp(OMe)$_2$ (508 mg, 2 mmol) and $NiCl_2 \cdot 6H_2O$ (238 mg, 1 mmol) in methanol (40 mL), whereupon the light yellow solution became colorless. The reaction mixture was then boiled under reflux (60 °C) for 48 h. After removal of the solvent the residue was dissolved in water (5 mL) and purified by HPLC (stationary C-18 reversed phase, mobile phase 100% of water). Yellow needles, yield: 287 mg (60%). $C_{12}H_{12}N_4Na_2NiO_8 \cdot 2H_2O$ (478.69): calcd. C 30.08, H 3.34, N 11.70; found C 30.56, H 4.21, N 11.20. IR (KBr): ν(OH) 3429 vs (H_2O), ν(C=O), 1687 s, 1661 s (COOH), 1597 vs (amide-I), 1463 s, 1421 cm^{-1} (COOH). ^{13}C NMR (CD_3OD, 67 MHz, ppm): δ = 41.5, 45.6, 54.2, 168.6, 171.1, 177.3. MS (ESI−): *m*/*z* = 365 [$M^{2-} - 2CO_2 + 2H_2O + H^+$].

{*cyclo*-[β-Ala-L-Orn(ω-NHBoc)-β-Ala-L-Orn(ω-NHBoc)-4H$^+$]Pd}-(PPN)$_2$ (8): MS (FAB−): *m*/*z* = 673 [$M^{2-} + H^+$], 691 [$M^{2-} + H^+ + H_2O$], 709 [$M^{2-} + H^+ + 2H_2O$], 1097 [$M^{2-} + PPN^+ - 2\cdot(CH_3)_3C$].

{*cyclo*-[β-Ala-L-Lys(ω-NHBoc)-β-Ala-L-Lys(ω-NHBoc)-4H$^+$]Pd}-(PPN)$_2$ (9): Colorless powder, yield: 1150 mg (61%). $C_{100}H_{106}N_8O_8P_4Pd \cdot 6H_2O$ (1884.42): calcd. C 63.68, H 6.26, N 5.94; found C 63.26, H 6.09, N 6.17. MS (FAB−): *m*/*z* = 701 [$M^{2-} + H^+$]. IR (KBr): ν(OH) 3414 vs (H_2O), ν(C=O) 1699 s (amide-I), 1588 vs (amide-I), 1567 vs (amide-I), 1548 vs (amide-I), ν(NH) 1628 s (amide-II).

{*cyclo*-[β-Ala-L-Lys(ω-NHBoc)-β-Ala-L-Lys(ω-NHBoc)-4H$^+$]Ni}-(PPN)$_2$ (10): Yellow powder, yield: 1131 mg (62%). $C_{100}H_{106}N_8NiO_8P_4 \cdot 3CH_3OH$ (1824.72): calcd. C 65.76, H 5.81, N 6.13; found C 68.70, H 6.13, N 5.13. ^{13}C NMR (CD_3OD, ppm): δ = 20.0, 28.6, 30.7, 26.0, 36.8, 37.5, 38.8, 61.5, 155.5, 172.1, 178.5. MS (FAB−): *m*/*z* = 653 [$M^{2-} + H^+$].

***cyclo*-[β-Ala-L-Lys(ω-NHBoc)-β-Ala-L-Lys(ω-NHBoc)] (11):** Colorless powder, yield: 270 mg (90%). $C_{28}H_{50}N_6O_8$ (598.74): calcd. C 56.12, H 8.35, N 14.03; found C 55.77, H 8.43, N 13.94. MS (FAB+): *m*/*z* = 600 [$M + H^+$]; 500 [$M + 2H^+ - (COO\mathit{t}Bu^+)$], 400 [$M + 3H^+ - 2\cdot(COO\mathit{t}Bu^+)$]. IR (KBr, cm^{-1}): ν(OH) 3318 vs (H_2O), ν(C=O) 1689 s (amide-I), 1648 vs (amide-I), ν(NH) 1538 s (amide-II).

[*cyclo*-(Gly-β-Ala-Gly-β-Ala-4H$^+$)Cu](PPN)$_2$ (12): A solution of MeONa (6 mmol) in methanol was added dropwise to a mixture of Gly-β-AlaOMe·HCl (425 mg, 2 mmol) and $CuCl_2 \cdot 2H_2O$ (170 mg, 1 mmol) in methanol (40 mL), whereupon the initial green solution turned deep blue and NaCl was precipitated. The reaction mixture was then boiled under reflux for 24 h, filtered and the filtrate concentrated to 5 mL in vacuo. [Ph_3PNPPh_3]Cl (2 mmol) was then added. After the addition of water (100 mL), bronze-like plates of the cyclopeptide copper complexes were obtained, recrystallized from MeOH/H_2O, and dried in vacuo. Yield: 535 mg (37%). IR (KBr): $\tilde{\nu}$ = 1575, 1542 cm^{-1}. MS (FAB−, mNBA): *m*/*z* (%) = 316 (100) [$M^{2-} + H^+$], 853 (3) [$M^{2-}PPN^+$]. $C_{82}H_{72}CuN_6O_4P_4 \cdot 3H_2O$ (1447.0): calcd. C 68.00, H 5.39, N 5.81; found C 68.04, H 5.40, N 5.09.

Crystal Structure Determination of 12: An orange-brown block crystal was grown from acetonitrile solution and placed with a small amount of mother liquor inside a glass capillary that was sealed and transferred to a SYNTEX R3/Siemens P4 diffractometer equipped with a low-temperature measurement device, LT-1. The temperature was adjusted to −7 °C. As the LT-1 prevented the measurement of a psi-scan, no semi-empirical absorption correction could be applied. The data were processed with the Siemens XSCANS software, and the structure was solved with SHELXS-86 and refined with SHELXL-97.[23]

The refinement for the PPN cations and the complex anion as well as for the two acetonitrile and four of the water solvent molecules presented no difficulties, but that of the disordered methanol and two water molecules was less straightforward. The methanol was refined with a fixed C−O distance of 1.38 Å and common isotropic thermal parameters for each of the disordered carbon and oxygen positions and the sum of the s.o.f.s was fixed to 1.0. Three relatively weak peaks were found in the difference Fourier synthesis and assigned to the oxygen atoms of disordered water molecules. First, a common "reasonable" isotropic thermal parameter U of 0.09 was assigned to these atoms and the site occupancies were refined. This procedure led to approximate s.o.f.s of 0.7, 0.75 and 0.55, which were fixed afterwards on these values, since they added, reasonably, to an integer (2). With these fixed s.o.f.s the thermal parameters of the three oxygen atoms were refined freely isotropic. Geometrical analyses were performed with the program package WinGX v.1.64.04, the graphics were produced by the programs PLUTO and ORTEP3 for Windows, which are part of the WinGX suite.[24] CCDC-191607 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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