

SYNTHESIS, STRUCTURE AND DFT CALCULATIONS ON COMPLEXES OF PALLADIUM(II) WITH THEOPHYLLINE

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Mixed-ligand complexes of Pd(II) containing N(7)-coordinated theophylline (th) and N,N-donor ligands: 2,2'-bipyridine (2,2'-bipy) and 1,10-phenanthroline (1,10-phen) were prepared and characterized by IR, ¹H-NMR and ¹³C-NMR spectroscopy. Single crystal X-ray structure analysis showed that the [Pd(th)₂(2,2'-bipy)]·H₂O·(C₆H₁₄) complex crystallizes in the monoclinic system, space group C2/c. The Pd²⁺ centre has a distorted square planar configuration with Pd-N bond lengths of 2.018 Å (Pd-N(2) and Pd-N(2')) and 2.005 Å for Pd-N(7) and Pd-N(7'). The preferred site of coordination of theophylline to palladium was also investigated by DFT/B3LYP calculations.

INTRODUCTION

Several research groups investigated the coordination of metal ions to biologically important purine derivatives – adenine and guanine, which are major constituents of DNA and RNA – and xanthine and hypoxanthine, which are minor constituents of RNA.¹⁻⁵

The metal complexes of N-methyl substituted xanthines – theophylline (Fig. 1), theobromine and caffeine – are also of major interest, because these ligands can serve as models for biologically important analogues.²⁻⁹ Due to its similarity to guanine, theophylline has been studied most intensively.

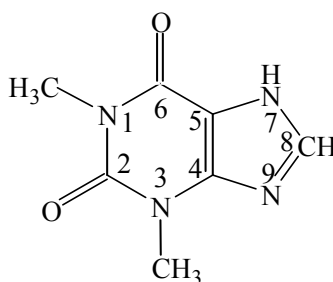


Fig. 1 – The structure of theophylline.

In general, the theophyllinato anion acts as a monodentate ligand, coordinating through N(7) atom to the metal ion⁵⁻⁸. However, coordination of the neutral theophylline ligand through N(9) was

reported in some Rh²⁺ and Pt²⁺ complexes,^{10, 11} and the N(7)/O(6) chelation was also demonstrated.¹²⁻¹⁴

In the present paper, we report the synthesis and spectroscopic studies on mixed-ligand complexes

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of Pd(II) containing N(7)-coordinated theophylline and N,N-donor ligands like 2,2'-bipyridine and 1,10-phenanthroline. The single crystal X-ray structure data of the bis(theophyllinato)(2,2'-bipyridine)palladium(II)-monohydrate hexane solvate were also determined and compared with those obtained by DFT/ B3LYP calculations.

EXPERIMENTAL

Syntheses

Synthesis of [Pd(th)₂(2,2'-bipy)]·H₂O. A mixture of 0.18 g (0.1 mmol) PdCl₂ in 5 ml H₂O/5 ml EtOH and 0.16 g (0.1 mmol) 2,2'-bipyridine in 5 ml EtOH was slowly added to an aqueous solution (20 ml) of 0.4 g (0.2 mmol) theophylline and triethylamine (1 ml). The solution was stirred for 1 h at 40 °C and the resulting yellow precipitate was filtered off and washed with acetone and distilled water. Yield: 60-70%. Melting point: 265-270 °C (decomp.). Calc. for [PdC₂₄H₂₄N₁₀O₅]: C 45.10; H 3.79; N 21.93%. Found: C 44.70; H 4.20; N 20.50%.

Synthesis of [Pd(th)₂(1,10-phen)]. A mixture of 0.18 g (0.1 mmol) PdCl₂ in 5 ml H₂O/ 5 ml EtOH and 0.2 g (0.1 mmol) 1,10-

phenanthroline-1-hydrate in 5 ml EtOH/7.5 ml H₂O was slowly added to an aqueous solution (20 ml) of 0.4 g (0.2 mmol) theophylline and triethylamine (1 ml). The solution was stirred for 1 h at 40 °C and the resulting yellow precipitate was filtered off and washed with distilled water. Yield: 75%. Melting point: 320 °C (decomp.). Recrystallisation from chloroform give [Pd(th)₂(1,10-phen)]·CHCl₃. Calc. for [PdC₂₇H₂₃N₁₀O₄Cl₃]: C 42.41; H 3.03; N 18.33%. Found: C 43.10; H 4.70; N 18.69%.

X-ray data collection and structure determination of [Pd(th)₂(2,2'-bipy)]·H₂O·(C₆H₁₄)

Single-crystal data were collected with a Bruker SMART diffractometer. The structure was solved by direct method with SHELXTL program¹⁵ and refined by the full-matrix least-squares on F² data using the SHELXTL program. CCDC-673898 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: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk. Crystal data and other experimental details are summarized in Table 1.

Table 1

Crystallographic data and refinement for [Pd(th)₂(2,2'-bipy)]·H₂O·(C₆H₁₄)

Empirical formula	C ₃₀ H ₂₂ N ₁₀ O ₅ Pd
Formula weight	708.98
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	C2/c
Unit cell dimensions	a = 16.969(3) Å b = 20.299(3) Å c = 9.6345(14) Å β = 91.043(2)°
Volume	3318.0(8) Å ³
Z	4
Density (calculated)	1.419 10 ³ kg m ⁻³
Absorption coefficient	0.612 mm ⁻¹
F(000)	1432
Crystal size	0.29 x 0.24 x 0.21 mm ³
Theta range for data collection	1.56 to 28.24°
Index ranges	-22 ≤ h ≤ 18, -26 ≤ k ≤ 18, -12 ≤ l ≤ 11
Reflections collected	9718
Independent reflections	3787 (R(int) = 0.0653)
Max. and min. transmission	0.882 and 0.8425
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3787 / 0 / 196
Goodness-of-fit on F ²	1.117
Final R indices (I > 2σ(I))	R1 = 0.0832, wR2 = 0.1779
R indices (all data)	R1 = 0.1151, wR2 = 0.1931
Largest diff. peak and hole	1.078 and -0.581 e Å ⁻³

NMR spectra

The ¹H- and ¹³C NMR spectra were recorded on a Bruker Topspin spectrometer, with a ¹H resonance frequency of 300 MHz. TMS was used as internal standard. The IR spectra (4000-400 cm⁻¹) were obtained with a Jasco FT-IR 615 infrared spectrophotometer on KBr pellets.

RESULTS AND DISCUSSION

IR spectra

In the IR spectra of the complexes (Table 2), the two ν(C=O) stretching vibrations (1697 cm⁻¹,

1637 cm^{-1} ; 1695 cm^{-1} , 1647 cm^{-1} , respectively) are recorded at lower frequencies than in free theophylline IR spectra (1717 cm^{-1} , 1669 cm^{-1}). These shifts are mainly due to the deprotonation at the N(7) atom and coordination of the theophyllinato anion through this atom to the metal centre. The $\nu(\text{C}=\text{N})$ vibrations are also shifted at lower frequencies due to the coordination through N(7) atom in the case of theophylline, and N(2) and N(2') atoms in the case of 2,2'-bipyridine. In

N(7)-bonded theophyllinato complexes, the carbonyl group is generally hydrogen-bonded with other ligands in the metal coordination sphere.^{5,6} Due to deprotonation, the $\nu(\text{NH})$ stretching vibration of the imidazole fragment (3122 cm^{-1}) are no longer recorded in the spectrum of the complexes. The $\nu(\text{CH})$ stretching vibrations of the coordinated 2,2'-bipyridine and 1,10-phenanthroline ligands are observed in the range of 3110-3050 cm^{-1} .

Table 2

IR spectral data of the complexes (cm^{-1})

Compound	$\nu(\text{OH})$	$\nu(\text{NH})$	$\nu(\text{CH})$	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{N})$
Theophylline ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$)	3348 w	3122 m	2985 m 2825 m	1717 s 1669 vs	1568 s
2,2'-Bipyridine ($\text{C}_{10}\text{H}_8\text{N}_2$)			3151-3000 m 2925 m		1577 vs 1560 s
1,10-phenanthroline-1-hydrate ($\text{C}_{12}\text{H}_8\text{N}_2 \cdot \text{H}_2\text{O}$)	3425 w		3070-3000 m 2983, 2921m		1587 m 1563 m
[Pd(th) ₂ (2,2'-bipy)]·H ₂ O	3463 w		3118-3050 w 2949 w	1695 vs 1637 vs	1529 s
[Pd(th) ₂ (1,10-phen)]·CHCl ₃	3431 w		3100-3050 w 2953 w	1695 vs 1647 vs	1529 s 1427 s

NMR spectra

The ¹H-NMR spectrum of theophylline (Table 3) shows four singlets at 13.57, 8.04, 3.44, 3.23 ppm which are assigned to N(7)H, C(8)H and the two methyl group protons, respectively. The absence of the HN(7) resonance from the ¹H-NMR spectrum of the complexes demonstrates that theophylline coordinates in the deprotonated form. The upfield shift of HC(8) by 0.36 ppm in the [Pd(th)₂(2,2'-bipy)]·H₂O and the downfield shift by 0.04 ppm in the case of [Pd(th)₂(1,10-phen)], provides evidence of the coordination of theophylline through the adjacent N(7) atom. The upfield shift of HC(8) by 0.4 ppm was observed in [Pd(th)Cl]₂ complex too.⁹

The signals of the CH₃ protons of theophylline are shifted downfield by 0.15 and 0.21 ppm in [Pd(th)₂(2,2'-bipy)]·H₂O, 0.19 and 0.20 ppm in [Pd(th)₂(1,10-phen)], respectively. This is probably due to the hydrogen bonding involving also the C=O groups from theophylline.

The ¹H-NMR spectrum of 2,2'-bipyridine shows four signals at 8.71, 8.41, 7.84 and 7.33 ppm, respectively, which are assigned to HC(5), HC(2), HC(3), HC(4) protons. Due to coordination, the resonances of HC(5) and HC(2) protons are shifted upfield, and the resonances of HC(3) and HC(4) are shifted downfield (Table 3). In the case of [Pd(th)₂(1,10-phen)] complex the resonances of all protons undergo an upfield shift.

In the ¹³C-NMR spectrum of the [Pd(th)₂(2,2'-bipy)]·H₂O complex (Table 4), one can observe that the C(8) and C(5) of the theophylline undergo a downfield shift of 6.97 and 5.66 ppm; the C(4), C(6) and C(2) are also shifted downfield by 2.26, 1.66 and 0.97 ppm, respectively. The larger downfield shifts of C(8) and C(5) confirm the coordination of the theophylline through the adjacent N(7) atom.¹⁶ The carbon atoms of the 2,2'-bipyridine ring also undergo a downfield shift, the largest shift value (3.99 ppm) being for the C(3) and C(4) atoms.

Table 3
¹H-NMR chemical shifts data (ppm)

Compound	Theophylline			2,2'-Bipyridine/ 1,10-phenanthroline			
	N(7)H	C(8)H	CH ₃	C(5)H	C(4)H	C(3)H	C(2)H/ C(6)H
Theophylline	13.57	8.04	3.44; 3.23				
Theophylline (DFT calc.)	7.82	7.04	3.37; 3.12				
2,2'-Bipyridine				8.71	7.33	7.84	8.41
2,2'-Bipyridine (DFT calc.)				8.84	6.97	7.47	7.33
1,10-phenanthroline-1-hydrate				9.20	7.65	8.26	7.80
[Pd(th) ₂ (2,2'-bipy)]·H ₂ O		7.68	3.59; 3.44	7.60	7.50	8.18	8.11
[Pd(th) ₂ (2,2'-bipy)]·H ₂ O (DFT calc.)		6.74	3.31; 3.09	8.21	7.10	7.69	7.68
[Pd(th) ₂ (1,10-phen)]·H ₂ O		8.08	3.63; 3.43	8.64	7.80	7.89	7.77

Table 4
¹³C-NMR chemical shifts data (δ ppm)

Compound	Theophylline						
	C ₁	C ₂	C ₃	C ₄	C ₅	C ₆	C ₈
Theophylline	29.61	151.13	27.63	147.79	106.34	154.32	140.27
Theophylline (DFT calc.)	26.62	141.96	29.25	143.70	106.83	147.91	141.44
[Pd(th) ₂ (2,2'-bipy)]·H ₂ O	29.97	152.10	27.63	150.05	112	155.98	147.24
[Pd(th) ₂ (2,2'-bipy)]·H ₂ O (DFT calc.)	26.61	141.95	29.24	143.70	106.82	147.90	141.41
Compound	2,2'-Bipyridine						
	C ₁	C ₂	C ₃	C ₄	C ₅		
2,2'-Bipyridine	156.14	121.00	136.75	123.63	149.12		
2,2'-Bipyridine (DFT calc.)	147.34	114.45	130.99	119.47	146.66		
[Pd(th) ₂ (2,2'-bipy)]·H ₂ O	157.31	122.31	140.74	127.62	150.60		
[Pd(th) ₂ (2,2'-bipy)]·H ₂ O (DFT calc.)	147.35	114.44	130.99	119.47	146.66		

For this purpose, we used X-ray diffraction and NMR techniques coupled with quantum chemical calculations performed in the framework of DFT approach, by using the hybrid B3LYP exchange-correlation functional.^{17, 18} This functional in combination with the Pople's group split valence basis sets (6-31G(d))¹⁹ was shown previously²⁰⁻²² to provide an excellent compromise between accuracy and computational efficiency of molecular structures and NMR spectra for large and medium-sized molecules. Shielding tensors of the theophylline molecule were evaluated by using the GIAO (Gauge-Including Atomic Orbitals)

formalism,^{23, 24} implemented in the Gaussian package, with the B3LYP functional, in conjunction with the basis set given above. In order to express the chemical shifts in ppm, the geometry of bipyridine, theophylline and complexes of [Pd(th)₂(2,2'-bipy)]·H₂O·(C₆H₁₄) was optimized and next its NMR spectrum was calculated by using the same method and basis set. The calculated isotropic shielding constants σ_i were then transformed to chemical shifts relative to theophylline by $\delta_i = \sigma_{\text{TMS}} - \sigma_i$.

Crystal and molecular structure of $[\text{Pd}(\text{th})_2(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}\cdot(\text{C}_6\text{H}_{14})$

Crystals of $[\text{Pd}(\text{th})_2(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}\cdot(\text{C}_6\text{H}_{14})$ for X-ray diffraction determination were obtained from CHCl_3 solution by slow diffusion of hexane.

An ORTEP view of the molecular structure is displayed in Fig. 2. Selected structural parameters are shown in Table 6.

In the $[\text{Pd}(\text{th})_2(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}\cdot(\text{C}_6\text{H}_{14})$ complex, the palladium atom is bonded to two theophylline ligands through the deprotonated N(7) atoms and

to the 2,2'-bipyridine molecule. The coordination polyhedron of the metal atom adopts a distorted square-planar geometry, with angles involving intraligand nitrogens [$\text{N}(7')\text{-Pd-N}(7) = 87.1(3)^\circ$ and $\text{N}(2)\text{-Pd-N}(2') = 80.3(3)^\circ$], which are smaller than the angles involving interligand nitrogens [$\text{N}(7)\text{-Pd-N}(2) = 96.5(2)^\circ$, $\text{N}(7')\text{-Pd-N}(2') = 96.48(19)^\circ$]. This is mainly caused by the steric repulsion between the two theophylline and 2,2'-bipyridine ligands. The Pd-N(2) distance of 2.018(4) Å is close to the values of 2.022(3) found in planar bis(2,2'-dipyridyliminato)palladium(II).²⁵

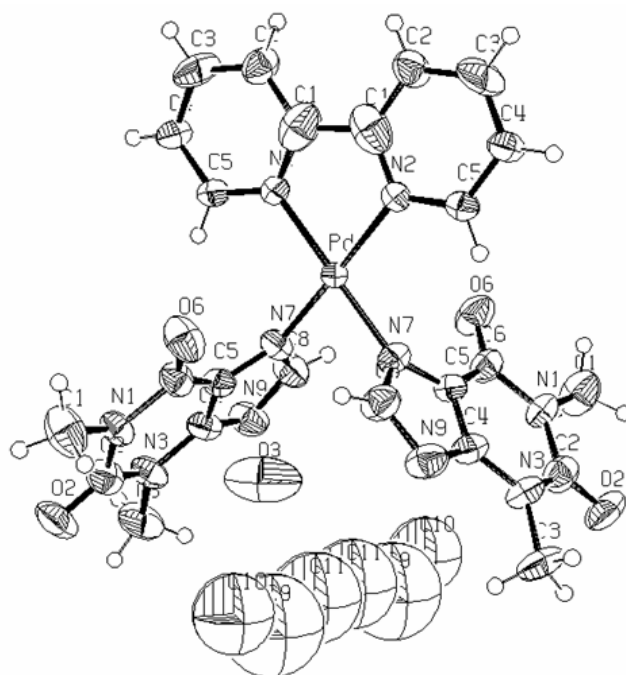


Fig. 2 – ORTEP view and numbering of the $[\text{Pd}(\text{th})_2(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}\cdot(\text{C}_6\text{H}_{14})$ complex.

The water molecule is hydrogen-bonded to the N(9) atoms of the theophylline rings of two adjacent $[\text{Pd}(\text{th})_2(2,2'\text{-bipy})]$ units, as shown in Fig. 3; the distance between the O(3) and N(9) is 2.933 Å. The bipyridine ligands are stacked along the c-axis; the distance between the center of two benzol rings of the partially overlapped bipyridine fragments is 3.56 Å, which is the normal range for $\pi\cdots\pi$ stacking interactions.

Calculations

DFT structure optimization of $[\text{Pd}(\text{th})_2(2,2'\text{-bipy})]$ was performed with the Gaussian '98 program,²⁶ starting from a pre-optimized X-ray geometry in PC Spartan Pro. The calculations employed the B3LYP exchange functional using

LANL2DZ basis set. The Molekel view of the optimized structure of $[\text{Pd}(\text{th})_2(2,2'\text{-bipy})]$ is shown in Fig. 4.²⁷ In order to assess the preferred site of coordination (N7 or N9) of theophylline, the same type of calculations were carried out on its deprotonated form. Table 5 includes electrostatic, Mulliken and Natural charges on these atoms and the total/relative energies of the isomers corresponding to the theophyllinato anion coordinated through N(7) or N(9), as well.

The charges on the nitrogen atoms (irrespective of the method of calculation) suggest that N(9), with a higher negative charge, would be the preferred coordination site. The N(9) coordinated isomer is however 114 kJ/mol higher in energy, showing that the steric congestion brought by the proximal methyl group (on N3) is determinant in stabilizing the N(7) coordinated isomer.

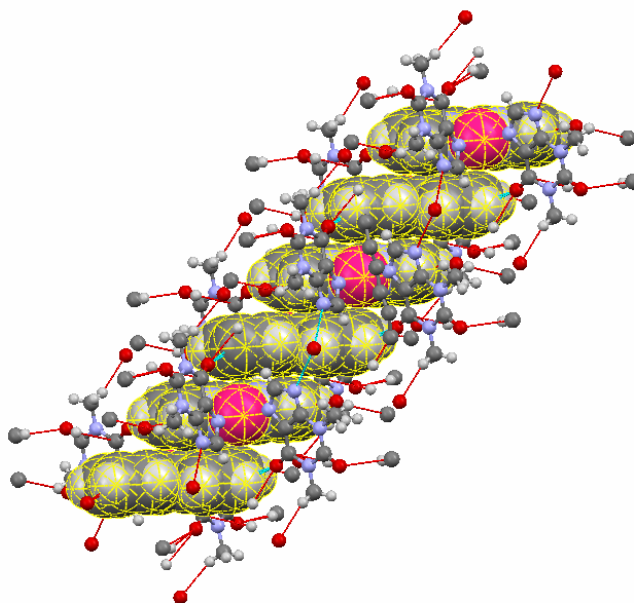


Fig. 3 – The packing in the crystal of $[\text{Pd}(\text{th})_2(2,2'\text{-bipy})]\cdot\text{H}_2\text{O}\cdot(\text{C}_6\text{H}_{12})$ emphasizing the $\pi\cdots\pi$ stacking through the bipyridine rings.

Table 5

Electric charges on the N(7), N(9) atoms in the deprotonated form of theophylline.

Charges	N(7)	N(9)
Electrostatic	-0.604	-0.656
Mulliken	-0.527	-0.567
Natural	-0.525	-0.607
Total energies(a.u.)/relative energies (kJ/mol)	-1902.8209782/ 0.0	-1902.777417/+114.26

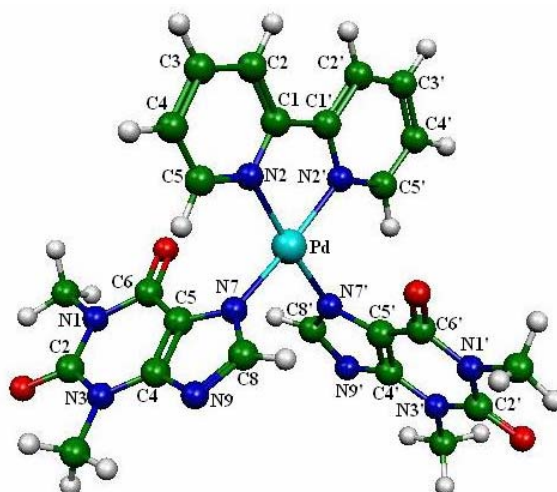


Fig. 4 – Molekel view of the optimized structure of $[\text{Pd}(\text{th})_2(2,2'\text{-bipy})]$ complex.

Slight differences can be noticed between the bond distances and angles of the X-ray and the optimized structure, which is normal considering that the calculated data refer to the gas phase. In the optimized structure the square coordination is almost planar. Furthermore, the atoms of the 2,2'-bipyridine rings are almost coplanar and the purine

molecules are also practically planar. In the solid-state structure, the 2,2'-bipyridine rings are twisted around the 1,1'-carbon bond, the N2-C1-C1'-N2' dihedral angle being -7.5° , which is 3.3° greater than that of the average of palladium complexes containing a Pd(bipy) unit. These deviations from planarity can be attributed to packing effects.

Table 6

Selected structural parameters by X-ray and theoretical calculations

Bond distances (Å) and angles (°)	Experimental	B3LYP
N(2)-Pd	2.018(4)	2.064
Pd-N(2')	2.018(4)	2.064
Pd-N(7')	2.005(5)	2.018
N(7)-Pd	2.005(5)	2.018
N(2)-Pd-N(2')	80.3(3)	80.006
N(7)-Pd-N(7')	87.1(3)	89.187
N(7)-Pd-N(2)	96.5(2)	95.405
N(7')-Pd-N(2')	96.48(19)	95.405
N(7)-Pd-N(2)	174.1(2)	175.400
C(2)-C(1)-C(1')	124.4(4)	124.250
C(1')-C(1)-C(2)-C(3)	179.1(7)	179.684
N(2)-C(1)-C(1')-N(2')	-7.534	1.184
N(2)-C(1)-C(2)-C(3)	-2.2(10)	0.000
C(4)-C(5)-N(2)-C(1)	-1.9(9)	0.000
C(2)-C(1)-N(2)-C(5)	2.9(9)	0.000
N(1)-C(2)-N(3)-C(4)	2.4(9)	0.000
N(3)-C(2)-N(1)-C(6)	-4.7(9)	-0.316
N(9)-C(4)-C(5)-N(7)	1.7(7)	0.316
N(7)-C(8)-N(9)-C(4)	-0.4(8)	0.775

CONCLUSIONS

Two mixed-ligand complexes of Pd(II) containing N(7)-coordinated theophylline and N,N-donor ligands were synthesized and characterized by IR, ¹H-NMR and ¹³C-NMR spectroscopy. Single crystal X-ray diffraction analysis demonstrated that the [Pd(th)₂(2,2'-bipy)]·H₂O·(C₆H₁₄) has a distorted square planar coordination around the Pd(II). The deviation from planarity is a consequence of packing effects.

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