

X-ray and Solution Structure of Inosine 5'-Monophosphate Coordinated to (Ethylenediamine)palladium(II). – The Importance of Intramolecular Hydrogen Bonding

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The compound $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2] \cdot 11 \text{H}_2\text{O}$, where 5'-IMP = inosine 5'-monophosphate, crystallizes in the tetragonal space group $P4_322$ with the unit cell parameters: $a = b = 12.060(5)$ and $c = 28.510(5)$ Å, $V = 4147(3)$ Å³, $Z = 4$. A head-to-tail orientation with Δ configuration is observed for the nucleotides which are coordinated through the N(7) positions such that $d[\text{Pd}-\text{N}(7)] = 2.053(8)$ Å. The sugar moieties exhibit *anti* orientations toward the purine bases while their puckers adopt C(3')-*endo* conformation. The overall conformation about the phosphate backbone is *gauche*^{*}. Intramolecu-

lar hydrogen bonding is observed between the phosphates and the NH groups of the en ligand with a donor-acceptor distance of 2.88 Å. The coordination mode of the solid-state structure is shown to be identical to that observed by ¹H-NMR spectroscopy in solution under slightly acidic conditions, where the N(1) positions of the nucleotides are protonated. The results are discussed in reference to closely related systems reported in the literature with emphasis on the importance of hydrogen bonding in such complexes.

Introduction

The interaction of DNA building blocks with Pt(II) and Pd(II) complexes has been a widely studied field in understanding the mechanism of action of Pt(II) antitumor drugs. Various structures of nucleobases^{[1][2]} and oligonucleotides^{[3][4]} with platinum amine complexes have been reported. Recently the crystal structure of cisplatin-bound duplex DNA^[5] confirmed the GG intrastrand crosslink as the main binding mode in DNA. NMR studies^{[6][7]} on am(m)ine platinum nucleotide adducts provided evidence for intramolecular hydrogen bonding between the phosphates of the nucleic acid components and the NH protons of the am(m)ine ligands. This was initially postulated from a decrease in the $\text{p}K_a$ values of the phosphates. Phosphate-amine interactions were also found in the crystal structure of *cis*- $[\text{Pt}(\text{NH}_3)_2\{\text{d}(\text{pGpG})\}]$,^[8] and the possibility for duplex-bound cisplatin was considered.^[5] However, only few Pt(II) or Pd(II) structures of mononucleotide adducts revealed the presence of intramolecular hydrogen bonding between the phosphate groups and the amines.^[9] This interaction is thought to be of major importance for the antitumor-activity of Pt(II) complexes. It has been shown that the majority of complexes with *cis* geometry having at least one NH group are active, whereas complexes without NH groups are generally inactive,^[10] although some exceptions have been reported.^{[1][11][12][13]}

Complexes of the type $[\text{Pd}(\text{R}_4\text{en})(\text{H}_2\text{O})_2]^{2+}$ (R = H, Me, Et) have been used in our laboratories to study the substitution kinetics of such complexes with nucleosides and nu-

cleotides.^[14] The substitution lability drastically decreased on increasing the steric hindrance from H to Me and Et, due to the axial sites being blocked for the incoming ligand by steric hindrance. A significantly higher reactivity for the nucleotides 5'-IMP and 5'-AMP over their corresponding nucleosides was ascribed to a transition state stabilization induced by the phosphate.^[15] However, the introduction of the π -accepting 2-picolyamine ligand resulted in a higher reactivity for inosine than for 5'-IMP.^[16]

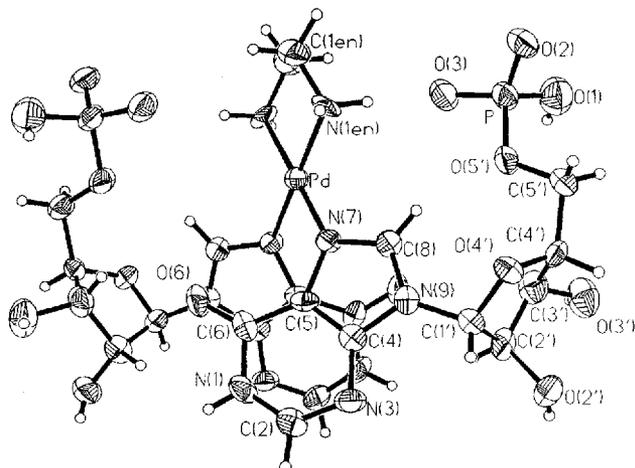
Here we report the crystal structure of $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2] \cdot 11 \text{H}_2\text{O}$, which clearly exhibits the presence of this $\text{NH} \cdots \text{OP}$ hydrogen bonding. A comparison with related systems is made.

Results

Crystal Structure: The molecular structure of $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2] \cdot 11 \text{H}_2\text{O}$ is shown in Figure 1 and selected bond lengths and angles in Table 1. The Pd atom has a nearly square-planar coordination sphere and lies on a two-fold symmetry axis. The 5'-IMP molecules are coordinated through the N(7) positions with a Pd–N(7) distance of 2.053(8) Å and an N(7)–Pd–N(7)#1 angle of 91.6(5)°. The Pd–N(1)_{en} distance is 2.011(8) Å and the N(1)–Pd–N(1)#1 angle 81.6(6)°. The mean deviation from the least-squares plane of the five atoms describing the square planar coordination sphere is 0.063 Å. The dihedral angle of this plane with respect to that of the purine systems is 48.2°. The purine bases exhibit a head-to-tail orientation with their dihedral angle having a magnitude of 33.3°. Furthermore, a

Δ configuration is ascribed to the purine orientation.^[17] The N(7)···N(7)#1 distance is 2.943 Å. A notably short distance of 2.957 Å exists between the O(6) and C(8)#1 atoms of the two 5'-IMP moieties.

Figure 1. X-ray crystal structure of $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2] \cdot 11 \text{H}_2\text{O}$; water molecules are omitted for clarity



The backbone angle γ [O(5)'-C(5)'-C(4)'-C(3)'] of 50.5° suggests a *gauche*⁺ conformation for the phosphate backbone.^[18] The glycosidic torsion angle χ [O(4)'-C(1)'-N(9)-C(4)] has a value of -156.0° resulting in an *anti* orientation for both purine bases with respect to the ribose sugars. The sugar conformation is C(3)'-*endo*, since the C(3)' atom is located above the plane which is described by C(1)', C(2)', C(4)' and O(4)'.

The shortest Pd···Pd* distance is 8.575 Å which is shown in the unit cell diagrams (Figures 2 and 3). It has to be mentioned that close contacts exist between the pyrimidine rings of two 5'-IMP units of neighboring molecules. The N(1)···C(2*) distance of 3.26 and the N(3)···C(6*) distance of 3.35 Å are strongly indicating intercomplex base-base stacking interactions.

The possibility of intramolecular hydrogen bonding between the nucleotides and the ethylenediamine ligand arises from an O(3)···N(1)_{en} distance of 2.88 Å.

Furthermore, the phosphate oxygen atoms O(1), O(2) and O(3) are involved in hydrogen bonding to the surrounding lattice-water molecules. Water O(1) is close to O(13) being separated by a distance of 2.62 Å, as are O(2) to O(11) (2.71 Å), and O(3) to O(8) and O(9) (2.69 and 2.93 Å, respectively). The O(6) at the base is in close contact to O(9) with 2.85 Å. The sugar O(2)' is close to O(12) (2.74 Å) and the O(3)' close to O(10) and O(11) separated by 2.72 and 2.67 Å, respectively. An intensive hydrogen bonding network between the water molecules also surrounds $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2] \cdot 11 \text{H}_2\text{O}$.

NMR Spectra: If crystals of the complex $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2] \cdot 11 \text{H}_2\text{O}$ are dissolved in D₂O the formation of various species, depending on pH*, is observed. At pH* = 2.2 and 4.3, the most predominant species is the complex formed

Figure 2. Unit cell diagram of $[\text{Pd}(\text{en})(5'\text{-IMP})_2] \cdot 11 \text{H}_2\text{O}$, looking down the *z* axis; H atoms are omitted for clarity

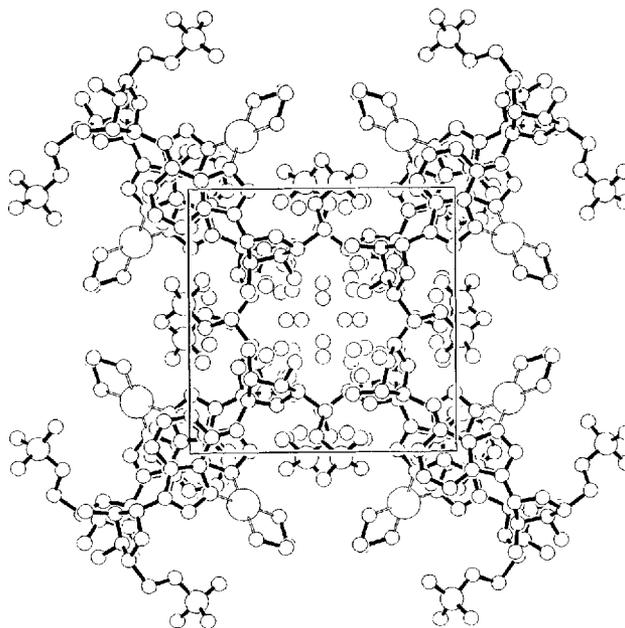
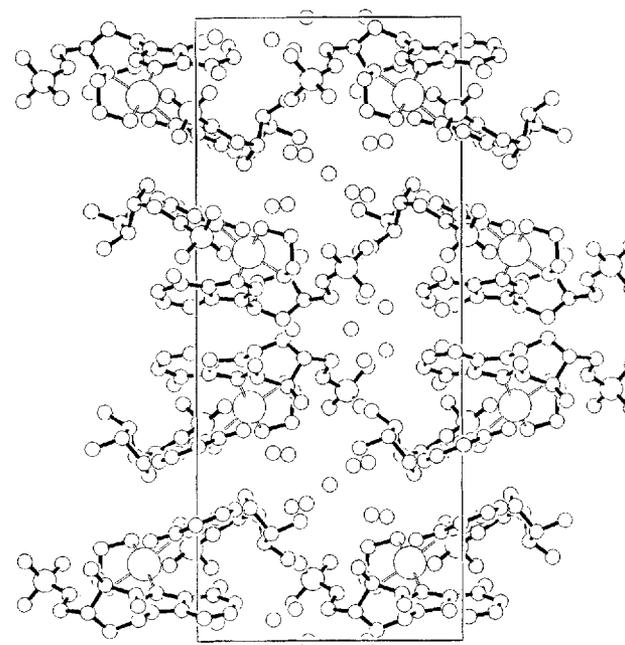


Figure 3. Unit cell diagram of $[\text{Pd}(\text{en})(5'\text{-IMP})_2] \cdot 11 \text{H}_2\text{O}$, looking down the *x* axis; H atoms are omitted for clarity



by $[\text{Pd}(\text{en})]^{2+}$ coordinated to the N(7) sites of two 5'-IMP, which is characterized by signals at $\delta = 8.82$ and 8.21 for the H(8) and H(2) protons of the purine bases, respectively. From the large downfield shift of the H(8) signal with respect to the free ligand at $\delta = 8.44$, N(7) coordination with the N(1) site remaining uncoordinated [signal of the N(1) site of the free ligand is observed at $\delta = 8.24$] is obvious. The H(1)' proton is only shifted slightly from $\delta = 6.16$ to 6.10 for the free ligand and the complex, respectively. These observations correspond well to those reported in the litera-

ture.^[19] A species, previously being assigned as an N(1),N(7)-bridged polymeric product,^[19] represented by signals at $\delta = 8.86$, 7.98 and 6.93 for H(8), H(2) and H(1)', respectively, is only present in minor concentrations. Here the largest shift is observed for the H(1)' signal, being shifted downfield by 0.77 ppm with respect to the free ligand. The observation of such large shifts corresponds well to the influence of two-coordinated Pd(II) per 5'-IMP. It was suggested before, that stacking interactions between 5'-IMP bound through N(1) and N(7) to two different $[\text{Pd}(\text{en})]^{2+}$ units bound to two different 5'-IMP units account for the shifts, since monofunctional $[\text{Pd}(\text{dien})]^{2+}$ did not show such interactions.^[20] The coupling constant $J[\text{H}(1)'\text{-H}(2)']$ for the N(1),N(7)-coordinated adduct ($J = 2.6$ Hz) is much smaller than those for $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2]$ ($J = 4.1$ Hz) or free 5'-IMP ($J = 5.3$ Hz). This adduct is similar to a previously proposed cyclic adduct containing four Pd(en)(guanine ring) moieties.^[21] On increasing the pH* further to 6.9 the N(1),N(7)-coordinated species become the major adduct whereas no singly N(7) coordinated 5'-IMP is detected. Since the N(1), N(7) species has a metal to ligand ratio of 1:1, one molar equivalent of non-coordinated 5'-IMP is present.

Discussion and Conclusions

The coordination mode of the 5'-IMP molecules in solution as observed by ¹H-NMR spectroscopy under acidic conditions and in the solid state as shown by X-ray crystallography, are in good agreement as expected. It is evident from the X-ray structure and the lowfield-shift of the H(8) signal that the 5'-IMP molecules are coordinated through the N(7) position ($\text{p}K_{\text{a}} = 1.3$ for the free base),^[22] which is the preferred binding site under the chosen pH. The N(1) position is not accessible under these conditions ($\text{p}K_{\text{a}} = 9.27$ for the free base).^[22] The Pd–N(7) distance of the solid state structure is in close agreement with that of the closely related complexes $[\text{Pd}(\text{en})(5'\text{-GMP})_2] \cdot 9\text{H}_2\text{O}$,^[9] *trans*- $[\text{Pd}(\text{ino})\text{Cl}_2] \cdot 5\text{H}_2\text{O}$ ^[23] and $[\text{Pd}(\text{dien})(\text{guo})]^{2+}$.^[24] The Pd–N(1)_{en} distance also corresponds to that of other $[\text{Pd}(\text{en})]^{2+}$ complexes with a PdN₄ coordination sphere.^{[9][25]}

The dihedral angle between the purine bases,^[2] as well as that of the purine bases and the square-planar coordination sphere,^[26] are rather small in comparison to those of related Pt(II) complexes. However, the corresponding octahedral Ni(II) complex, $[\text{Ni}(\text{en})(5'\text{-IMPH})_2(\text{H}_2\text{O})_2] \cdot 13\text{H}_2\text{O}$,^[27] is an exception by exhibiting a dihedral angle of even less than 30°. The structure of $[\text{Pt}(\text{en})(5'\text{-IMP})_2]^{2-}$ also shows a small dihedral angle of 31° with an N(7)⋯N(7) distance of 3.26 Å.^[28]

The small dihedral angle and the short distance between the two coordinated purine bases strongly indicate intracomplex interbase stacking interactions as observed for *cis*- $[\text{Pt}(\text{tn})(\text{Me-5'-GMP})_2]$.^[29] The purines stack with one pyrimidine ring overlapping with the pyrimidine ring of the other purine base. Intercomplex base stacking interactions were also found between the pyrimidine moieties of two neighboring $[\text{Pd}(\text{en})(5'\text{-IMP})_2]$ units.

The riboses exhibit C(3)'-endo (N-type) conformations, which is in reasonable agreement with the nucleotide 5'-GMP in *cis*- $[\text{Pt}(\text{NH}_3)_2(5'\text{-GMP})_2]^{2+}$ which adopts a predominantly C(3)'-endo,anti conformation.^[30] For the binding of cisplatin to GpG sequences in oligonucleotides, a change in the sugar conformations from C(2)'-endo to C(3)'-endo was proposed.^[3] These observations of a predominantly C(3)'-endo conformation correspond well to the structure reported here. The sugar puckers contrast those of the crystal structure of *cis*- $[\text{Pt}(\text{NH}_3)_2(5'\text{-IMP})_2]^{2-}$ exhibiting a C(2)'-endo pucker.^[13] The latter complex was crystallized from an aqueous solution at pH = 6.9 where the phosphate groups remained deprotonated ($\text{p}K_{\text{a}} = 6.00$)^[22] and were involved in close contacts with the sodium counterion. A C(2)'-endo sugar pucker was also observed for two 5'-dGMP units coordinated to a Ni(en) moiety.^[32] Here the sugar pucker also led to intermolecular rather than intramolecular hydrogen bonding of the phosphates. The complex $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2] \cdot 11\text{H}_2\text{O}$ was crystallized under acidic conditions with the phosphate groups being monoprotonated leading to a neutral complex.

In the analogous structure *cis*- $[\text{Pt}(\text{NH}_3)_2(5'\text{-IMP})_2]^{2-}$, no intramolecular H bonding was found between the phosphates and the NH groups.^[31] The structures of $[\text{Pt}(\text{en})(5'\text{-GMP-N7})_2] \cdot 9\text{H}_2\text{O}$ and $[\text{Pd}(\text{en})(5'\text{-GMP-N7})_2] \cdot 9\text{H}_2\text{O}$ ^[9] exhibited this kind of intramolecular hydrogen bonding between the phosphates and the en ligands. With an O⋯N distance of 2.92 Å there does not seem to be a major difference to the structure of $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2] \cdot 11\text{H}_2\text{O}$ reported in this study. By way of comparison, the latter 5'-GMP structures are nearly identical to the 5'-IMP structure reported here. Intermolecular hydrogen bonds between the O(6) and the en ligands of neighboring molecules were found to stabilize the structure of $\text{Na}_2[\text{Pt}(\text{en})(5'\text{-GMP})_2] \cdot 6\text{H}_2\text{O}$.^[33] A strong hydrogen bond formed between the phosphate group of the nucleotide and the NH group of the en ligand was reported for the dimeric structure of $[\text{Pt}(\text{en})(5'\text{-CMP})_2]$.^[34] Here one oxygen of the phosphate was directly bonded to the Pt(II) atom, whereas another oxygen atom was involved in NH hydrogen bonding with $d(\text{O} \cdots \text{N}) = 2.75$ Å. With the N(3) site coordinated to another Pt(II) moiety two nucleotides functioned as bridges between two $[\text{Pt}(\text{en})]^{2+}$ groups. Crystallographic evidence for intramolecular H bonding of the phosphate group was also reported for 5'-IMP complexes of Co and Ni.^[35] Close contacts were found between the phosphate and the metal bound H₂O molecules. The conformation of the 5'-IMP units are very similar to the one reported here. The structure of $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2] \cdot 11\text{H}_2\text{O}$ does not exhibit the kind of hydrogen-bonding interaction between the N(1)_{en} and the O(6) atoms as reported for other Pt-purine structures.^{[36][37]}

The X-ray crystal structure of $[\text{Pd}(\text{en})(5'\text{-IMP-N7})_2] \cdot 11\text{H}_2\text{O}$ showed that the N(7) position of 5'-IMP is the main binding site for Pd(II) at pH < 5 similar to that observed in solution by NMR studies. The N(1) position, which is also an attractive target for Pd(II) at neutral pH, is only of

minor importance since it is protonated under the acidic conditions used for crystallization and NMR measurements. If the helical structure of duplex DNA is considered, the N(1) position of guanine is involved in intensive base-pairing and unlikely to serve as a coordination site for Pt(II) anticancer drugs. The C(3')-endo sugar pucker and anti conformation about the glycosidic torsion angle correspond well to those observed for the cisplatin adducts of larger DNA fragments, whereas the head-to-tail orientation of the nucleotides is biologically improbable. The nucleotide orientation is mainly controlled by intracomplex interbase interactions and intramolecular hydrogen bonding. Hydrogen bonding between the phosphate of the nucleotides and the NH groups of the ethylenediamine ligand strongly suggests that this interaction is of major importance for the mechanism of action of cisplatin and related antitumor drugs.

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Experimental Section

PdCl₂ was donated by Degussa, and inosine 5'-monophosphate (disodium salt; 5'-IMPNa₂) was obtained from Sigma. [Pd(en)Cl₂]^[38] was prepared by standard methods. Demineralized water was used for all preparations. – Chemical analyses were performed on a Carlo Erba Elemental Analyser 1106. – ¹H and ¹³C NMR measurements were performed on a Bruker Avance DPX 300 spectrometer at 300.1 MHz and 75.5 MHz, respectively, using D₂O as solvent. Spectra were recorded at 25 ± 1 °C with TSP (sodium 3-trimethylsilylpropionate) for ¹H and ¹³C as an internal reference. – pH values of solutions were measured with a Mettler-Toledo electrode on a Metrohm 632 pH meter. Standard buffers of pH = 1.68, 4.00 and 6.87 were used for calibration. – Measurements of NMR samples in D₂O were performed directly in the NMR tube with an Aldrich 4 mm combination electrode, and pH* values were adjusted using diluted DNO₃ and NaOD. These values were not corrected for the deuterium isotope effect and are designated as pH* values.

Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100526. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336-033, e-mail: deposit@chemcrs.cam.ac.uk].

[Pd(en)(5'-IMP-N7)₂]₂ · 9 H₂O: 67 mg (0.28 mmol) of [Pd(en)Cl₂] were reacted with 293 mg (0.56 mmol) of 5'-IMPNa₂ in 15 ml of H₂O for 30 min at 60 °C. After cooling to room temp., 0.56 ml of 1 N HCl was added to the solution. The final yellow solution was stored for one week at 4 °C which allowed yellow needles suitable for X-ray crystallography to be obtained. – C₂₂N₁₀H₅₀O₂₅P₂Pd: calcd. C 25.83, H 4.93, N 13.69; found C 25.77, H 4.83, N 13.47. – ¹³C NMR (D₂O; pH* = 1.0): δ = 159.2 [C(6)], 150.7, 150.5 [C(2), C(4)], 144.0 [C(8)], 125.1 [C(5)], 92.1 [C(1)], 86.8 [C(4)'], 77.6 [C(2)'], 72.6 [C(3)'], 67.0 [C(5)'], 50.2 (C_{en}).

Table 1. Selected bond lengths [Å] and angles [°] for [Pd(en)(5'-IMP)₂] · 11 H₂O

Pd–N(1) _{en}	2.011(8)
Pd–N(7)	2.053(8)
P–O(3)	1.495(9)
P–O(2)	1.511(9)
P–O(1)	1.535(10)
P–O(5)'	1.583(9)
N(1) _{en} #1–Pd–N(1) _{en}	81.6(6)
N(1) _{en} #1–Pd–N(7)	173.3(4)
N(1) _{en} –Pd–N(7)	93.6(4)
N(7)–Pd–N(7)#1	91.6(5)
O(3)–P–O(2)	117.7(5)
O(3)–P–O(1)	113.0(6)
O(2)–P–O(1)	104.9(6)
O(3)–P–O(5)'	104.2(4)
O(2)–P–O(5)'	109.9(5)
O(1)–P–O(5)'	106.8(6)

Symmetry transformations used to generate equivalent atoms: #1–y,–x,–z+3/4.

Table 2. Crystallographic data for [Pd(en)(5'-IMP-N7)₂] · 11 H₂O

Formula	C ₂₂ H ₅₄ N ₁₀ O ₂₇ P ₂ Pd ^[a]
<i>Mr</i>	1059.1 ^[a]
Cryst. dimensions	0.5 × 0.4 × 0.4
Cryst. system	tetragonal
Space group (No.)	P4 ₃ 22 (No. 95)
<i>a</i> = <i>b</i> [Å]	12.060(5)
<i>c</i> [Å]	28.510(5)
α = β = γ [°]	90.000
<i>V</i> [Å ³]	4147(3)
<i>Z</i>	4 ^[a]
Cell weight	4236.37
<i>T</i> [K]	293(2)
<i>d</i> _{calcd.} [g cm ⁻³]	1.696
μ [mm ⁻¹]	0.63
Index ranges	–12 ≤ <i>h</i> ≤ 12, 0 ≤ <i>k</i> ≤ 12, 0 ≤ <i>l</i> ≤ 30
<i>F</i> (000)	2192
θ range [°]	3–22
Radiation (Mo–K _α) [Å]	0.71069(graphite monochromator)
<i>R</i> _{int}	0.083
Data/restraints/parameters	2565/120/285
Goodness-of-fit on <i>F</i> ₂	1.540
<i>R</i> ₁ ^[b]	0.0744 (for observed data)
<i>wR</i> ₂ ^[c]	0.2054 (for observed data)

^[a] A formula of C₁₁H₂₇N₅O_{13.5}PP_{0.5} with *Mr* = 529.55 and *Z* = 8 was resolved, since Pd is located on a unique position. For consistency it is multiplied by the factor of 2. – ^[b] *R*₁ = Σ(|*F*_o| – |*F*_c|) / Σ|*F*_o|. – ^[c] *wR*₂ = [Σw[(*F*_o² – *F*_c²)² / Σw(*F*_o²)²]^{1/2}; *w* = 1/[σ²(*F*_o²) + (0.1000*P*)² + 0.00*P*], where *P* = [max(*F*_o²) + 2(*F*_c²)]/3.

Crystal Structure Determination: A yellow crystal was mounted on a glass rod and used for data collection. X-ray structural data were obtained on a Philips PW 1100 diffractometer with a graphite monochromator at 20 °C using Mo–K_α radiation. A total number of 5514 reflections with 3 < θ < 22° using ω/2θ scans was collected, of which 2305 were considered observed [*I* > 2σ(*I*)]. At θ > 22° the decrease in intensity was too high in order to collect further reflections. Data refinement was conducted using the programs SIR-92 and SHELXL-93.^[39] The full-matrix least squares refinement resulted in final agreement factors *R* = 0.0744 and *R*_w = 0.2054. No absorption correction was applied. Hydrogen atoms were fixed on the basis of geometrical considerations. The location of the H(1) [P–O(1) group] was estimated by considering the difference electron density in 15° intervals around O(1). A 2.25 e Å⁻³ peak was found in the final difference Fourier map, which was located at a distance of 0.95 Å from the Pd atom. Selected bond lengths and angles are given in Table 1 and crystal data and details

on data collection in Table 2. The X-ray structural data indicated 11 H₂O molecules per formula unit of [Pd(en)(5'-IMP)₂]:11 H₂O which disagrees with the 9 H₂O molecules per formula unit found using C, H, N analysis. Hence, we assume that the crystals loose H₂O on standing.

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