Synthesis and Molecular Structure of the First Metal Complex of an Analogue of Guanine with Pd^{II}−C(8) Binding

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Introduction

The interaction of metal complexes with nucleobases has been extensively studied with the aim of determining the mode of action of these metal complexes as antitumor agents, as useful tools for molecular biology, and as regulators of gene expression.[1−5] Many of these studies have focused on modeling the bonding of transition metals to the DNA polymer in an effort to ascertain the preferred metal-binding sites. Of all the recognized metal-binding sites on DNA nucleobases, N(7) of guanine is the site preferred by most metal species, although examples of metalation at other donor sites are known.[6,7] In particular, site C(8) in purines has been observed to coordinate only for caffeine (a 6-oxopurine with no NH free groups) in the complexes $[(caf)Cl_2(NH_3)Ru]Cl\cdot H_2O$[8] and $[(caf)(NH_3)_5Os]Cl_3\cdot 2H_2O$.[9] Interestingly enough, in the course of our studies on purine−metal ion interactions,[10] we have succeeded in obtaining from an N(7)−Pd^{II} precursor a C(8)−Pd^{II} purine complex. The structure of the latter is significant because it is the first structural example of a C(8)−Pd^{II} purine complex and because the purine contains an acidic proton. This paper is devoted to the synthesis and characterization of both complexes.

Experimental Section

Preparation of Complexes. All reagents were of analytical grade and were used without further purification. The ligand 8-(methylthio)-theophylline (abbreviated hereafter as HL) was prepared as described in the literature.[11]

(a) *trans*-[PdCl(L)(PPh_3)$_2$] (1). A suspension of *cis*-[$PdCl_2(PPh_3)_2$] (0.15 g, 0.21 mmol) in 10 mL of ethanol was added to a stirred solution of HL (0.1 g, 0.44 mmol) and NaOH (0.018 g, 0.45 mmol) in 3 mL of water, and the mixture was heated at reflux for 2 h. The resulting red solution was filtered through silica and left to stand at room temperature. After several days, brown prismatic crystals suitable for X-ray analysis were obtained (yield 37%). Anal. Calcd for $C_{44}H_{39}N_4O_2P_2SClPd$: C, 59.27; H, 4.41; N, 6.28; S, 3,60; Pd, 11.93. Found: C, 59.07; H, 4.32; N, 5.71; S, 3.23; Pd, 12.36. ^{1}H-NMR in $CDCl_3$ (δ, ppm): 2.23 (s, 3H, S−CH_3), 3.14 (s, 3H, N(3)−CH_3), 3.15 (s, 3H, N(1)−CH_3), 7.75−7.30 (m, 30H, PPh_3). ^{31}P-NMR in CD_2Cl_2 (δ, ppm): 21.85 (s).

(b) [Pd(L)(L′)(PPh_3)$_2$] (2). A solution of NaOH (0.007 g, 0.0175 mmol) in water (14 mL) was added to a red solution of **1** (0.1g, 0.0112 mmol) in Cl_2CH_2 (14 mL), and the mixture was stirred and heated at reflux for 6 h. After cooling, the mixture was extracted with two 15 mL portions of Cl_2CH_2. Organic extracts were washed with two 5 mL portions of water, dried over $MgSO_4$, concentrated to one-third volume, and passed through a silica column. Two major bands developed. From the first orange band was obtained a red-orange solution, which, kept at room temperature, provided orange, needlelike, X-ray-quality crystals (yield 25%). Anal. Calcd for $C_{51}H_{46}N_8O_4P_2SPd$: C, 59.16; H, 4.48; N, 10.82; S, 3.10; Pd, 10.20. Found: C, 58.87; H, 46.63; N, 10.51; S, 2.86; Pd, 10.46. ^{1}H-NMR in $CDCl_3$ (δ, ppm): 3.08, 3.21, 3.24, 3.27 (s, 3H, 3H, 3H, 3H, N−CH_3), 2.31 (s, 3H, S−CH_3), 7.75−7.30 (m, 30H, PPh_3), 15.75 (s, 1H, N(7)−H). ^{31}P-NMR in Cl_2CD_2 (δ, ppm): 18.50 (s). The second band, which was red, contained a mixture of products that could not be identified.

Physical Measurements. Microanalyses and ^{1}H- and ^{31}P{^{1}H}-NMR spectra were obtained as already described.[10]

X-ray Crystallography. Single-crystal data collections were performed at 294 K with a Stoe-Siemens AED diffractometer, using graphite-monochromatized Mo Kα radiation (λ = 0.710 69 Å). The unit cell parameters were obtained from least-squares refinement of 25 well-centered reflections (25 < θ < 35°). Crystal data for **1**, $C_{44}H_{39}N_4O_2SP_2ClPd$ (MW = 891.6): monoclinic, $P2_1/n$, a = 14.112(3) Å, b = 16.208(3) Å, c = 18.054(4) Å, β = 99.92(3)°, V = 4065.5(15) Å^3, Z = 4, ρ_{calc} = 1.547 g cm^{-3}, μ = 0.684 cm^{-1}, $F(000)$ = 1824, 4345 unique reflections and 1666 as observed with $F > 6\sigma(F_o)$, 507 parameters, $R(F_o)$ = 0.0498, $R_w(F_o)$ = 0.0487, and S = 1.05. Crystal data for **2**, $C_{51}H_{46}N_8O_4SP_2Pd$ (MW = 1035.4): monoclinic, *Cm*, a = 18.641(5) Å, b = 14.788(5) Å, c = 10.507(3) Å, β = 123.06(2)°, V = 2247.5(13) Å^3, Z = 2, ρ_{calc} = 1.416 g cm^{-3}, μ = 0.545 cm^{-1}, $F(000)$ = 1064, 3652 unique reflections and 2202 as observed with $F > 5\sigma(F_o)$, 344 parameters, $R(F_o)$ = 0.0454, $R_w(F_o)$ = 0.0498, and S = 2.89. The data were collected by the $\omega-2\theta$ scan mode (3 < 2θ < 65°) and were corrected for Lorentz and polarization effects and for absorption.

The structures were solved by a combination of Patterson and Fourier techniques using the SHELXTL-Plus program.[12] In the final refinement, all non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at calculated positions and then refined isotropically.

Results and Discussion

The reaction of sodium 8-(methylthio)theophyllinato (prepared in situ from the reaction of 8-(methylthio)theophylline with NaOH in ethanol) with *cis*-[$PdCl_2(PPh_3)_2$] in a 1:1 molar ratio leads to the complex *trans*-[PdCl(L)(PPh_3)$_2$], **1**. Refluxing **1** with NaOH in a water/dichlorometane mixture leads to the formation of the mixed-ligand complex *trans*-[Pd(L)(L′)(PPh_3)$_2$], **2** (where HL′ is theophylline).

The ^{1}H-NMR of **1** lacks the low-field signal due to a proton at either N(7) or N(9), thus indicating that coordination of the

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(1) *Transition Metal Complexes of Naturally Occurring Nucleobases and Their Derivatives*; Lusty, J. R., Ed.; CRC Handbook of Nucleobase Complexes, Vol. I; CRC Press: Boca Raton, FL, 1990; pp 9−99.
(2) Reedijk, J. *Chem. Commun.* **1996**, 801.
(3) Sherman, S. E.; Lippard, S. J. *Chem. Rev.* **1987**, *87*, 1153.
(4) Takahara, P. M.; Rosenzweig, A. C.; Frederik, C. A.; Lippard, S. J. *Nature* **1995**, *377*, 649.
(5) Pyle, A. M.; Barton, J. K. *Prog. Inorg. Chem.* **1990**, *38*, 413.
(6) Reedijk, J.; Fichtinger-Shepman, A. M.; van Oosterom, A. T.; van de Putte, P. *Struct. Bonding* **1987**, *67*, 53.
(7) Lippert, B. *Prog. Inorg. Chem.* **1989**, *37*, 1.
(8) Krentzien, H.; Clarke, M. J.; Taube, H. *Bioinorg. Chem.* **1975**, *4*, 143.
(9) Johnson, A.; O'Connell, L. A.; Clarke, M. J. *Inorg. Chim. Acta* **1993**, *210*, 151.
(10) (a) Colacio, E.; Romerosa, A.; Ruiz, J.; Román, P.; Gutiérrez-Zorrilla, J. M.; Vega, A.; Martínez-Ripoll, M. *Inorg. Chem.* **1991**, *30*, 3743. (b) Colacio, E.; Suárez-Varela, J.; Domínguez-Vera, J. M.; Avila-Rosón, J. C.; Hidalgo, M. A.; Martín-Ramos, D. *Inorg. Chim. Acta* **1992**, *202*, 219. (c) Colacio, E.; Cuesta, R.; Gutiérrez-Zorrilla, J. M.; Luque, A.; Román, P.; Giraldi, T.; Taylor, M. R. *Inorg. Chem.* **1996**, *33*, 4232.
(11) Merz, K. W.; Sthal, P. H. *Arzneim.-Forsch.* **1965**, *15*, 10.
(12) *SHELXTL-Plus*; Nicolet Instrument Corp.: Madison, WI, 1990.

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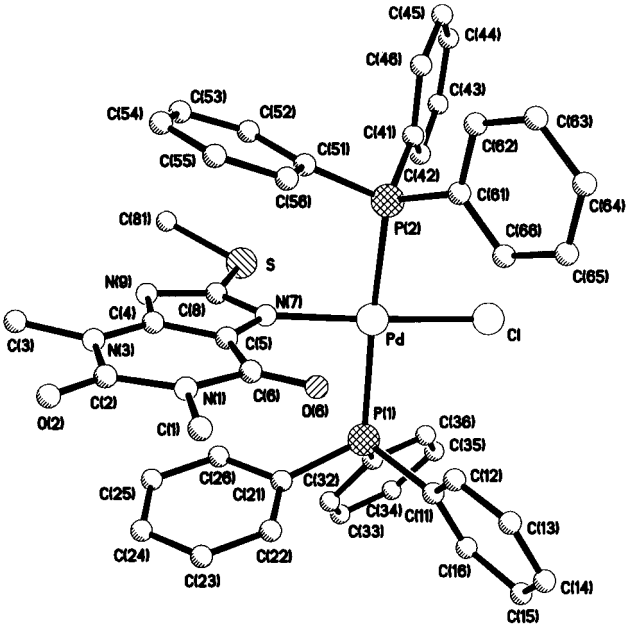

Figure 1. Molecular structure of **1** in the crystal. Selected bond lengths (Å) and angles (deg): Pd−P(1) 2.353(5), Pd−P(2) 2.355(5), Pd−N(7) 2.02(1), Pd−Cl 2.291(4), N(7)−C(8) 1.32(3), N(9)−C(8) 1.35(2); P(1)−Pd−P(2) 170.9(2), P(1)−Pd−Cl 89.5(2), P(1)−Pd−N(7) 91.7(4), N(7)−Pd−Cl 175.1(4), N(7)−Pd−P(2) 89.1(4), P(2)−Pd−Cl 90.5(2), C(5)−N(7)−C(8) 103.7(14), N(7)−C(8)−N(9) 117.0(16), C(8)−N(9)−C(4) 100.0(15).

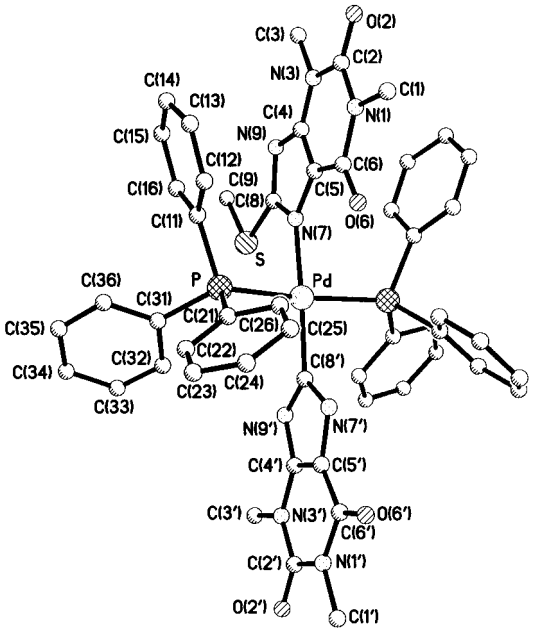

Figure 2. Molecular structure of **2** in the crystal. Selected bond lengths (Å) and angles (deg): Pd−P 2.344(3), Pd−N(7) 2.03(2), Pd−C(8′) 2.01(1), N(7)−C(8) 1.33(4), C(8)−N(9) 1.37(2), N(7′)−C(8′) 1.41(3), C(8′)−N(9′) 1.30(3); P−Pd−N(7) 89.3(1), P−Pd−C(8′) 91.1(1), N(7)−Pd−C(8′) 175.4(11), P−Pd−P′ 169.9(4), C(5)−N(7)−C(8) 105.0(17), N(7)−C(8)−N(9) 112.9(24), C(8)−N(9)−C(4) 103.6(20), C(5′)−N(7′)−C(8′) 107.0(25), N(7′)−C(8′)−N(9′) 108.4(15), C(8′)−N(9′)−C(4′) 107.5(25).

purine ligand must occur through one of the imidazole nitrogen atoms, possibly N(7), to avoid the steric hindrance from N(3)−CH_3. The lack of coordinated chloride on going from **1** to **2** is suggested by the absence, in the IR spectrum, of any band assignable to a Pd−Cl stretching vibration (ν(Pd−Cl) = 330 cm^{-1} for **1**). Integration of the ^{1}H-NMR spectrum of **2** indicated the absence of the SCH_3 group in one of the purine ligands, which is consistent with the presence of both 8-(methylthio)-theophyllinato and theophyllinato anions in the compound. In good accord with this, the methyl groups at N(1) and N(3) are seen as four singlets as a result of the nonequivalence of the purine ligands. Noteworthy is the appearance of one signal due to N(7)−H or N(9)−H in the low-field region (15.7 ppm), which, together with the absence of any C(8)−H signal, points to C(8)-coordination of the theophyllinato ligand. The ^{31}P-NMR spectra of **1** and **2** exhibit a single resonance consistent with a square-planar geometry with two equivalent *trans* phosphine ligands.

The results of X-ray structure determinations for **1** and **2** confirm the above proposed structures for these complexes. Both structures consist of discrete, essentially square-planar neutral molecules. The results of the crystal structure analyses for **1** and **2** are summarized in Figures 1 and 2, respectively.

In **1**, the palladium atom is coordinated by two *trans* PPh_3 molecules, one chloride anion, and one N(7)-bonded 8-(methylthio)theophyllinato ligand. It should be noted that, in **2**, the chloride anion has been substituted by a C(8)-coordinated theophyllinato anion. Because of the C_s symmetry of **2**, both purine ligands are constrained to lie on the symmetry plane. Within the palladium coordination spheres, bond lengths and angles exhibit normal values; the deviation of the palladium atom from the mean coordination plane being 0.048 and 0.081 Å, for **1** and **2**, respectively. The Pd−N distance in **2** is longer than in **1**, reflecting the greater *trans* influence of imidazolate carbon relative to chloride. The essentially planar purine ligands are twisted away from the coordination plane (85.9 and 83.7°, for **1** and **2**, respectively) in order to minimize steric repulsions with the bulky triphenylphosphine ligands.

Bond distances and angles for the N(7)-bonded 8-(methylthio)theophyllinato ligands in **1** and **2** are similar to those found in other N(7)-bonded purine complexes.[10] When compared with the case of the latter complexes, C(8)-coordination of the theophyllinato ligand in **2** causes significant changes in the imidazole ring bond angles. Thus, the N(7′)−C(8′)−N(9′) bond angle decreases whereas the two adjoining angles, C(5′)−N(7′)−C(8′) and C(4′)−N(9′)−C(8′), undergo a similar overall change in the other direction. The smaller C−N−C angle at the deprotonation site can be ascribed to the greater repulsion experienced by the adjacent N−C bonds from the C(8) lone pair no longer retained along the C(8)−S(8) bond. The N(7′)−C(8′) and C(8′)−N(9′) bond distances of 1.41(3) and 1.30(3) Å, respectively, which are opposite in order to those found in N(7)-bonded 8-(methylthio)theophyllinato complexes, clearly indicate that the double bond is localized between C(8′) and N(9′). This fact confirms that N(7) is protonated even though this H atom could not be found in the structural refinement. Finally, it should be noted that, unfortunately, neither N(7) nor N(9) is involved in hydrogen bonds, which would provide definitive evidence of the imidazole NH location.

The only remaining question regards the reaction pathway leading from **1** to **2**. It should be pointed out that 8-(methylthio)theophylline does not lose the SCH_3 group when a H_2O/Cl_2CH_2 mixture containing 8-(methylthio)theophylline and NaOH is refluxed for 6 h. Then, it seems that, for such elimination, the presence of Pd is needed. In addition, the reaction of theophylline with *cis*-[$PdCl_2(PPh_3)_2$] leads to the N(7)-bonded complex [$Pd(L')_2(PPh_3)_2$]. These results seem to indicate that complex **2** can only be prepared from **1**. It is interesting to note that the reaction of **1** with adenine, in the presence of base, gives rise to **2** instead of the expected mixed purine complex. In view of all this, the process leading from **1** to **2** might be, in a sense, similar to the well-known activation

of the C(8)−H bond in purine nucleosides upon coordination of CH_3Hg^+ to N(7), to give rise to C(8)-bound CH_3Hg^{II} species.[13] Finally, the reaction was monitored by ^{31}P-NMR spectroscopy at 60 °C. The spectrum exhibits two wide and overlapping signals in the range −15 to −25 ppm, which are not significantly shifted with time. These results seem to indicate that **2** is involved in a rapid equilibrium with another species which might be an intermediate in the conversion of **1** to **2**.

In order to gain insight into the reaction mechanism, reactivity studies on Pd^{II}−N(7)-bonded complexes with 8-substituted purine derivatives other than HL are planned for the future.

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Supporting Information Available: Tables of atomic coordinates and isotropic thermal parameters, crystallographic data, anisotropic thermal parameters, and complete bond distances and angles (13 pages). Ordering information is given on any current masthead page.

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(13) Buncel, E.; Norris, A. R.; Racz, W. J.; Taylor, S. E. *J. Chem. Soc., Chem. Commun.* **1979**, 562.