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Spectroscopic characterization and molecular modeling of novel palladium(II) complexes with carbazates and hydrazides

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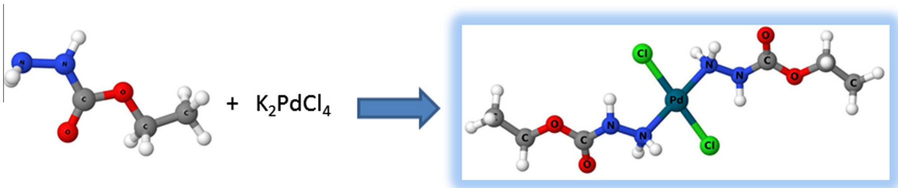
HIGHLIGHTS

- New palladium complexes with carbazates or hydrazides were synthesized and characterized.
- The structures of the palladium(II) complexes were optimized and theoretical data show that the *trans* isomer is more stable.
- The coordination mode was determined by IR, and NMR (^{1}H, ^{13}C, ^{15}N).
- Cytotoxic activity of some these new palladium complexes in a chronic myelogenous leukemia cell line is also reported.

GRAPHICAL ABSTRACT



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ABSTRACT

Palladium(II) complexes of the type *trans*-$[Pd(L)_2Cl_2]$, where L = 4-methoxybenzylcarbazate (4-MC), benzyl carbazate (BC), 4-fluorophenoxyacetic acid hydrazide (4-FH), 3-methoxybenzoic acid hydrazide (3-MH), ethyl carbazate (EC) and *tert*-butyl carbazate (TC) were synthesized by the slow addition of the ligand to K_2PdCl_4 previously dissolved in water or ethanol. These complexes were characterized by elemental analyses, conductivity measurements, TG/DTA, FT-IR, mass spectrometric and NMR spectroscopy (solution and solid-state). All coordination compounds exhibit a square planar coordination geometry in which the palladium(II) ion coordinates to two nitrogen atoms and two chlorine atoms. The structures of the palladium(II) complexes were optimized and theoretical data show that the *trans* isomer is more stable, in accordance with the experimental data. Preliminary *in vitro* tests of some these new palladium complexes in a chronic myelogenous leukemia cell line (k562 cells) are also reported.

Introduction

Palladium(II) complexes have attracted considerable attention in the last years due to their medicinal and catalytic properties. Regarding the use of palladium complexes as drugs, several coordination compounds have been obtained and some exhibit good antitumoral and antibacterial activity [1]. Therefore, the synthesis

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of new palladium(II) complexes with potential pharmacological activity is highly desired. For instance, our research group showed that the palladium(II) complex of tetracycline is 16 times more potent than free tetracycline against *E. coli HB101/pBR322*, a bacterial strain resistant to tetracycline [2].

Hydrazides (R—CO—NH—NH_2) and their derivatives are of interest due to their several biological activities such as antimycobacterial, antifungal, antibacterial, and antitumoral. For example, isonicotinic acid hydrazide (isoniazid) is the first-line drug in prevention and treatment of *Mycobacterium tuberculosis* H37Rv [3]. In addition, the formation of metallic complexes plays an important role in the improvement of their biological activities [4–6]. Indeed, many complexes containing hydrazides exhibit remarkable biological properties [7–16]. Recently, the effect of copper(II) complexes with 2-furoic acid hydrazide or 2-thiophenecarboxylic acid hydrazide on the growth of tumoral cells was studied. These complexes were able to enter cells and inhibit cellular growth in a concentration-dependent manner, with an activity higher than that of the corresponding free ligands [13].

Regarding the use of carbazates (R—O—CO—NH—NH_2) and derivatives as potential biological agents, there are few reports in the literature [17–19]. For instance, Milenković et al [18] reported a cobalt(III) complex with the condensation product of 2-(diphenyl phosphino)benzaldehyde and ethyl carbazate that shows a very high cytotoxic activity, which was approximately twofold higher than cisplatin on cervix (HeLa), and melanoma tumor cell lines (FemX), and almost threefold higher in colorectal tumor cell line (LS-174). In other studies, Pd(II) and Fe(III) complexes containing ligands derived from 2-(diphenylphosphino)benzaldehyde and ethyl carbazate were synthesized and the antimicrobial studies revealed that the activity of the ligand is enhanced upon complexation [19]. These results are in accordance with works previously published for hydrazides [13–16].

Considering the biological activities of the ligands and their complexes, this work describes the syntheses, spectroscopic characterization, DFT studies and cytotoxic activity of new Pd(II) complexes with 4-methoxybenzylcarbazate (4-MC), benzyl carbazate (BC), 4-fluorophenoxyacetic acid hydrazide (4-FH), 3-methoxybenzoic acid hydrazide (3-MH), ethyl carbazate (EC) and *tert*-butyl carbazate (TC).

Experimental

Physical measurements

Carbon, nitrogen, and hydrogen were determined on a Perkin–Elmer 2400 elemental analyzer. Analyses by atomic absorption (% metal) were made in a spectrophotometer Hitachi 8200.

Conductivity studies were carried out with a Tecnopon mCA-150 conductivity meter using a cell of constant 1.03 cm^{-1}, spectroscopic grade dimethyl sulfoxide (Merck) ($\Lambda_M = 0.95$ µs/cm) and tetraethylammonium bromide ($\Lambda_M = 79.01$ µs/cm) as a standard.

Thermogravimetric data (TG/DTA) were obtained on a TGA-50 Shimadzu, using 7.0 mg of samples packed in aluminum crucible. Samples were heated at 10 °C/min from room temperature to 500 °C, in a dynamic nitrogen atmosphere (flow rate of 200 mL min^{-1}).

IR spectra were registered in KBr (4000–400 cm^{-1}) or CsI (400–200 cm^{-1}) pellets on a FTIR spectrometer Bomem-Michelson spectrometer.

Electrospray ionization mass spectrometric (ESI(+)/MS) measurements were carried out in a Waters Micromass Quattro MicroTM API. Samples containing 1 mg the Pd(II) complexes with BC and 4-FH were dissolved in 10 µL of dimethylformamide and dimethylsulfoxide, respectively, and then diluted in methanol to form 1 mg mL^{-1} solutions. Resulting solutions were further diluted 100-fold in methanol and directly infused into the instrument's ESI source at a flow rate of 50 µL min^{-1} with an auxiliary flow of 50:50 water/methanol (0.1% formic acid). Typical acquisition conditions were capillary voltage 3 kV, sampling cone voltage 15 V, source temperature 150 °C, desolvation temperature 200 °C, cone gas flow 50 L h^{-1}, desolvation gas flow 800 L h^{-1}.

The ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer (9.4 T). Samples were evaluated by dissolving the complexes in deuterated dimethylsulfoxide-d_6 solutions. The solution state {^{15}N, ^{1}H} HSQC NMR correlation spectra were acquired on a Bruker 500 MHz spectrometer (11.746 T). Samples of 4-FH and the $[Pd(4FH)_2Cl_2]$ complex were analyzed at 298 K in deuterated dimethylsulfoxide-d_6 solutions, while BC and the $[Pd(BC)_2Cl_2]$ complex were analyzed in deuterated dimethylformamide-d_7 solutions. The chemical shifts were given relative to tetramethylsilane (TMS).

The solid state ^{13}C nuclear magnetic resonance (SS-NMR) ^{13}C spectra of the complexes were recorded on a Bruker 300 MHz Avance II (7.046 T) operating at 75.47 MHz using cross polarization, proton decoupling and magic angle spinning (CP/MAS) at 10 kHz. The solid-state ^{15}N nuclear magnetic resonance spectra were also recorded on a Bruker 300 MHz operating at 30.42 MHz, using the combination of cross-polarization, proton decoupling and magic angle spinning (CP/MAS) at 10 kHz.

Starting materials

All solid reagents were purchased from Sigma–Aldrich. The solvents were purchased from Vetec.

Preparation of the complexes

The complexes were synthesized following the procedures described below:

Complex **I** or $[Pd(4\text{-}MC)_2Cl_2]$

Potassium tetrachloropalladate (0.25 mmol, 0.0816 g) was dissolved by heating in 5 mL ethanol. Thereafter, 5.0 mL of an ethanolic solution of 4-methoxybenzylcarbazate (0.5 mmol) was added dropwise. The mixture was heated at 50 °C for 24 h, when the solid formed was separated by filtration, washed with water, ethanol and dried under reduced pressure. Yield: 87%. Color: Yellow. Molar weight (g mol^{-1}): 569.73. Anal. Calcd. for $[Pd(C_9H_{12}N_2O_3)_2Cl_2]$: C, 37.94; H, 4.25; N, 9.83; Pd, 18.68%; Found: C, 38.07; H, 4.26; N, 9.57; Pd, 18.41%. ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 8.48, 7.31, 6.92, 6.47, 5.01, 3.41. IR spectra in KBr, ν (cm^{-1}): 3239, 3205, 3119, 3004, 2836, 1704, 1619, 1508, 1471, 1453, 1387, 1327, 1287, 1264, 1246, 1236, 1174, 1131, 1032, 943, 921, 843, 813, 751, 611, 557, 443. $\Lambda_M = 2.01$ µs/cm.

Complex **II** or $[Pd(BC)_2Cl_2]$

To a solution of K_2PdCl_4 0.0816 g (0.25 mmol) in water (5 mL), 5.0 mL of an ethanolic solution of benzyl carbazate (0.5 mmol) was added dropwise. The mixture was stirred for 24 h and the solid formed was separated by filtration, washed with water and ethanol, and dried under reduced pressure. Yield: 89%. Color: Yellow. Molar weight (g mol^{-1}): 509.68. Anal. Calcd. for $[Pd(C_8H_{10}N_2O_2)_2Cl_2]$: C, 37.70; H, 3.96; N, 10.90; Pd, 20.88%; Found: C, 37.54; H, 3.92; N, 10.78; Pd, 20.71%. ^{1}H NMR (400 MHz; DMSO-d_6) δ (ppm): 9.08, 7.36, 6.51, 5.09. IR spectra in KBr, ν (cm^{-1}): 3264, 3175, 3148, 3082, 2954, 2896, 1720, 1550, 1499, 1465, 1455, 1381, 1330, 1295, 1254, 1143, 1023, 962, 851, 783, 766, 743, 697, 644, 621, 468. $\Lambda_M = 1.5$ µs/cm.