Synthesis, Structure and Noncovalent Interactions of Palladium(II) Complexes with *N*-Benzoyl-β-phenylalaninate Dianion and Aromatic Diimine

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Two palladium(II) complexes, [Pd(bipy)(BzPhe-N,O)] and [Pd(phen)(BzPhe-N,O)]·4H_2O were synthesized by reactions between Pd(bipy)Cl_2 and $BzPheH_2$ (*N*-benzoyl-β-phenylalanine), Pd(phen)Cl_2 and $BzPheH_2$ in water at pH ~ 9, with their structures determined by X-ray diffraction analysis. The Pd atom is coordinated by two nitrogen atoms of bipy (or phen), the deprotonated amido type nitrogen atom and one of the carboxylic oxygens of BzPhe (BzPhe = *N*-benzoyl-β-phenylalaninate dianion). In the complex [Pd(phen)(BzPhe-N,O)]·4H_2O, the side chain of phenylalanine is located above and approximately parallels to the coordination plane. Both the aromatic-aromatic stacking interaction between the phenyl ring of phenylalanine and phen, and the metal ion-aromatic interaction between the phenyl ring of phenylalanine and Pd(II) were observed. [Pd(bipy)(BzPhe-N,O)] has the phenylalanyl side chain oriented outwards from the coordination plane, which is mainly due to the interaction between the carbonyl oxygen atom of the amido group and the phenyl ring of phenylalanine. The reason for the different orientation of phenylalanyl side chain in the complexes was suggested.

Keywords palladium(II) complex, crystal structure, noncovalent interaction, *N*-benzoyl-β-phenylalanine

Introduction

Non-covalent interactions have a big influence on the conformational organization of the biomolecules which is responsible for the regio- and stereo-specificity of various biological processes.[1] Among these interactions, the intramolecular stacking interaction between suitable aromatic moieties of ligands in mixed-ligand complexes is especially fascinating. For instance, this interaction may be regarded as a model of metalloenzyme-substrate or metalloenzyme-inhibitor systems[2] and used to interpret the antitumor mechanism of a novel class of antitumor compounds with general formula *cis*-[Pt(NH_3)$_2$(N-het)Cl].[3]

As RCON-amino acids are the models for *O*-terminal end of peptides, great attention has been paid to the elucidation of their coordination reactivity.[4] Usually, RCON-amino acids coordinate to metal ions only with carboxylic oxygen, acting as a carboxylic acid. However, recently it has been found that the amido group of the RCON-amino acids could be deprotonated and coordinate to Pd(II) or Pt(II) centers under suitable conditions.[5-7] To a great extent, this may provide insight into the reaction of the anticancer drug *cis*-Pt(NH_3)$_2$$Cl_2$ with peptides and proteins. Based on our previous work on the complexes of Pd(II) with *N*-benzoyl amino acids,[8] here the synthesis of the mixed-ligand complexes of Pd(II) with *N*-benzoyl-β-phenylalaninate and an aromatic diimine and their structural characterization by X-ray diffraction analysis are reported, and the main aim of this study was to investigate the possibility of aromatic-aromatic interaction between the aromatic diimine and the phenyl ring of the phenyalanine, and the effect of this non-covalent interaction on the conformational organization of the phenylalanyl side chain.

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Experimental

Reagents and instruments

N-Benzoyl-β-phenylalanine was prepared according to a established procedure and was characterized by elemental analysis and IR spectra.[9] Pd(bipy)Cl_2 and Pd(phen)Cl_2 were prepared as described in literature and characterized by elemental analysis.[10] Other chemicals are of reagent grade and were used as received. Elemental analysis was performed on a Carlo Erba 1106 automated analyzer. The IR spectra were measured on a Perkin-Elmer 683 instrument using KBr pellets.

General procedure for preparing complexes

[Pd(bipy)(BzPhe-N,O)] (**1**) Pd(bipy)Cl_2 (0.33 g, 1.0 mmol) was added to an aqueous solution (30 mL) of *N*-benzoyl-β-phenylalanine (0.27 g, 1.0 mmol) at pH ~ 12 under vigorous stirring. During the reaction, the pH value of the reaction mixture decreased spontaneously and was maintained close to ~ 9 by permanent addition of KOH. When the initial Pd(bipy)Cl_2 almost disappeared, the reaction mixture was filtered, the solution was concentrated down to about 60% of the original volume under heating, and the liquor was left to stay at room temperature. After several days, yellow crystals of the product formed and were separated from the solution by filtration. Yield 67%. IR ν: 1645, 1596, 1564, 1472, 1449, 1390, 760, 721 cm^{-1}. Anal. calcd for $C_{26}H_{21}N_3O_3Pd$: C 58.93, H 3.99, N 7.93; found C 58.98, H 4.06, N 7.98 .

[Pd(phen)(BzPhe-N,O)]·$4H_2O$ (**2**) was prepared similarly. Thus, starting from 0.354 g (1.0 mmol) of Pd(phen)Cl_2 and 0.27 g (1.0 mmol) of *N*-benzoyl-β-phenylalanine, **2** was obtained as yellow crystals. Yield 72%. IR ν: 3450, 1648, 1595, 1560, 1447, 1390, 1157, 851, 709 cm^{-1}. Anal. calcd for $C_{28}H_{29}N_3O_7Pd$: C 53.73, H 4.67, N 6.71; found C 53.64, H 4.57, N 6.79.

Structural Characterization

Single crystals of complexes **1** and **2** suitable for X-ray diffraction analysis were obtained by recrystallization from water. Diffraction data were collected on an Enraf-Nounius CAD-4 diffractometer at 293 K with Mo Kα radiation (λ = 0.071073 nm, graphite monochromator) using ω/2θ scans. *L*p and empirical absorption corrections were applied. The structures were solved by heavy atom method from the experimental Patterson function and subsequent Fourier difference technique, and refined by full-matrix least squares analysis. Non-hydrogen atoms were put into calculated positions and refined anisotropically using a riding model. The calculation was performed on a DEC Micro VAX II computer using SDP V5.0. Crystallographic data and structure refinement parameters for the complexes **1** and **2** were listed in Table 1.

Results and discussion

Infrared spectra

In IR spectra of both complexes, the ν(NH) band is absent, which is indicative of the deprotonation of amido group. The binding of the deprotonated amido-nitrogen to the metal center is confirmed by the amide band I shift from 1630 cm^{-1} down to 1550 cm^{-1} and the disappearance of the amide band II in the area around 1540 cm^{-1}.[7] The values of ν_a(OCO) and ν_s(OCO) of the complexes **1** (1646 cm^{-1} and 1390 cm^{-1}) and **2** (1648 cm^{-1} and 1390 cm^{-1}) are very different from those of the carboxylic $BzPheH_2$ (1738 cm^{-1} and 1230 cm^{-1}), and Δν [ν_a(OCO) − ν_s(OCO)] of the complexes **1** (256 cm^{-1}) and **2** (258 cm^{-1}) are larger than that of the carboxylate BzPheHNa (1620 − 1408 = 212 cm^{-1}), indicating that in both complexes the carboxylic groups coordinate to the metal ions as monodenate, which is in good agreement with the results revealed by the X-ray diffraction analysis.

Crystal structure

Selected bond lengths and angles for the complexes **1** and **2** are listed in Table 2, and the ORTEP drawings of the complexes are shown in Fig.1. The structure analysis indicates clearly that in both complexes the palladium atom is coordinated by the deprotonated amido-nitrogen and one carboxylic oxygen atom of BzPhe, and two nitrogen atoms of bipy or phen. However, reactions between [$MLCl_2$] (M = Cu, L = phen, bipy; M = Zn, L = phen) and the $BzPheH_2$ under similar conditions afford the complexes where the deprotonation of the amido group does

Table 1 Crystal data and structure refinement parameters for complexes **1** and **2**

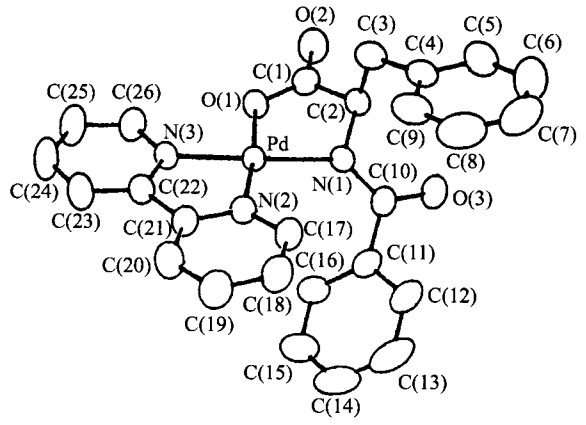
Complex	**1**	**2**
Empirical formula	$C_{26}H_{21}N_3O_3Pd$	$C_{28}H_{29}N_3O_7Pd$
M_c	529.88	625.95
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a (nm)	1.0455(3)	1.0715(1)
b (nm)	1.8857(1)	1.1022(1)
c (nm)	1.1593(1)	2.3326(1)
β (°)	103.29(1)	97.81(1)
V (nm^3)	2.2242(7)	2.7291(3)
Z	4	4
D_c(g/cm^3)	1.582	1.533
F (000)	536	1280
Crystal size (mm)	0.53 × 0.27 × 0.17	0.60 × 0.35 × 0.20
θ (°)	2—25	2—25
Reflections measured	4300	4913
Independent reflections	3834	4653
Observed reflections [$I > 3\sigma(I)$]	3151	3823
R [a]	0.032	0.036
R_w [b]	0.044	0.055
Weighting scheme, w	$1/\sigma^2(F)$	$1/\sigma^2(F)$
$(\Delta/\sigma)_{max}$	0.02	0.06
Largest difference peaks ($\times 10^3 e/nm^3$)	0.79 and −0.88	0.55 and −0.97

[a] $R = \sum(|F_0| - |F_c|)/\sum|F_0|$. [b] $R_w = [\sum w(|F_0| - |F_c|)^2/\sum|F_0|^2]^{0.5}$.

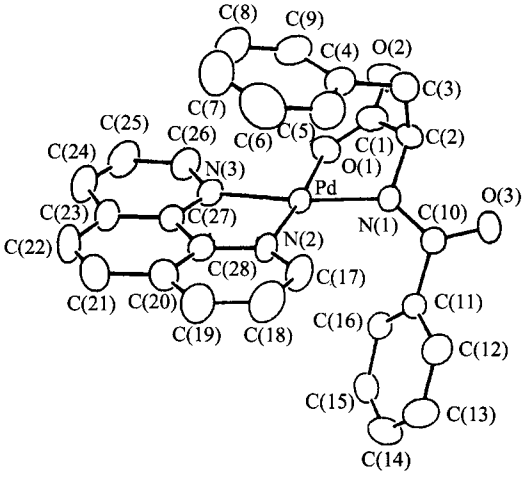
Table 2 Selected bond lengths (nm) and angles (°) for complexes **1** and **2**

Complex	**1**	**2**
Pd—N(1)	0.2006(2)	0.1991(2)
Pd—N(2)	0.2020(2)	0.2015(2)
Pd—N(3)	0.2006(2)	0.2019(2)
Pd—O(1)	0.1992(1)	0.2000(2)
N(2)-Pd-N(3)	80.0(1)	80.8(1)
N(2)-Pd-O(1)	172.1(1)	174.1(11)
N(3)-Pd-O(1)	94.0(1)	95.9(1)
N(2)-Pd-N(1)	104.7(1)	102.9(1)
N(3)-Pd-N(1)	175.2(1)	173.6(1)
N(1)-Pd-O(1)	81.4(1)	79.9(1)

not occur and the amido group does not coordinate to the metal ions.[11-13] This is in good agreement with the good ability of the palladium ion to promote amide deprotonation.[4a] The Pd—N (the deprotonated amide) bond lengths [0.2006(2) nm in **1**, 0.1991(2) nm in **2**] are close to that observed in [Pd(en)(BzPhe-N,O)]·H_2O (**3**) [0.1997(2) nm].[8] The Pd—N (the deprotonated amide) bonds are shorter than the Pd—N (imine) bonds {0.2020(2) nm and 0.2006(2) nm in **1**, 0.2015(2) nm and 0.2019(2) nm in **2**, 0.2033(9) nm and 0.2208(9) nm in [(2,6-(^{i}Pr)$_2$C$_6$H$_3$)N=CHCH=N(2,6-(^{i}Pr)$_2$C$_6$H$_3$)]Pd(CH_3)Cl,[14] 0.2028(3) nm and 0.2022(3) nm in [(2,6-(^{i}Pr)$_2$C$_6$H$_3$)N=CHC_5H_4N]$PdCl_2$[14]}, and also shorter than the Pd—N (amine) bonds [0.2038(3) nm and 0.2049(3) nm in **3**]. This is due to the strong electron-donating ability of the deprotonated amido-nitrogen. Sigel *et al*. surmised that the coordinating qualities of the deprotonated amido-nitrogen are "O-like" as the deprotonated amido group is isoelectronic with the carboxylate group, and this has been confirmed by the stability constants of some complexes in solution.[15] It is interesting that the Pd—N (the deprotonated amide) bond lengths are very close to the Pd—O bond lengths [0.1992(2) nm in **1**, 0.2000(2) nm in **2**, 0.1996(2) nm in **3**] in complexes **1**, **2** and **3**.



Complex 1



Complex 2

Fig. 1 Molecular structure of complexes **1** [Pd(bipy)(BzPhe-N,O)] and **2** [Pd(phen)(BzPhe-N,O)]·$4H_2O$ (the water molecules are omitted).

The phenyl ring of the phenylalanine in complex **2** is located above and oriented approximately parallel to the coordination plane. The shortest contact [Pd···C(4) = 0.316 nm] between the atoms of the phenyl ring and the metal ion is significantly smaller than the sum of the appropriate Van der Vaals radii of carbon atom and palladium atom, which is indicative of the Pd(II) ion-aromatic interaction. The phenyl ring forms a dihedral angle of 13.8° with the plane of the phen ring, with several close contacts between the nitrogen or carbon atoms of the phen ring and carbon atoms of the phenyl ring [N(2)···C(5) = 0.337, N(2)···C(6) = 0.342, C(17)···C(5) = 0.338, C(17)···C(6) = 0.355, N(3)···C(8) = 0.372 nm] (Table 3). This is indicative of aromatic-aromatic interaction between the phenyl ring and the phen ring in **2**.

The tightly stacked form in **2** can be explained by the synergistic action of the Pd(II) ion-aromatic and aromatic-aromatic interactions. The Pd(II) ion "pulls" the phenyl ring of the phenylalanine close to the coordination plane. At the same time, this position of phenyl-group favors the aromatic-aromatic interaction between the phenyl ring and the phen ring, which in its turn attracts the phenyl ring even more close to the coordination plane and thus strengthens the Pd(II) ion-aromatic interaction. In order to accommodate the strain due to tightly stacking in **2**, Pd atom is shifted 0.009 nm out of the coordination plane. Complex **2** exhibits an extensive network of hydrogen bonds involving carboxylic oxygen, carbonyl oxygen and water molecules (Fig. 2) [$O(1)\cdots O(4)_{water}$ = 0.288, $O(2)\cdots O(5)_{water}$ = 0.279, $O(3)\cdots O(5)_{water}$ = 0.276, $O(6)_{water}\cdots O(7)_{water}$ = 0.282 nm].

The phenylalanyl side chain may exist as three different rotamers with respect to the α-β carbon-carbon bond, and Martin *et al.* designated these three rotamers as *t*, *g* and *h*.[16] In the complexes **2** and **3**, the disposition of the phenyl group is in *anti* position towards the α-hydrogen in rotamer *h*, with the phenyl ring located above the coordination plane. The orientation of the phenyl group is similar to that observed for some Pd(II) and Cu(II) complexes with aromatic acids and their derivatives.[17] The main factor favoring this conformation can be due to the Pd(II) ion-aromatic and/or aromatic-aromatic interactions, as noted above.

Table 3 Close contacts (nm) in complexes **1** and **2**

Complex **2**	Pd···C(4) = 0.316	N(2)···C(5) = 0.337	N(2)···C(6) = 0.342
	C(17)···C(6) = 0.355	C(17)···C(5) = 0.338	N(3)···C(8) = 0.372
Complex **1**	O(3)···C(4) = 0.336	O(3)···C(5) = 0.360	O(3)···C(6) = 0.411
	O(3)···C(7) = 0.436	O(3)···C(8) = 0.411	O(3)···C(9) = 0.367

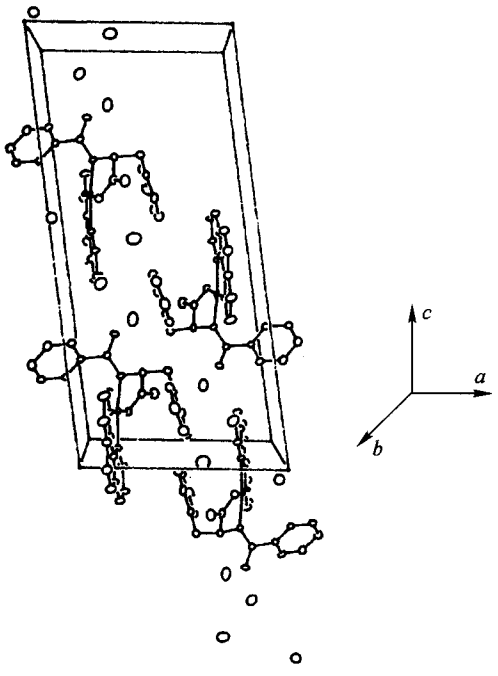


Fig. 2 Drawing of the unit cell of complex [Pd(phen)-(BzPhe-N,O)]·$4H_2O$.

The disposition of the phenyl group of the phenylalanine in **1**, where the phenyl substituent is in the *anti* position to the carboxylic group in rotamer *t*, is noteworthy. What kind of force stabilizes the conformation of the phenyl group in **1** being in rotamer *t*, and what is the reason for so different conformations observed for these three complexes? It has been found in protein crystal structures that phenyl rings of phenylalaninyl residues interact with the carbonyl oxygen atoms, and quantum mechanical calculation performed for the benzene-formamide model has revealed that the net energy of carbonyl oxygen-phenyl ring interaction is between − 8 kJ/mol and − 6 kJ/mol while the distance between carbonyl oxygen and ring carbon atoms vary from 0.33 nm to 0.40 nm, and the formamide-benzene carbon angle varies from 0° to15°.[18] In **1** the distances from the carbonyl oxygen atom of the amido group to the carbon atoms of the phenyl group, *i.e.*, C(4), C(5), C(6), C(7) ,C(8) and C(9), is 0.336, 0.360, 0.411, 0.436, 0.414 and 0.367 nm, respectively. Such arrangement in **1** is appropriate for the carbonyl oxygen atom-phenyl ring interaction. Martin *et al.* suggested that the enhanced stability of ΔG^0 of − 0.3 — − 1.5 kJ/mol be due to a Pd(II) ion-aromatic interaction and − 2.6— − 3.8 kJ/mol be due to an aromatic-aromatic interaction.[16] The net energy of the carbonyl oxygen atom-aromatic interaction is ~ − 7 kJ/mol. So, for **1**, the preference of rotamer *t* could be mainly caused by the interaction between the carbonyl oxygen atom of the amido group and the phenyl ring of the phenylalaninyl side chain. In **2** and **3**, the carbonyl oxygen atom of the amido group participates in formation of a hydrogen bond with water molecules, thus preventing it from interacting with the phenyl ring of the phenylalanine. So, for **2** and **3**, the phenylalanyl side chain exists preferably as the rotamer *h*, in which Pd(II) ion-aromatic and aromaticaromatic interactions are effective. Furthermore, the size of the phen ring is larger than that of the bipy ring, and the phenyl ring of the phenylalanyl side chain can interact with the phen ring of **2** more easily than with the bipy ring of **1**.

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