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Synthesis, characterization, crystal structure and DNA binding studies of Pd(II) complexes containing thiosemicarbazone and triphenylphosphine/triphenylarsine

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ABSTRACT

2-Oxo-1,2-dihydro-benzo[h]quinoline-3-carbaldehyde *N*-ethylthiosemicarbazone (H_2L) and its palladium(II) metal complexes containing triphenylphosphine/triphenylarsine were synthesized and characterized. The structures of two new complexes [Pd(L)(PPh_3)] (**1**) and [Pd(L)($AsPh_3$)] (**2**) were determined by single crystal X-ray diffraction. The Pd atom in both complexes is coordinated by the planar ligand and the P/As atom in square planar fashion, thus rendering the L-metal part of the molecules flat and suited for intercalation into DNA. The binding mode of the two new complexes to Calf thymus DNA was investigated by absorption spectroscopy, through the ethidium bromide (EB) displacement technique and viscosity measurements. These results indicate that the complexes bind to DNA via intercalation. Complex **2** shows stronger binding than that of complex **1** due to the deeper intercalation of the chromophore into the DNA because of the longer Pd–As versus the Pd–P distances in **2** and **1**.

1. Introduction

The anti-cancer activity of platinum-containing drugs such as cis-platin, carboplatin and oxaliplatin are based on *in-vivo* interaction of the metal complexes with the DNA of a cancerous cell, which ultimately leads to programmed cell death. In the development of new such metal-based therapeutics, detailed studies on the interactions between DNA and the transition-metal complexes is needed [1]. Depending on the exact nature of the metal and the ligand the complexes can bind with nucleic acid covalently as well as noncovalently [2,3]. Noncovalent interactions between transition-metal complexes and DNA can occur by intercalation, groove binding, or external electrostatic binding. Therefore, the study on the interaction of the transition metal complexes with DNA is of great significance for the design of new drugs and their application.

For a metal complex to be considered a potential DNA intercalating drug, its active form has to be flat, i.e., the ligands have to be planar and the metal should be in a square planar coordination environment. These criteria can be met by platinum–thiosemicarbazone complexes, and a number of such complexes have previously been investigated for their potential anti-cancer activities. In addition, thiosemicarbazones have also aroused considerable interest because of antibacterial [3–5], antioxidative [6,7], antineoplastic [8] and antiviral activities [9] that some of them exhibit. In many cases coordination to a metal induces an increase of the activity when compared to the thiosemicarbazone alone. In an earlier investigation several palladium complexes containing auxiliary triphenylphosphine ligands had shown promising results as antimalarial and anti-cancer agents [10,11].

The quinoline ring system is an important structural unit ubiquitously found in alkaloids, alkaloid based therapeutics and synthetic analogs with interesting biological activities [12,13]. Thiosemicarbazone complexes that also feature quinoline ring systems have also been synthesized and some of them exhibit sought after biological activities such as, e.g., plasmid cleaving properties or radical scavenging properties [14,15]. However, the studies on the antioxidant activities and DNA-binding interaction of thiosemicarbazone transition metal complexes prepared from 2-oxo-benzoquinoline-3-carbaldehyde have not yet been reported. With the above encouraging background in mind, we synthesized two palladium(II) complexes containing this thiosemicarbazone and carried out their interaction with Calf-thymus-DNA. In this paper, we describe the synthesis, characterization, crystal structures and DNA binding studies of Pd(II) complexes containing 2-oxo-1,2-dihydro-benzo[h]quinoline-3-carbaldehyde *N*-ethylthiosemicarbazone [H_2L] and triphenylphosphine/triphenylarsine. The synthetic route of the complexes is given in Scheme 1.

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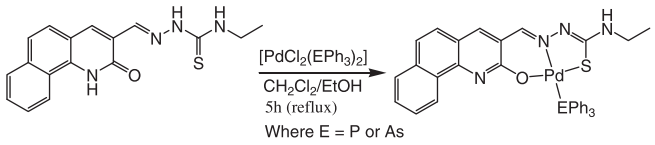

Scheme 1. Preparation of the palladium(II) complexes.

2. Experimental

2.1. Materials and methods

All the reagents used were of analytical or chemically pure grade. Solvents were purified and dried according to standard procedures [16]. The ligand and the starting complexes $[PdCl_2(PPh_3)_2]$ and $[PdCl_2(AsPh_3)_2]$ were prepared by literature methods [17,18]. Infrared spectra of the ligand and the metal complexes were recorded in the range of 4000–400 cm^{-1} using a Nicolet Avatar model FT-IR spectrophotometer from KBr discs. The electronic spectra of the complexes were recorded with a Jasco V-630 spectrophotometer using DMSO as the solvent. Emission spectra were measured using a Jasco FP6600 spectrofluorometer. ^1H NMR spectra were recorded on a Bruker AMX 500 at 500 MHz NMR spectrometer using TMS as an internal reference. The melting points were recorded with a Lab India Melting point apparatus.

2.2. Preparation of the ligands

2.2.1. 2-Oxo-1,2-dihydro-benzo[h]quinoline-3-carbaldehyde N-ethylthiosemicarbazone (H_2L)

A methanolic solution of ethylthiosemicarbazide (1.116 g, 0.005 mol) was added to a methanol solution (50 ml) containing 2-oxo-1,2-dihydro-benzo[h]quinoline-3-carbaldehyde (0.596 g, 0.005 mol). The mixture was refluxed for 2 h during which period an yellow precipitate separated out. The reaction mixture was then cooled to room temperature and the precipitate was filtered off. It was then washed with methanol and dried under vacuum. Yield: 82%. MP: 259–260 °C, *Anal.* calc. for $C_{17}H_{16}N_4OS$: C, 62.94; H, 4.97; N, 17.27; S, 9.89. Found: C, 62.85; H, 4.87; N, 17.21; S, 9.78%. IR (KBr, cm^{-1}): 3322(ms) ν(NH); 1647(s) ν(C=O); 1532(s) ν(C=N) + ν(C=C); 840(m) ν(C=S). UV–Vis (DMSO), λ_{max} (nm): 295, 359 ($\pi \rightarrow \pi^*$, $n \rightarrow \pi^{*)}$. ^1H NMR (DMSO-D_6); δ 12.43 (s, N(1)H); δ 11.67 (s, N(3)H); δ 8.91 (d, 1H, C(3)H); δ 8.81(s, 1H, C(14)H); 8.35 (s, 1H, N(4)H); 7.65–8.01 (m, 6H, aromatic); 3.34 (q, 2H, C(16)H); 1.21 (t, 3H, C(17)H).

2.2.2. Synthesis of [Pd(L)(PPh$_3$)] (**1**)

A dichloromethane solution (20 cm^3) of H_2L (0.046 g; 0.143 mmol) was mixed with an ethanolic (20 cm^3) solution of $[PdCl_2(PPh_3)_2]$ (0.100 g; 0.143 mmol) and the mixture was heated under reflux for 5 h. Upon slow evaporation, orange Pd(II) complex crystallized out. The crystals were filtered off, washed with petroleum ether (bp 60–80 °C), cold ethanol and dried in *vacuo*. The crystals obtained were found to be suitable for X-ray diffraction. Yield: 78%, MP: 281–282 °C. *Anal.* calc. for $C_{35}H_{29}N_4OPPdS$: C, 60.83; H, 4.23; N, 8.15; S, 4.64. Found: C, 60.78; H, 4.16; N, 8.09; S, 4.58%. IR (KBr disks, cm^{-1}): 3240(ms) ν(NH); 1341 (s) ν(C—O); 1550(s) ν(C=N) + ν(C=C); 751(m) ν(C—S); 1438, 1096, 702 (for PPh_3), λ_{max} (nm): 267, 318 (intra-ligand transition); 351, 423 (LMCT s/d); 449 (MLCT). ^1H NMR (DMSO-D_6); δ 8.71(s, 1H, C(14)H); δ 8.92 (d, 1H, C(3)H); 8.51 (s, 1H, N(4)H); 7.53–7.89 (m, 21H, aromatic); 3.07 (q, 2H, C(16)H); 1.21 (t, 3H, C(17)H).

2.2.3. Synthesis of [Pd(L)(AsPh$_3$)] (**2**)

It was prepared as described for **1** by the reaction of $[PdCl_2(AsPh_3)_2]$ (0.100 g; 0.127 mmol) with ligand (0.041 g; 0.127 mmol) and dark orange colored crystals obtained were found to be suitable for X-ray diffraction. Yield: 74%, MP: 277–278 °C, *Anal.* calc. for $C_{35}H_{29}AsN_4OPdS$: C, 57.20; H, 3.98; N, 7.62; S, 4.36. Found: C, 57.12; H, 3.91; N, 7.55; S, 4.27%. IR (KBr disks, cm^{-1}): 3316(ms) ν(NH); 1335 (s) ν(C—O); 1591(s) ν(C=N) + ν(C=C); 742(m) ν(C—S). λ_{max} (nm): 267, 315 (intra-ligand transition); 358, 425 (LMCT s/d); 448 (MLCT). ^1H NMR (DMSO-D6); δ 8.87(s, 1H, C(14)H); δ 8.94(d, 1H, C(3)H) 8.68 (s, 1H, N(4)H); 7.52–7.78 (m, 21H, aromatic); 3.05 (q, 2H, C(16)H); 1.24 (t, 3H, C(17)H).

2.3. Single crystal X-ray diffraction studies

X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 100(2) K using monochromatic MoKα radiation with the omega scan technique. Data for complexes **1** and **2** were collected, their unit cells determined, and the data integrated and corrected for absorption and other systematic errors using the APEX2 suite of programs [19] and the structures were solved and refined using SHELXTL 6.14 [20]. The structure of complex **1** was solved by direct methods. Complex **2** was found to be isostructural to complex **1** was solved by isomorphous replacement of phosphorous by arsenic. Both structures were refined by full matrix least squares against F^2. Refinement of an extinction coefficient was found to be insignificant. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions riding on their respective carrier atom with U_{iso}(-H) = 1.2 U_{eq}(C) (1.5 for the methyl hydrogen atoms). Reflections obstructed by the beam stop (0 0 1, 0 1 1 and 0 1 0 for complex **1**, 0 0 1 for complex **2**) and were omitted from the refinement. Crystal data and structure refinement for complexes **1** and **2** are listed in Table 1. ORTEP plots of the complexes are shown in Fig. 1 for complex **1** and in S1 for complex **2**.

2.4. DNA binding experiments

The UV–Vis absorption spectroscopy studies and the DNA binding experiments were performed at room temperature. The purity of the CT-DNA was verified by taking the ratio of the absorbance values at 260 and 280 nm in the respective buffer, which was found to be 1.8:1, indicating that the DNA was sufficiently free of protein. The DNA concentration per nucleotide was determined by absorption spectroscopy using the molar extinction coefficient value of 6600 $dm^3\ mol^{-1}\ cm^{-1}$ at 260 nm. The complexes were dissolved in a mixed solvent of 5% DMSO and 95% phosphate buffered saline for all the experiments. Absorption titration experiments were performed with a fixed concentration of the compounds (25 μM) while gradually increasing the concentration of DNA (5–50 μM). While measuring the absorption spectra, an equal amount of DNA was added to both the test solution and the reference solution to eliminate the absorbance of DNA itself.

Further support for the complexes binding to DNA via intercalation is given through emission quenching experiments. DNA was pretreated with ethidium bromide for 30 min. Then the test solutions were added to this mixture of EB-DNA, and the change in the fluorescence intensity was measured. The excitation and the emission wavelength were 515 and 603–607 nm, respectively.

2.5. Viscosity measurements

Viscosity experiments were carried out using a Schott Gerate AVS 310 automated viscometer that was thermo stated at 25 °C in a constant temperature bath. The lengthening of the DNA helix has been examined in the absence and presence of increasing