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Synthesis, spectral, X-ray crystallography, electrochemistry, DNA/protein binding and radical scavenging activity of new palladium(II) complexes containing triphenylarsine

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ABSTRACT

The reactions of $[PdCl_2(AsPh_3)_2]$ with equimolar amount of salicylaldehyde-4(N)-phenylthiosemicarbazone [H_2-(Sal-ptsc)] (H_2L^1) and 2-hydroxy-1-naphthaldehyde-4(N)-methylthiosemicarbazone [H_2-(Nap-mtsc)] (H_2L^2) were carried out in ethanol/dichloromethane medium. The obtained products (**1** and **2**) were characterized by variours spectral and analytical techniques. From the X-ray crystallographic studies, it is inferred that both the ligands coordinate as ONS tridentate dibasic donor by forming more common five and six member chelate rings. The complex **1** crystallizes in the triclinic space group $P\bar{1}$ with two molecules per unit cell, has the dimensions of $a = 10.1680(12)$ Å, $b = 10.5535(12)$ Å, $c = 13.3852(15)$ Å, $\alpha = 78.9980(10)°$, $\beta = 82.7610(10)°$ and $\gamma = 86.2490(10)°$. The complex **2** crystallizes in the monoclinic space group $P2(1)/n$ with four molecules per unit cell, has the dimensions of $a = 14.0981(3)$ Å, $b = 11.2881(2)$ Å, $c = 18.2678(3)$ Å, $\alpha = 90°$, $\beta = 111.00(10)°$ and $\gamma = 90°$. The complexes **1** and **2** have been tested for their binding towards Herring Sperm (HS)-DNA and BSA (bovine serum albumin). The new complexes bound to DNA by electrostatic binding mode and they had a strong binding affinity with BSA. The mechanism of quenching was found as static. In addition, the free radical bleaching ability of complexes with DPPH (1,1-diphenyl-2-picryl-hydrazyl) radical was carried out.

1. Introduction

The chemistry of thiosemicarbazones has gained importance because of their simple preparation, unpredictable complexation properties and their pharmacological applications [1]. The coordinating ability of thiosemicarbazones is attributed to the extended delocalization of electron density over the –NH–C(S)–NH–N = system, which is enhanced by substitution on the terminal nitrogen [1b,2–6]. Variation in the substitution on the azomethine (C2) carbon of the thiosemicarbazone ligands influences the mode of their binding. On introduction of nitrogen and/or oxygen containing substituents on azomethine carbon, it is anticipated that the binding ability of thiosemicarbazone becomes more capricious. The study of the interaction of transition metal complexes with DNA is a vibrant area of research [7]. The ability to selectively target and cleave DNA with high affinity and to report on the binding event by changes in luminescence is of great current interest [8]. An advantage of using transition metal complexes in such studies can be conveniently varied to suit individual applications. This may be due to their ability to inhibit the biosynthesis of DNA, possibly by binding with nitrogen base pair of DNA or RNA, which may hinder or block base replication [9]. In addition, palladium(II) thiosemicarbazones possess interesting antiproliferative effects on human cancer cell lines, including tumor cell lines resistant to cisplatin [10–13] and have also exhibited good antimycobacterial effects [14]. In continuation with our investigation [15–25] herein we report the reactions of salicylaldehyde-4(N)-phenylthiosemicarbazone (H_2L^1) and 2-hydroxy-1-naphthaldehyde-4(N)-methylthiosemicarbazone [(H_2L^2) with palladium(II) complexes containing triphenylarsine and their DNA and protein interactions.

2. Experimental section

2.1. Materials and methods

The ligands [H_2-(Sal-ptsc)] (H_2L^1), [H_2-(Nap-mtsc)] (H_2L^2) and palladium metallic precursor $[PdCl_2(AsPh_3)_2]$ were synthesized according to the standard literature procedures [26,27]. All the reagents used in this study were analar grade and the solvents were purified and dried according to the standard procedure [28]. HS-DNA, ethidium bromide (EB) and BSA were obtained from Sigma Aldrich and used as received. Infrared spectra were measured as

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KBr pellets on a Nicolet Avatar Model FT-IR spectrophotometer in the 400–4000 cm^{-1} range. Elemental analyses of carbon, hydrogen, nitrogen, and sulfur were determined using Vario EL III CHNS at the Department ofChemistry, Bharathiar University, Coimbatore, India. The electronic spectra of the complexes have been recorded in dichloromethane using a Systronics 119 Spectrophotometer in the 800–200 nm range. ^1H and ^{13}C NMR spectra were taken in DMSO at room temperature with a Bruker 400 MHz instrument with chemical shift relative to tetramethylsilane. Cyclic voltammograms were recorded on a CH instrument by using platinum wire working electrode and platinum disc counter electrode. All the potentials were referenced to the standard Ag/AgCl electrode and ferrocene was used as external standard. Melting points were recorded by using Lab India melting point apparatus.

2.2. Synthesis of the ligands

2.2.1. Synthesis of salicylaldehyde-4(N)-phenylthiosemicarbazone, [H_2-(Sal-ptsc)](H_2L^1) [26]

A 4.2 g (0.025 mol) of 4(N)-phenylthiosemicarbazide was dissolved in 20 cm^3 of hot ethanol and to this was added 2.7 g of (0.025 mol) salicylaldehyde in 10 cm^3 of ethanol over a period of 10 min with continuous stirring. The reaction mixture was further refluxed for 5 h and allowed to cool whereby a shining yellow compound began to separate which was filtered and washed thoroughly with ethanol and then dried *in vacuum*. The compound was recrystallized from hot ethanol. The product dissolves in common organic solvents such as acetone, methanol, ethanol, dichloromethane, chloroform, DMF and DMSO. Yield: 80%. M.p. 191 °C. *Anal.* Calc. for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49; S, 11.82. Found: C, 61.91; H, 4.79; N, 15.42; S, 11.78%. FT-IR (cm^{-1}) in KBr: 3419 (ν_{OH}), 1620 ($\nu_{C=N}$), 1270(ν_{C-O}), 815 ($\nu_{C=S}$); ^1H NMR (DMSO-d6, ppm): 11.40 (s, 1H, OH), 10.01 (s, 1H, NHCS), 9.59 (s, 1H, NHPh), 8.33 (s, 1H, CH=N), 6.79–7.58 (m, aromatic); ^{13}C NMR (DMSO-d6, ppm): 186.4 (C=S), 162.28 (C=N), 152.1 (C-2, aromatic), 132.08 (C-4, aromatic), 128.92 (C-11, C-13, aromatic), 123.7 (C-10, C-14, aromatic), 117.4 (C-5, aromatic), 112.0 (C-3, aromatic).

2.2.2. Synthesis of 2-hydroxy-1-naphthaldehyde-4(N)-methylthiosemicarbazone, [H_2-(Nap-mtsc)](H_2L^2) [26]

The method above described was followed for the preparation. The ligand [H_2-(Nap-mtsc)] was prepared from 4(N)-methylthiosemicarbazide (2.63 g, 0.025 mol) and 2-hydroxy-1-naphthaldehyde (4.30 g, 0.025 mol). A cream white compound began to separate out. Yield: 78%. M.p. 220 °C. *Anal.* Calc. for $C_{13}H_{13}N_3OS$: C, 60.21; H, 5.05; N, 16.20; S, 12.36. Found: C, 60.17; H, 4.99; N, 16.14; S, 12.31%. FT-IR (cm^{-1}) in KBr: 3423 (ν_{OH}), 1640 ($\nu_{C=N}$), 1250 (ν_{C-O}), 795 ($\nu_{C=S}$); ^{1}HNMR (DMSO-d6, ppm): 11.25 (s, 1H, OH), 10.65 (s, 1H, NHCS), 9.10 (s, 1H, $NHCH_3$), 8.02 (s, 1H, CH=N), 7.07–7.71 (m, 3H, aromatic), 2.50 (d (J = 2.4), 3H, CH_3); ^{13}C NMR (DMSO-d6, ppm): 181.4 (C=S), 157.24 (C=N), 135.12 (C-4, aromatic), 129.15 (C-6, aromatic), 126.4 (C-8, C-9, aromatic), 122.82 (C-1, aromatic), 118.19 (C-3, aromatic), 28.6 (CH_3).

2.3. Synthesis of [Pd(Sal-ptsc)($AsPh_3$)] (**1**)

An ethanolic (25 cm^3) solution of [$PdCl_2(AsPh_3)_2$] (0.200 g; 0.253 mmol) was slowly added to salicylaldehyde-4(N)-phenylthiosemicarbazone (H_2L^1) (0.068 g; 0.253 mmol) in dichloromethane (25 cm^3). The mixture was allowed to stand for 4 days at room temperature. Orange red crystals obtained were filtered, washed with n-hexane and dried. Yield: 52%. M.p. 218 °C. *Anal.* Calc. for $C_{32}H_{26}N_3OSPdAs$: C, 56.36; H, 3.84; N, 6.16; S, 4.70. Found: C, 56.30, H, 3.80; N, 6.13; S, 4.62 . FT-IR (cm^{-1}) in KBr: 1583 ($\nu_{C=N}$), 1342(ν_{C-O}), 743 (ν_{C-S}), 1440, 1070, 691 cm^{-1} (for $AsPh_3$) ; UV–Vis (CH_2Cl_2), λ_{max}: 240, 272 nm (intra-ligand transition); 320, 380 nm (LMCT s → d); 440 nm (MLCT); ^1H NMR (DMSO-d6, ppm): δ 8.6 (s, 1H, CH=N), 9.6 (s, terminal –NH), 6.7–7.8 (m, aromatic); ^{13}C NMR (DMSO-d6, ppm): 166.4 (C–S), 162.24 (C=N), 153.6 (C-2 Aromatic), 152.1 (aromatic $AsPh_3$), 132.08 (aromatic $AsPh_3$), 129.15 (aromatic, $AsPh_3$), 127.6 (C-11, C-13, aromatic), 126.6 (C-6,aromatic), 121.7 (C-5, aromatic), 115.1 (C-10, C-14 aromatic), 112.0 (C-1, aromatic).

The very similar method was followed to synthesize the following complex.

2.4. Synthesis of [Pd(Nap-mtsc)($AsPh_3$)] (**2**)

It was prepared by the procedure as has been used for (**1**) with naphthaldehyde-4(N)-methylthiosemicarbazone [H_2-(Nap-mtsc)] (0.066 g; 0.253 mmol). Evaporation of the solvent mixture gave an orange solid which was dissolved in dichloromethane and subjected to column chromatography. A yellowish orange band was isolated with benzene and on evaporation yielded orange compound. It was recrystallised from hot dimethylformamide which afforded reddish orange crystals. Yield: 68%. M.p. 260 °C. *Anal.* Calc. for $C_{31}H_{26}N_3OSPdAs$: C, 55.58; H, 3.91; N, 6.27; S, 4.79. Found:C, 55.49; H, 3.87; N, 6.18; S, 4.20%. FT-IR (cm^{-1}) in KBr: 1616 ($\nu_{C=N}$), 1259(ν_{C-O}), 738 (ν_{C-S}), 1428, 1074, 688 cm^{-1} (for $AsPh_3$) ; UV–Vis (CH_2Cl_2), λ_{max}: 254, 270 nm (intra-ligand transition); 318, 380 nm (LMCT s → d); 430 nm (MLCT); ^1H NMR (DMSO-d6, ppm): δ 8.07 (d (J = 11.2), CH=N), 9.29 (s, terminal –NH), 2.84 (d (J = 3.6), –CH_3), 6.80–7.99 (m, aromatic); ^{13}C NMR (DMSO-d6, ppm): 163.4 (C–S), 158.24 (C=N), 155.6 (aromaticAsPh_3), 151.4 (aromatic $AsPh_3$), 130.12 (aromatic $AsPh_3$), 129.15 (C-5, aromatic), 126.6 (C-8, C-9, aromatic), 123.7 (C-7, aromatic), 118.02 (C-1, aromatic), 28.8 (CH_3).

2.5. Single crystal X-ray crystallography

Single crystals of [$PdCl_2(AsPh_3)_2$], [Pd(Sal-ptsc)($AsPh_3$)] (**1**) and [Pd(Nap-mtsc)($AsPh_3$)] (**2**) were obtained from C_6H_6/CH_3CN, C_2H_5OH/CH_2Cl_2 mixture and DMF respectively. Single crystal data collections and corrections were done at 173 K with Bruker SMART 1000 CCD using graphite mono chromated Mo Kα (λ = 0.71073 Å) radiation. The structural solution were done by using SHELXS-97 [29] and refined by full matrix least square on F^2 using SHELXL-97 [30].

2.6. DNA binding study

HS-DNA solutions of various concentrations (0.05-0.5 μM) dissolved in a tris HCl buffer (pH 7) were added to the palladium complexes **1** and **2** (1 μM dissolved in DMSO/H_2O mixture). Absorption spectra were recorded after equilibrium at 20 °C for 10 min. The intrinsic binding constant K_b was determined by using Stern Volmer Eq. (1) [31,32].

$$[DNA]/[\varepsilon_a - \varepsilon_f]) = [DNA]/[\varepsilon_b - \varepsilon_f] + 1/K_b[\varepsilon_b - \varepsilon_f] \quad (1)$$

The absorption coefficients ε_a, ε_f, and ε_b correspond to A_{obsd}/[DNA], the extinction coefficient for the free complex and the extinction coefficient for the complex in the fully bound form, respectively. The slope and the intercept of the linear fit of the plot of [DNA]/[$\varepsilon_a - \varepsilon_f$] versus [DNA] give 1/[$\varepsilon_a - \varepsilon_f$] and 1/$K_b$[$\varepsilon_b - \varepsilon_f$], respectively. The intrinsic binding constant K_b can beobtained from the ratio of the slope to the intercept (Table. 4) [31]. Emission measurements were carried out by using a JASCO FP-6600 spectrofluorometer. Tris–buffer was used as a blank to make preliminary adjustments. The excitation wavelength was fixed and the emission range was adjusted before measurements. All measurements were made at 20 °C. For emission spectral titrations, complex concentration was maintained constant as 1 μM and the concentration of HS-DNA was varied from 0.05 to 0.5 μM. The emission