Inorg. Chem. **2007**, *46*, 5448–5449

Inorganic Chemistry Communication

A Novel Metal-Binding Mode of Thymine Nucleobases: N(3) and O(4) Chelation†

José Ruiz,*,‡ María Dolores Villa,‡ Venancio Rodríguez,‡ Natalia Cutillas,‡ Consuelo Vicente,‡ Gregorio López,‡ and Delia Bautista§

Departamento de Química Inorgánica and SUIC, Edificio SACE, Universidad de Murcia, 30071 Murcia, Spain

Received May 2, 2007

The syntheses and crystal structures of the first examples of an anionic 1-methylthymine [deprotonated at the endocyclic NH group N(3)] acting as a chelating ligand for the *cis*-Pd($C_6F_3H_2$)$_2$ and *cis*-Pd(C_6F_5)$_2$ moieties through N(3) and O(4) are reported.

Metal ion−nucleobase interactions are of significance with respect to changes in the nucleic acid structure and the possible biological consequences. Thus, new nucleoside complexes having the metal covalently bonded to the nucleobase can be used in biological experiments as potential anticancer drugs[1] or as metalated nucleoside building blocks that can be incorporated into synthetic oligonucleotides.[2] Selective coordination to nucleobases is influenced by structural and electronic factors arising from the nucleobase and the complex itself.[3−5]

After more than 40 years of research in this area, it is well-known that the transition-metal-binding sites on the thymine consist primarily of the deprotonated nitrogen atom N(3) and the oxygen positions 2 and 4, depending on the coordinating metal (Figure 1).[6−8] To the best of our knowledge, there are no examples of thyminate-chelated metal complexes.[9]

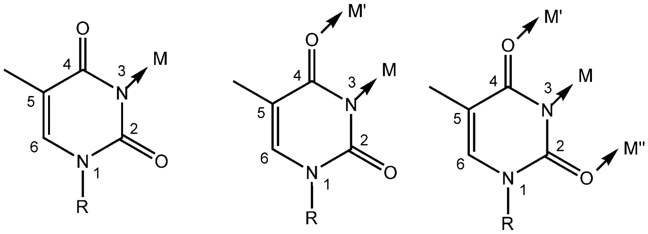
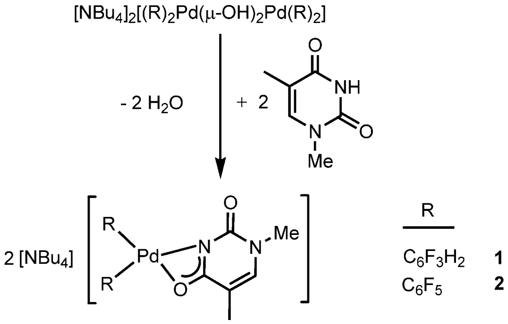


Figure 1. Transition-metal coordination modes to N(1)-substituted thymines.

Scheme 1



In this work, we report the syntheses and crystal structures of the first thyminate-chelated metal complexes, $[NBu_4][Pd(R)_2(\eta^2\text{-1-Methy})]$ [1-Methy = 1-methylthymine; R = $C_6F_3H_2$ (**1**), C_6F_5 (**2**)], in which strained Pd−N−C−O four-membered rings are observed. Both compounds are easily prepared by reaction of the corresponding hydroxopalladium complex $[NBu_4]_2[(R)_2Pd(\mu\text{-OH})_2Pd(R)_2]$[10,11] with 1-Methy (Scheme 1) and with the concomitant release of water.

Complexes **1** and **2** have been characterized on the basis of partial elemental analyses and spectroscopic data (IR and ^1H and $^{19}F\{^1H\}$ NMR; see the Supporting Information for details).

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† Dedicated to Prof. Alfonso Castiñeiras on the occasion of his 65th anniversary.

* To whom correspondence should be addressed. E-mail: jruiz@um.es. Fax: +34 968 364148. Tel: +34 968 367455.

‡ Departamento de Química Inorgánica.

§ SUIC, Edificio SACE.

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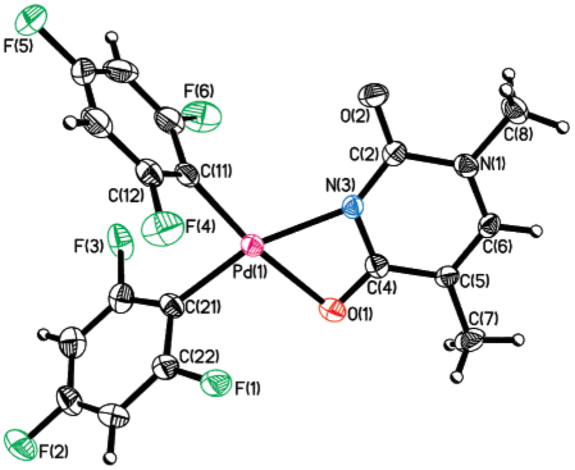

Figure 2. ORTEP representation (50% probability) of **1**. Selected bond lengths (Å) and angles (deg): Pd(1)−C(21) 1.987(5), Pd(1)−C(11) 1.976(6), Pd(1)−N(3) 2.129(4), Pd(1)−O(1) 2.181(4); N(3)−Pd(1)−O(1) 61.71(15), N(3)−Pd(1)−C(11) 109.45(18), C(21)−Pd(1)−O(1) 102.07(18), C(21)−Pd(1)−C(11) 86.7(2).

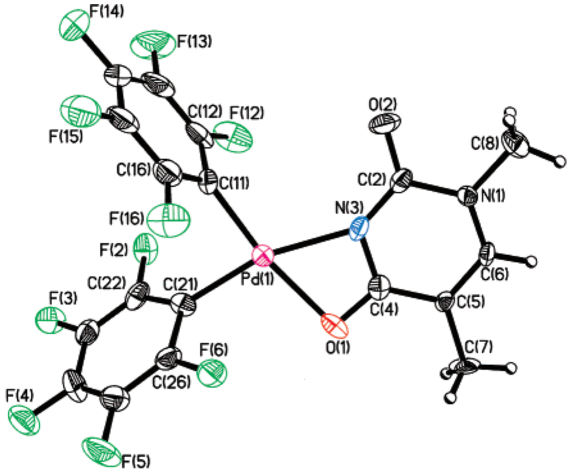

Figure 3. ORTEP representation (50% probability) of **2**. Selected bond lengths (Å) and angles (deg): Pd(1)−C(21) 1.974(10), Pd(1)−C(11) 1.966(10), Pd(1)−N(3) 2.095(8), Pd(1)−O(1) 2.189(8); N(3)−Pd(1)−O(1) 62.1(3), N(3)−Pd(1)−C(11) 109.0(4), C(21)−Pd(1)−O(1) 102.1(4), C(21)−Pd(1)−C(11) 86.8(4).

X-ray-quality crystals of **1** and **2** were obtained by slow diffusion of hexane in a saturated solution of the complexes in toluene/dichloromethane, which were allowed to univocally establish their crystal structures.[12] The crystal structures of complexes **1** and **2** (Figures 2 and 3) show the palladium atom bound to a chelate thyminate and two polyfluoroaryl groups. The geometry of the palladium center is square-planar with a very strong distortion around the palladium atom due to the very small bite of the thyminate ligand [N(1)−Pd(1)−O(1) = 61.71(15)° in **1** and 62.1(3)° in **2**]. These values are smaller than those previously observed in the related platinum-chelated cytosinate complex *trans*,*trans*-[Pt$(NH_3)_2$(1-Mecyt)$_2$]$(NO_3)_2$·$2H_2O$ [1-MecytH = 1-methylcytosine; N−Pt−N = 64°][13] and a bit larger than those found in the palladium triazenide chelated compound [NBu_4][Pd$(C_6F_5)_2$(η^2-PhNNNPh)] [N−Pd−N = 59.5(2)°].[14] In complexes **1** and **2**, the Pd(1)−N(1)−C(21)−O(1) four-membered ring is planar. There is extensive π delocalization over the entire N(1)−C(21)−O(1) ring. The X-ray structure revealed in both complexes a short Pd−N(1) bond distance, suggesting a very strong interaction between the metal and the imidic nitrogen.[2] The different Pd−C bond distances observed [for example, in complex **1**, Pd−C(1) = 1.987(5) Å and Pd−C(11) = 1.976(6) Å] are in agreement with the higher trans influence of the endocyclic nitrogen of the methylthyminate ligand atom compared to the oxygen atom and are in the range found in the literature for fluorophenylpalladium complexes.[15]

Intermolecular interactions contacts C−H···F−C, C−H···O, and C−H···π are observed.[16,17] Thus, for example, in complex **1** there is intermolecular C−H···F hydrogen bonding between the fluorine atoms of the fluorophenyl groups and the hydrogen atoms of NBu_4^+, with the three shortest hydrogen bonds being F(2)···H(72B), F(6)···H(73B), and F(3)···H(71B) (2.439, 2.436, and 2.452 Å, respectively). Also, in complex **1**, short C−H···π contacts between H63A (of NBu_4^+) and one of the $C_6F_3H_2$ rings (C21−C26) have been found (H63A···centroid distance of 2.578 Å).

In conclusion, these complexes represent the first crystallographically confirmed examples of N(3) and O(4) chelation of a metal to a thymine nucleobase. Strong supramolecular interactions are present.

Acknowledgment. This work was supported by the Dirección General de Investigación del Ministerio de Ciencia y Tecnología (Project CTQ2005-09231-C02-01/BQU), Spain, and the Fundación Séneca de la Comunidad Autónoma de la Región de Murcia (Project 00448/PI/04), Spain.

Supporting Information Available: X-ray crystallography data in CIF format for complexes **1** and **2** and experimental procedure and characterization data for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Crystal data of **1**: $C_{34}H_{47}F_6N_3O_2Pd$, orthorhombic, *Pbca*, $a = 10.1862(5)$ Å, $b = 17.8341(9)$ Å, $c = 38.0036(19)$ Å, $V = 6903.8(6)$ Å^3, $Z = 8$, $\mu = 0.604$ mm^{-1}, 76328 reflections collected, 8192 independent reflections ($R_{int} = 0.0630$), R1 [$I > 2\sigma(I)$] = 0.0752, wR2 (all data) = 0.1954. Crystal data of **2**: $C_{34}H_{43}F_{10}N_3O_2Pd$, orthorhombic, *Pbca*, $a = 10.3080(4)$ Å, $b = 18.2252(7)$ Å, $c = 38.2076(14)$ Å, $V = 7177.9(5)$ Å^3, $Z = 8$, $\mu = 0.604$ mm^{-1}, 75145 reflections collected, 7341 independent reflections ($R_{int} = 0.0904$), R1 [$I > 2\sigma(I)$] = 0.1241, wR2 (all data) = 0.3280. Crystal data of **1** and **2** were measured at 100(2) K using a Bruker Smart CCD diffractometer with Mo Kα radiation in ω scan mode. The structure was solved by heavy-atom and direct methods *SHELXS-97* (Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Göttingen, Germany, 1998) and refined anisotropically on F^2. Hydrogen atoms were included using a riding model.

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