Reactions of $Pd(PPh_3)_4$ with 3′,5′-Di-*O*-acetylthymidine: Oxidative Addition of $Pd(PPh_3)_4$ on Thymidine N3 and C4 Atoms

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Oxidative addition reactions of $Pd(PPh_3)_4$ on the pyrimidine nucleosides 3′,5′-di-*O*-acetylthymidine and 3′,5′-di-*O*-acetyl-4-chlorothymidine and on the nucleobase 1-methylthymine have been investigated. N3 and C4 metal coordinated complexes **3** and **7** were isolated and characterized by spectroscopic techniques. Moreover, the crystal structure of the *trans*-[PdCl(1-methyl thymine)$(PPh_3)_2$]·H_2O (**4**) is reported.

Introduction

In the past few years numerous chemical modifications to nucleic acid constituents have been investigated. Modified bases and backbone DNA analogues have been synthesized with the aim of creating new structures and imparting new functions to oligonucleotides. Introduction of metals into oligonucleotide fragments by insertion of ligandosides, in which the heterocyclic base is substituted by a strong chelator, allowed the development of new energy and electron-transfer systems, such as semiconductors and molecular magnets.[1] Hydroxypyridone-based ligandosides complexed to Cu^{2+} ions have been employed to build artificial DNA strands, giving rise to self-assembled metal arrays.[2] In the medicinal chemistry field metal-complexed oligonucleotides can be used to obtain more stable and biologically active compounds.

The biological activity of some transition-metal complexes is now well established. Pt, Ag, Zn, and Au complexes have been widely investigated, and some of those complexes are used for therapeutic purposes. The most well known of these compounds is the anticancer therapeutic *cis*-$PtCl_2$, a compound that forms complexes with DNA and is a highly effective treatment for growth of certain types of cancers. Zn complexes, for example, selectively recognize DNA GC boxes, inhibiting the binding of transcriptional factors, such as Sp1, with its target DNA.[3] Furthermore, phosphine complexes of Ag(I), Au(I), and Sn(IV) and phosphine ligands by themselves have been shown to be anticancer, anti-HIV, or antimitochondrial agents. [4−6] The study of metal complex based drugs is still very challenging. In this frame a better understanding of the role of the metal ligands and the nature of the metal in the interaction with biological systems will help in the development of new drugs. In investigations aimed at understanding the binding sites of antitumor Pt(II) compounds to nucleic bases, Pd(II) compounds have been also employed. The interest arises from the similarity in the chemical properties of palladium(II) and platinum(II); in fact, both metal ions possess similar ionic radii, prefer nitrogen rather than oxygen donor atoms, and form strongly tetragonal complexes, but those with Pd(II) react faster. The advantage of the much faster (10^5 times) ligand substitution reactions that the Pd(II) presents in vitro makes it a good model for studies of reactions in vivo with biological molecules.[7−9]

The aim of this work is the synthesis of new Pd-nucleoside complexes having the metal covalently bonded to the nucleobase which can be used in biological experiments as potential anticancer drugs or as metalated nucleoside building blocks that can be incorporated into synthetic oligonucleotides. Oligonucleotides meta-

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lated at fixed positions could possess improved and site-specific biological activity. Nephrotoxic side effects associated with therapies based on metal complexes, caused by the excess of metal used and by their uncontrolled biodistribution, can be reduced by linking the metal to specific biological targets such as oligonucleotides.[10−13] Therefore, even today, the synthesis of metallonucleosides is still very interesting.

In a previous paper we reacted $Pt(PPh_3)_4$ with methylthymine (**2**) and observed the formation of *cis* Pt phosphine complexes in which the Pt atom was coordinated to the N3 of the thymine base.[14] We also investigated the reaction of $Pt(PPh_3)_4$ with 3′,5′-di-*O*-acetylthymidine (**1**) in the presence of KCl. This reaction resulted in a mixture of two diastereoisomeric products, due to the restricted rotation around the Pt−N3 bond, which rapidly interconverted in solution. Here we report studies on the reactions of the $Pd(PPh_3)_4$ complex with 3′,5′-di-*O*-acetylthymidine (**1**), its C4 chlorine-activated derivative, 3′,5′-di-*O*-acetyl-4-chlorothymidine (**6**), and 1-methylthymine (**2**). The synthesis and NMR characterization of the N3 and C4 3′,5′-di-*O*-acetylthymidine oxidative addition complexes **3** and **7**, together with the X-ray structure of the Pd complex with 1-methylthymine, **4**, are described.

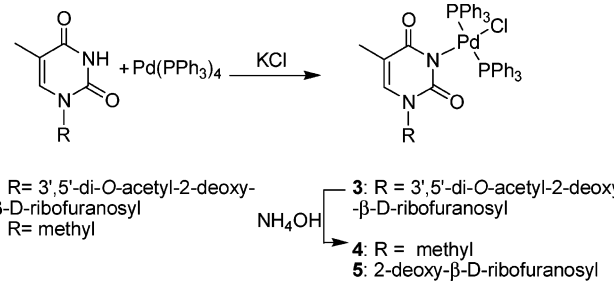
Results and Discussion

Reactivity of the thymidine ring and its activated 4-chloro derivative with a zerovalent palladium complex $Pd(PPh_3)_4$ was investigated. It is well known that the metal-binding sites on the thymidine consist primarily of the nitrogen atom N3 and the oxygen positions 2 and 4, depending on the coordinating metal.[15−18] The aim of this work was to investigate whether activation of position 4 of the nucleoside could create a new coordination site for the metal and generate a new stable metal-bound nucleoside derivative.

To synthesize a Pd-thymidine complex that could be functionalized on the sugar moiety and inserted into oligonucleotides, we carried out reactions using nucleotides in which the sugar moiety was protected on the 3′ and 5′ OH by acetyl groups.

Reaction of 3′,5′-di-*O*-acetylthymidine (**1**) with $Pd(PPh_3)_4$ in refluxing toluene in the presence of KCl afforded compound **3** in high yields (80%) (Scheme 1).[19] The stoichiometry of complex **3** was determined by NMR and mass measurements. The ^1H NMR and FAB-MS analyses indicated the presence of a complex in which a single 3′,5′-di-*O*-acetylthymidine coordinated with a single $Pd(PPh_3)_2$ unit and one chloride atom. In the ^1H NMR spectrum signals relative to CH_3-C5, H6, and H1′ were all subjected to upfield shifts of respectively 0.7, 1.1, and 0.5 ppm as compared to the uncomplexed nucleoside. The N3 proton signal was absent, suggesting the involvement of this nitrogen in the metal coordination. The sugar protons, other than the H1′, were not significantly influenced by the complexation. Comparing ^{13}C spectra of **1** and **3** we found a downfield shift for C2 and C4 of 3.5 and 5.5 ppm, respectively, and an upfield shift of 1.2 ppm for C5. On the basis of these data we hypothesised that the coordination of the metal occurred on the N3 atom of the nucleobase as observed in most of the Pd(II)-thymidine complexes reported in the literature.[20] The ^{31}P NMR spectrum at 25 °C showed just one signal at 23.5 ppm, suggesting the presence of two equivalent phosphines and a *trans* Pd configuration for complex **3**. Further, in the ^{31}P NMR spectra measured at a lower temperature (−15 °C) we did not observe changes in the spectrum appearance, thus confirming at that temperature the presence of *trans* magnetically equivalent phosphines.

Scheme 1



Unlike analogous Pt complexes, no diastereoisomers (rotaxamers) due to the chiral centers on the sugar were isolated, very likely because of the low rotational barrier around the Pd−N bond.

To explore the potential coordination of the Pd to N3 through the effect of the metal on the N3 chemical shift by ^{15}N NMR, we synthesized the $^{15}N3$-labeled 3′,5′-di-*O*-acetylthymidine Pd complex **3a**.[21] The ^{15}N chemical shift of the N3 did not change after complexation.

Attempts to crystallize complex **3** in order to further confirm the proposed structure by X-ray analysis were unsuccessful. Instead, we repeated the same reaction on 1-methylthymine, a molecule containing the same coordination sites as 3′,5′-di-*O*-acetylthymidine.

The reaction between $Pd(PPh_3)_4$ and 1-methylthymine[22] in refluxing toluene in the presence of KCl afforded complex **4** with a 59% yield (Scheme 1). A comparison between the ^1H, ^{13}C, and ^{31}P NMR of the complexes **3** and **4** suggested the same coordination. Suitable crystals of *trans*-[PdCl(1-methylthymine)-$(PPh_3)_2$]·H_2O (**4**) for X-ray crystallographic analysis were obtained by slow evaporation of its $MeOH/CHCl_3$ solu-

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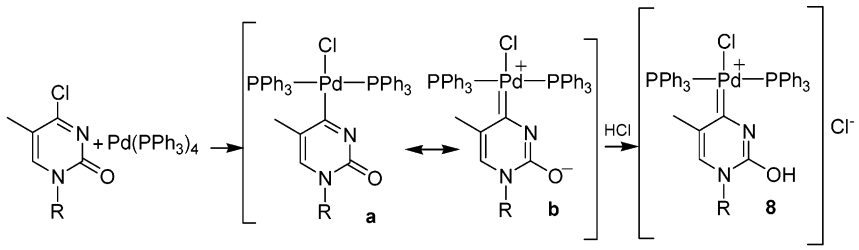
Scheme 2



6: R= 3',5'-di-*O*-acetyl-2-deoxy-–β-D-ribofuranosyl

7: R = 3',5'-di-*O*-acetyl-2-deoxy--β-D-ribofuranosyl

8: R = 3',5'-di-*O*-acetyl-2-deoxy--β-D-ribofuranosyl

tion. The X-ray crystallographic data revealed that Pd coordinates N3 of thymine, the chloride atom is *trans* to the nitrogen N3, and the two phosphines are respectively *trans*. $Pd(PPh_3)_4$ behaves in an analogous way to $Pt(PPh_3)_4$, except for the coordination of phosphines, which are *cis* in the Pt complex and *trans* in the Pd one.

The X-ray structure revealed a 2.035 Å Pd−N3 bond distance, suggesting a very strong interaction between the metal and the imidic nitrogen, similar to what was previously found in other phosphine Pt, Zn, and Au thymidine complexes in which the metal is bound to N3.[16,17,23]

Further evidence for the coordination of the metal to the deprotonated imidic N3 atom comes from the lowered C=O stretching frequencies, from 1705 and 1685 cm^{-1} in N1-methylthymine to 1690 and 1640 cm^{-1} in complex **4**, which reflects the longer carbonyl bonds due to deprotonation of the N3-H group. Those data are consistent with other literature reports of thymidine N3-metal complexes.

No hypothesis can be formulated on the mechanism of this reaction, since no intermediate was isolated, probably due to their lability. Reasonably, complexes **3** and **4** are the thermodynamically stable products: in fact ligand exchange and temperature shift experiments, followed by ^1H and ^{31}P NMR analysis, revealed no modification of their structure. Oxidative addition of the Pd complex occurs on the endocyclic nitrogen N3, confirming the high affinity of the palladium(II) ion for nitrogen ligands.

To explore the reactivity of $Pd(PPh_3)_4$ on the activated thymidine ring, in which the N3 was in a different electronic environment, we reacted $Pd(PPh_3)_4$ with 3′,5′-di-*O*-acetyl-4-chlorothymidine.[24] From the reaction, performed in refluxing toluene, complex **3** and the new complex **7** were isolated in 70% and 30% yield, respectively (Scheme 2). ^1H, ^{13}C, and ^{31}P NMR spectra, together with the FAB-MS data, allowed the characterization of complex **7**. As for complex **3** the metal coordinates two phosphines, one chloride, and a nucleobase. The FAB-MS spectrum of compound **7** showed a molecular weight lower than **3** by 16 u, thus suggesting the lack of the oxygen atom on the thymidine C4. In the ^{31}P NMR spectrum of compound **7** there was only one signal detected at 23.5 ppm, indicating the presence of two equivalent phosphines. In the ^1H NMR spectrum no significant proton shifts relative to compound **6** for either the base or the sugar protons were observed. Analysis of the ^{13}C NMR spectrum of complex **7** on comparison with the ^{13}C chemical shift of **6** allowed us to determine the palladium coordination site. In fact we observed a 52.9 ppm downfield shift of C4, a 4.5 ppm upfield shift of C2, a 9.2 ppm downfield shift of C5, and a 4.4 ppm downfield shift for CH_3-C5. Complex **7** can be considered as a palladium(II) carbene complex, stabilized by two heteroatoms situated at the α and γ positions of the metal-bonded carbon. In the literature there are numerous examples of carbene complexes stabilized by a heteroatom in α position with respect to the metal-bound carbon atom; γ-stabilized palladium(II) and platinum(II) carbene complexes can be obtained via oxidative addition by displacement reactions. Pd(II) complex synthesis is carried out by reacting Pd(0) complexes with aryl carbon atoms activated as tosylates or halides.[25−28] The nature of the metal−C(aryl) bond has been investigated by NMR.

In the ^{13}C NMR spectra a large shift in metal-coordinated carbon atoms has already been observed in several other metal complexes containing a covalent bond between the metal and a carbon atom. For example in a dinuclear Pd-MOP (MOP = (*S*)-2-diarylphosphino-1,1′-binaphthyl) complex in which a σ bond between the binaphthyl C4 and palladium is formed a 45 ppm downfield shift with respect to the uncomplexed MOP was observed.[29] In complex **7** the 52.9 ppm downfield shift of the metal-bound carbon atom can be explained by virtue of the strong electron donor character of the Pd. It is reported that the $M(PR_3)X$ moiety (M = Pd or Pt and X = halide) are π donors in inductive and resonance modes, interacting with the π framework of the aryl substituent. Complex **7** is a resonance hybrid between two forms: **7a**, in which the metal is connected to the C4 through a σ bond, and **7b**, in which the positively charged metal is bonded to the C4 through a double bond, thus stabilizing the enolate form of the nucleobase. The ^{13}C chemical shift of the C4 atom, which appears at 221.0 ppm, strongly suggests the presence

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of a covalent bond between the metal and the C4, thus stabilizing the enol form of the pyrimidine base (Scheme 2).

Experiments carried out by Meyer et al.[26] demonstrated that on the neutral quinolin-2-one-4-yl and the cationic quinolin-4-ylidene palladium and platinum complexes the chemical shifts of the metal-bound carbon atoms were different, depending on which of the forms (M−C single bond or M−C double bond with positive charge on the metal) was stabilized. In the neutral form of the quinoline complex the metal-bound carbon atom resonates at 176 ppm, 32 ppm downfield shifted with respect to the uncomplexed molecule; in the cationic form, stabilized through derivatization of the γ oxygen, the metal-bound carbon atom resonates around 207 ppm.[26]

Complex **7** bears a $Pd(PPh_3)_2Cl$ unit directly bound to the pyrimidine ring through the C4 atom; phosphines are *trans* positioned and chloride is therefore *trans* to the C4 of thymidine. To the best of our knowledge, **7** is the first complex in which the palladium is directly bound to the C4 of the thymidine.

Some aspects of reactivity of the new compounds **3** and **7** were also explored. Complex **3** dissolved in deuteriochloroform was treated with a stoichiometric amount of gaseous HCl. The NMR spectrum of the fresh reaction mixture disclosed rapid cleavage of the Pd−N bond with formation of $[PdCl_2(PPh_3)_2]$ and free thymidine. The organic compound could be separated from the metal complex by usual workup.

Very interestingly the same treatment on **7** had a different outcome. The NMR spectrum recorded immediately after the addition of the protic acid showed the presence of a new complex with the H6 signal markedly shifted to higher frequency with respect to that of the parent compound. Addition of an aqueous solution of KOH in deuterium oxide instantaneously restored the starting complex **7**. These evidences indicate that HCl does not cleave the Pd−C bond, leaving the organic moiety linked to the metal center. Alternatively, it is likely that the proton attacks the basic O site of **7b** with formation of a cationic product **8**, having the chloride as the counterion (Scheme 2). It should be noted that preparing corresponding salts might be a useful way to tune the physical properties of **7** without substantially altering its structure.

The stability of the palladium−nucleobase linkage to the basic conditions has been tested for **3** and **7**. Removal of the acetyl groups at the 3′ and 5′ sugar positions of **3** was achieved by treatment with a solution of 32% aqueous ammonia in methanol (1:1, v/v), giving complex **5** (60%), whose structure was confirmed by spectroscopic data (Scheme 1). Importantly the palladium−N3 nucleobase linkage is stable to the basic conditions, making it a suitable compound for insertion in oligonucleotide chains. On the other hand, compound **7** was not stable in these conditions nor in a solution of Na_2CO_3 in H_2O/methanol, affording a complex mixture of products.

Finally, as it is known that amides coordinated to metals can undergo insertion of unsaturated molecules, a functionalization of the nucleoside complex **3** was attempted by reaction with an excess of CS_2 in a chloroform solution. After some days the starting complex **3** was recovered unaltered and formation of the expected dithiocarbamate was not observed.

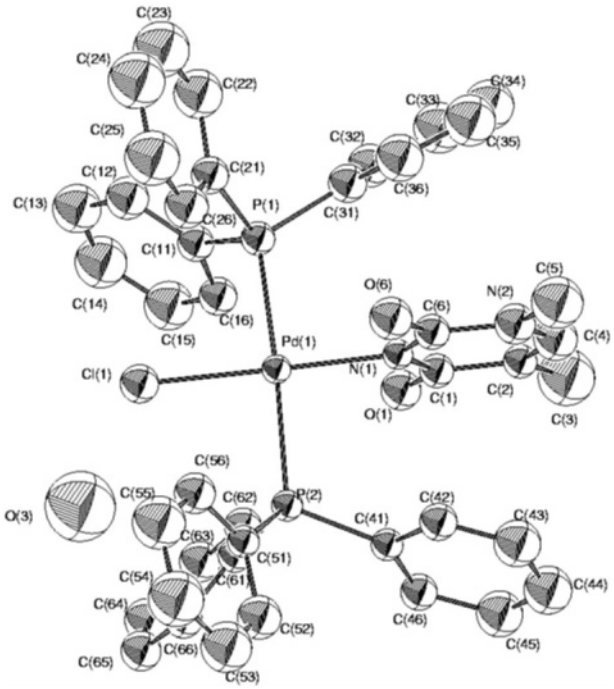

Figure 1. ORTEP[36] projection of two molecules of *trans*-$[PdCl(1\text{-MeThy})(PPh_3)_2]$, **4**. Thermal ellipsoids are drawn at the 30% probability level.

Table 1. Intramolecular Bond Distances for *trans*-[PdCl(1methylthymine)$(PPh_3)_2$] with Estimated Standard Deviations in Parentheses

atoms	bond distance (Å)
Pd(1)−N(1)	2.035(11)
Pd(1)−P(1)	2.303(4)
Pd(1)−P(2)	2.319(4)
Pd(1)−Cl(1)	2.297(4)
N(1)−C(6)	1.32(2)
N(1)−C(1)	1.37(2)
N(2)−C(4)	1.35(2)
N(2)−C(6)	1.38(2)
N(2)−C(5)	1.50(2)
O(1)−C(1)	1.24(2)
O(2)−C(6)	1.26(2)
C(2)−C(1)	1.39(2)
C(2)−C(4)	1.34(2)
C(2)−C(3)	1.46(3)

Molecular Structure of *trans*-[PdCl(1-methylthymine)$(PPh_3)_2]\cdot H_2O$, 4. The crystal structure of *trans*-$[PdCl(1\text{-methylthymine})(PPh_3)_2]\cdot H_2O$, **4**, is illustrated in Figure 1, which also gives the atom-numbering scheme. Selected bond distances and angles are in Table 1. The palladium atom displays square planar coordination: two *trans* corners of the square plane are occupied by the phosphorus atoms of two triphenylphosphines. The chlorine atom and the amide nitrogen of the 1-methylthymine ligand are *trans*. The dihedral angles P(1)−Pd−P(2) [172.8(11)°] and N(1)−Pd−Cl(1) [179.0(3)°] show a slight distortion from the planarity of the square planar coordination mode of the Pd atom. The plane of the 1-methylthymine ligand is approximately perpendicular to the palladium coordination plane, as seen by the torsion angles P(1)−Pd−N(1)−C(1) and P(1)−Pd−N(1)−C(6) of −89.3(10)° and 91.7 (11)°, respectively.

Table 2. Selected Angles for *trans*-[PdCl(1-methylthymine)(PPh_3)$_2$] with Estimated Standard Deviations in Parentheses

atoms	bond angle (deg)
C(6)−N(1)−C(1)	124.4(12)
Pd(1)−N(1)−C(6)	118.7(10)
Pd(1)−N(1)−C(1)	116.9(9)
C(6)−N(2)−C(4)	117.8(14)
C(4)−N(2)−C(5)	122.3(15)
C(6)−N(2)−C(5)	119.9(14)
O(1)−C(1)−N(1)	120.6(13)
O(1)−C(1)−C(2)	123.3(14)
N(1)−C(1)−C(2)	116.1(13)
C(1)−C(2)−C(4)	119.4(15)
C(4)−C(2)−C(3)	122.2(17)
C(1)−C(2)−C(3)	118.4(15)
N(2)−C(4)−C(2)	123.3(17)
O(2)−C(6)−N(1)	120.2(14)
O(2)−C(6)−N(2)	120.8(14)
N(1)−C(6)−N(2)	119.0(14)

The analysis of the two triphenylphosphine moieties in *cis* position with respect to the Cl(1) atom shows the Cl(1) atom in a staggered conformation with respect to the C(41), C(51), C(61) and C(11), C(21), C(31) atoms of the phenyl rings: the dihedral angles Cl(1)−Pd−P(2)−C(41), Cl(1)−Pd−P(2)−C(51), Cl(1)−Pd−P(2)−C(61), Cl(1)−Pd−P(1)−C(11), Cl(1)−Pd−P(1)−C(21), and Cl(1)−Pd−P(1)−C(31) are 173.9(6)°, 55.7(5)°, −62.3(6)°, −55.2(5)°, −171.7(6)°, and 67.4(6)°, respectively.

In the two phosphine ligands, all the C−C bond lengths are typical for conjugated aromatic rings (1.32−1.41 Å).[30] In the crystal packing the molecules are characterized by one intermolecular hydrogen bond between the oxygen (O_3) of the water molecule and O(2) atom of the 1-methylthymine ligand [distance $O_3\cdots O(2)$ 2.75(1) Å; angle $O_3\cdots O(2)=C(6)$ 127.64(5)°]. The crystal structure is further stabilized by van der Waals interactions involving the phenyl and the methyl groups.

Conclusions

Palladium oxidative addition reactions were carried out on the pyrimidine nucleobase 1-methylthymine (**2**) and the nucleosides 3′,5′-di-*O*-acetylthymidine (**1**) and 3′,5′-di-*O*-acetyl-4-chlorothymidine (**6**). Reactivity of the pyrimidinic ring can be tuned by activating the ring, and the oxidative addition reaction of the zerovalent Pd(PPh_3)$_4$ complex can be directed on either N3 or C4 of thymidine. When the pyrimidine ring is not chlorinated, the metal prefers coordinating the endocyclic nitrogen in position 3, giving rise to the *trans* complex **5**. Activation of the nucleobase by halogenation on C4 directs the metal coordination on C4, to form the *trans* carbene-Pd complex **7**. The strong π-electron interaction between Pd and thymidine is demonstrated in the ^{13}C spectra by the C4 resonance at 221.0 ppm, which is diagnostic for the Pd(II) carbene complex. Complex **7** is the first example of oxidative addition of palladium on the C4 of a thymidine reported so far.

Experimental Section

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer at 400 and 100.13 MHz, respectively. All chemical shifts are expressed in ppm with respect to the signal of the protonated solvent ($CDCl_3$, δ 7.26 and 77.0; DMSO-d_6, δ 2.55 and 39.5). The ^{31}P NMR spectra were run on a Bruker WM-400 spectrometer at 161.98 MHz, with external reference to 85% H_3PO_4 (δ 0.0). The FAB mass spectra (positive) were recorded on a ZAB 2SE spectrometer. The HPLC analyses and purifications were carried out on a Beckman System Gold instrument equipped with a UV detector module 166 and a Shimadzu Chromatopac C-R6A integrator. Pd(PPh_3)$_4$ was used as supplied by Sigma.

Synthesis of Complex 3. A 0.30 g sample of 3′,5′-di-*O*-acetylthymidine (**1**) (0.92 mmol) was reacted with 1.06 g of Pd(PPh_3)$_4$ (0.92 mmol) in refluxing dry toluene in the presence of KCl (0.92 mmol). After stirring 5 h, toluene was evaporated. The crude mixture was redissolved in chloroform and purified by silica gel chromatography using chloroform as eluent. Pure complex **3** (0.76 g) was obtained (87% yield of pure product).

R_f = 0.7 (eluent $CHCl_3$/CH_3OH 98:2 v/v). ^{1}H NMR (DMSO-d_6): δ 1.2 (3H, bs, CH_3-C5); 2.0 (3H, s, CH_3-CO); 2.1 (3H, s, CH_3-CO); 2.5 (2H, m, H2′); 4.1 (1H, m, H4′); 4.2 (2H, m, H5′); 5.1 (1H, m, H3′); 5.8 (1H, dd, H1′); 6.4 (1H, bs, H6); 7.7−7.5 (15H, m, C_6H_5-P). ^{13}C NMR ($CDCl_3$): δ 13.4 (CH_3-C5); 20.4, 20.6 (CH_3−CO); 36.7 (C2′); 63.4 (C5′); 73.8 (C4′); 80.7 (C3′); 84.2 (C1′); 108.9 (C5); 134.7−127.71 (C_6H_5-P); 153.7 (C2); 168.9 (C4); 169.8 and 170.1 (CH_3-*C*O). ^{31}P NMR (DMSO-d_6): δ 23.5. FAB-MS: (^{106}Pd) 991 *m/z*; $[M + H]^+$. Anal. Calcd for $C_{43}H_{38}ClN_2O_5P_2Pd$: C, 59.60; H, 4.42; Cl, 4.09; N, 3.23; O, 9.23; P, 7.15; Pd, 12.28. Found: C, 59.69; H, 4.60; Cl, 3.92; N, 3.10; P, 7.03.

Synthesis of Complex 3a. Complex **3a** was synthesized following the same procedure described for **3**, using ^{15}N3-labeled 3′,5′-di-*O*-acetyl thymidine. ^{15}NMR (DMSO-d_6): δ 160.9.

Synthesis of Complex 4. See procedure described for **3**, using 1-methylthymine as substrate.

Complex **4** was purified by silica gel column chromatography using 7:3 v/v C_6H_6/$CH_3COOCH_2CH_3$ as eluent (59% yield of pure product). R_f = 0.4 (eluent C_6H_6/$CH_3COOCH_2CH_3$ 7/3 v/v). ^{1}H NMR (DMSO-d_6): δ 1.2 (3H, bs, CH_3-C5); 2.6 (3H, s, CH_3-N1); 6.3 (1H, bs, H6); 7.8−7.4 (15H, m, C_6H_5-P). ^{13}C NMR ($CDCl_3$): δ 13.1 (CH_3-C5); 36.1 (CH_3-N1); 107.9 (C5); 134.8−127.7 (C_6H_5-P); 154.7 (C2); 170.1 (C4). ^{31}P NMR (DMSO-d_6): δ 23.5. FAB-MS: (^{106} Pd) 771 *m/z*; $[M + H]^+$.

Synthesis of Complex 5. Derivative **3** (0.1 g, 0.1 mmol) was dissolved in 2 mL of CH_3OH; then 2 mL of NH_4OH (37%) was added. The mixture was treated at 50 °C for 2 h; the solvent was evaporated, and the product was purified by silica gel column chromatography, eluting using increasing amounts of CH_3OH in $CHCl_3$ (from 0 to 5%) to give 0.6 mmol of pure complex **5** (60% yield of pure product).

R_f = 0.8 (eluent 85:15 $CHCl_3$/CH_3OH v/v). ^{1}H NMR (CD_3OD): δ 1.4 (3H, bs, CH_3-C5); 1.7 (1H, m, H2′); 2.1 (1H, m, H2′); 3.7 (2H, m, H5′); 3.8 (1H, m, H4′); 4.2 (1H, m, H3′); 5.7 (1H, dd, H1′); 6.9 (1H, bs, H6); 7.9−7.4 (15H, m, C_6H_5-P). ^{13}C NMR (CD_3OD): δ 13.9 (CH_3-C5); 41.7 (C2′); 63.1 (C5′); 71.9 (C3′); 88.5 (C4′); 87.1 (C1′); 110.2 (C5); 136.2−129.6 (C_6H_5-P); 156.1 (C2); 172.3 (C4).

Synthesis of Complex 7. See procedure described for **3**, using 3′,5′-di-*O*-acetyl-4-chlorothymidine as substrate. The crude mixture was redissolved in chloroform and purified by silica gel chromatography using chloroform as eluent (30% yield of pure product).

R_f = 0.3 (eluent 98:2 $CHCl_3$/CH_3OH v/v). ^{1}H NMR (DMSO-d_6): δ 1.9 (3H, bs, CH_3-C5); 2.1 (6H, s, CH_3-CO); 2.5 (2H, m, H2′); 4.2 (1H, m, H4′); 4.4 (2H, m, H5′); 5.1 (1H, m, H3′); 6.3 (1H, dd, H1′); 6.5 (1H, bs, H6); 8.1−7.2 (15H, m, C_6H_5-P). ^{13}C NMR ($CDCl_3$): δ 20.2 (CH_3-C5); 21.4, 21.5 (CH_3-CO); 39.0 (C2′); 64.0 (C5′); 74.1 (C4′); 82.6 (C3′); 86.1 (C1′); 122.0 (C5); 136.5−129.5 (C_6H_5-P, C6); 148.4 (C2); 221.0 (C4); 169.9 and 170.1 (CH_3-*C*O). ^{31}P NMR (DMSO-d_6): δ 23.49. FAB-MS: (^{106} Pd) 974 *m/z*; $[M + H]^+$. Anal. Calcd for $C_{48}H_{43}ClN_2O_6P_2Pd$: C,

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60.83; H, 4.57; Cl, 3.74; N, 2.96; O, 10.13; P, 6.54; Pd, 11.23. Found: C, 61.19; H, 4.63; Cl, 3.90; N, 2.53; P, 6.46.

Addition of HCl to complexes **3** and **7**: a solution of the appropriate complex (0.025 mmol) in 0.5 mL of deuteriochloroform was treated with 0.6 mL of gaseous HCl (0.025 mmol). The reaction mixture was analyzed by NMR spectroscopy (see text). Addition of a KOH solution in D_2O to the NMR tube containing **8** restored complex **7** according to the ^{1}H NMR analysis.

^{1}H NMR (**8**) ($CDCl_3$): δ 1.9 (3H, bs, CH_3-C5); 2.1 (6H, s, CH_3-CO); 2.4 (2H, m, H2′); 3.9 (1H, br s, OH−C2), 4.1 (1H, m, H4′); 4.2 (2H, m, H5′); 4.9 (1H, m, H3′); 5.6 (1H, dd, H1′); 6.9 (1H, br s, H6); 8.1−7.2 (15H, m, C_6H_5-P).

Crystallography. Suitable crystals of *trans*-[PdCl(1-methylthymine)(PPh_3)$_2$]·H_2O (**4**) for X-ray analysis were obtained by slow evaporation of MeOH/$CHCl_3$ at 4 °C. Intensity data collection was performed using graphite-monochromated Mo Kα radiation (λ = 0.70930 Å) and a pulse-high discrimination on an automated MACH3 Enraf-Nonius. Data analysis was performed with the maXus program.[31] Intensities for complexes were corrected empirically for absorption effects with the DIFABS program and corrected for absorption effects using the package.[32] The independent reflections were measured in the θ range 2−25°. Unit cell parameters were determined by least-squares refinement of the setting angles of 25 high-angle reflections (5° < θ < 12°). Three standard reflections were monitored periodically and showed no significant change during data collection. A total of 7473 independent reflections were measured with the $\omega-2\theta$ scan mode. Using a prescan speed of 4.12° min, reflections with a net intensity $I < 0.5\sigma(I)$ were flagged as "weak"; those with $I \geq 0.5\sigma(I)$ were measured at lower speed depending on the value of $\sigma(I)/I$. The structure was solved by direct methods using the SIR 92 program.[33] The best E maps revealed all the non-H atoms and the water solvent molecule.

Refinement by the full-matrix least-squares procedure on F^2 (all data) used the SHELXL 97 program with anisotropic thermal factors for all non-hydrogen atoms.[34] Hydrogen atom positions were calculated and allowed to ride on their attached atoms, with $U_{iso} = 1.2U_{eq}$ of the attached atom. The scattering factors for all atomic species were calculated from Cromer and Waber.[35]

Crystal Data. $C_{42}H_{34}ClN_2O_2P_2Pd\cdot H_2O$, MW = 822.01, monoclinic, space group name $P2_1/c$ (no. 14), a = 17.780(10) Å, b = 12.955(6) Å, c = 19.190(10) Å, β = 117.08(5)°, V = 3936(4) Å^3, T = 298 K, Z = 4, μ(Mo Kα) = 0.794 mm^{-1}, 7473 unique reflections (R_{int} = 0.0) used in all calculations. The final $R_w(F^2)$ was 0.1908; R1 = 0.0707.

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