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Benzaldehyde thiosemicarbazone complexes of platinum: Syntheses, structures and cytotoxic properties

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ABSTRACT

The reaction of 4-R-benzaldehyde thiosemicarbazones (denoted in general as H_2L-R, where H_2 stands for the two dissociable protons and R (R = OCH_3, CH_3, H, Cl and NO_2) for the substituent on the phenyl ring) with $[Pt(PPh_3)_2Cl_2]$ in the presence of NEt_3 afforded a family of organometallic complexes of platinum(II) of the type $[Pt(PPh_3)(L\text{-}R)]$. Reaction of the same group of ligands with $K_2[PtCl_4]$ in the presence of NEt_3 afforded complexes of the type $[Pt(HL\text{-}R)_2]$. The crystal structure of $[Pt(PPh_3)(L\text{-}CH_3)]$ and $[Pt(HL\text{-}CH_3)_2]$ have been determined. In the $[Pt(PPh_3)(L\text{-}R)]$ complexes, the benzaldehyde thiosemicarbazones are coordinated to platinum as dianionic tridentate C,N,S-donors. In the $[Pt(HL\text{-}R)_2]$ complexes, the benzaldehyde thiosemicarbazones are coordinated to the metal center as bidentate N,S-donors, forming five-membered chelate rings, and with reference to the structure of the uncoordinated thiosemicarbazone ligand, this coordination mode is associated with a change in stereochemistry around the C=N bond. All the $[Pt(PPh_3)(L\text{-}R)]$ and $[Pt(HL\text{-}R)_2]$ complexes display intense absorptions in the visible and ultraviolet regions. The cytotoxic effects of these complexes, examined on the human leukemia cell line HL-60 and human lymphoma cell line U-937, have shown that all the $[Pt(PPh_3)(L\text{-}R)]$ and $[Pt(HL\text{-}R)_2]$ complexes are cytotoxic in nature and their IC_{50} values indicate their potential use as antitumor agents.

1. Introduction

The chemistry of thiosemicarbazone complexes of transition metal ions has been receiving significant current attention, primarily because of the bioinorganic relevance of these complexes [1–23]. A large majority of thiosemicarbazone complexes have found wide medicinal applications owing to their potentially beneficial biological (*viz.* antibacterial, antimalarial, antiviral and antitumor) activities [24–41]. Systematic studies on the binding of thiosemicarbazones of selected types to different transition metal ions are of considerable importance in this respect. However, we have been exploring the chemistry of platinum metal complexes of thiosemicarbazones [42–57], mainly because of the variable binding mode displayed by these ligands in their complexes and also to gain chemical control over the mode of binding, and the present work has emerged out of this exploration. For the present study, a group of 4-R-benzaldehyde thiosemicarbazones (**I**) have been chosen, which, in the solid state, are known to have the stereochemistry shown in **I**. Our earlier studies have shown that these selected ligands usually display three modes of binding, *viz.* a N,S-mode of binding forming a four-membered chelate ring (**II**) [56,57], a N,S-mode of binding forming a five-membered chelate ring (**III**), and a C,N,S-mode of binding (**IV**). Among these three modes of binding, mode **III** is associated with a stereochemical change across the C=N bond. The primary objective of the present study has been to induce, if possible, the C,N,S-mode of coordination (**IV**) of the 4-R-benzaldehyde thiosemicarbazones to platinum. The selected thiosemicarbazone ligands (**I**) are abbreviated in general as H_2L-R, where H_2 stands for the two protons, *viz.* the hydrazinic proton and one *ortho* proton of the phenyl ring, which need to be dissociated to induce the C,N,S-mode of binding (**IV**), and R for the substituent in the phenyl ring. It may be relevant to mention here that though the chemistry of platinum complexes of several thiosemicarbazones has received considerable attention [50,58–83], the binding of platinum to the chosen ligands (**I**) has remained unexplored. Two different platinum compounds, *viz.* $[Pt(PPh_3)_2Cl_2]$ and $K_2[PtCl_4]$, have been utilized in this study as the source of platinum. Interactions of the chosen thiosemicarbazones (**I**) with these two platinum compounds have afforded two sets of interesting complexes, including a group of organoplatinum complexes. The

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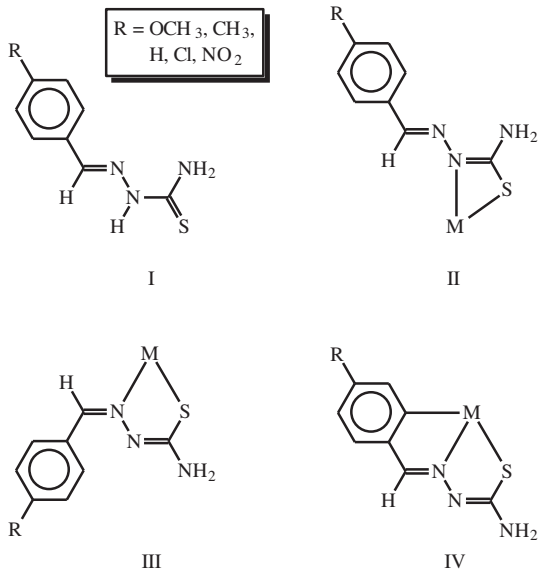
chemistry of all these complexes is described in this paper, with special reference to their formation, structure and cytotoxic properties.



2. Experimental

2.1. Materials

Choloroplatinic acid was obtained from Arora Matthey, Kolkata, India. Potassium chloride and triphenylphosphine were purchased from Loba, India, and Hydrazinium sulfate was purchased from Merck, India. The $[Pt(PPh_3)_2Cl_2]$ and $K_2[PtCl_4]$ complexes were prepared by following reported procedures [84,85]. The thiosemicarbazide and *para*-substituted benzaldehydes were purchased from Merck, India. The 4-R-benzaldehyde thiosemicarbazones (H_2L-R) were prepared by reacting equimolar amounts of the thiosemicarbazide and the respective *para*-substituted benzaldehyde in a 1:1 ethanol-water mixture. All other chemicals and solvents were reagent grade commercial materials and were used as received.

2.2. Preparation of the complexes

2.2.1. $[Pt(PPh_3)(L\text{-}R)]$ complexes

The $[Pt(PPh_3)(L\text{-}R)]$ (R = OCH_3, CH_3, H, Cl and NO_2) complexes were prepared by following a general procedure. Specific details are given below for a particular complex.

2.2.1.1. $[Pt(PPh_3)(L\text{-}OCH_3)]$. 4-Methoxybenzaldehyde thiosemicarbazone (27 mg, 0.13 mmol) was dissolved in ethanol (40 mL) and to this solution was added triethylamine (13 mg, 0.13 mmol) followed by $[Pt(PPh_3)_2Cl_2]$ (100 mg, 0.13 mmol). The mixture was then heated to reflux for 6 h to yield a reddish-orange solution. Evaporation of this solution gave a reddish-orange solid, which was subjected to purification by thin layer chromatography on a silica plate. With benzene–acetonitrile (10:1) as the eluant (*CAUTION!* Benzene is carcinogenic.) an orange band separated, which was extracted with acetonitrile and evaporation of this extract gave $[Pt(PPh_3)(L\text{-}OCH_3)]$ as an orange crystalline solid. Yield: 55%. *Anal.* Calc. for $C_{27}H_{24}N_3OPSPt$: C, 48.79; H, 3.61; N, 6.33. Found: C, 48.71; H, 3.62; N, 6.34%. ^1H NMR (300 MHz; $CDCl_3$) δ (ppm) (*J* (Hz)): 3.08 (OCH_3); 4.98 (NH_2); 5.91 (s, 1H), 6.33 (d, 1H, *J* = 9.9), 7.00 (d, 1H, *J* = 8.2), 7.41–7.78 (azomethine + PPh_3). IR (cm^{-1}): 1622, 1598, 1579, 1553, 1501, 1462, 1453, 1431, 1217, 1181, 1133, 752, 695, 515.

2.2.1.2. $[Pt(PPh_3)(L\text{-}CH_3)]$. Yield: 59%. *Anal.* Calc. for $C_{27}H_{24}N_3PSPt$: C, 50.00; H, 3.70; N, 6.48. Found: C, 50.04; H, 3.71; N, 6.47%. ^1H NMR (300 MHz; $CDCl_3$) δ (ppm) (*J* (Hz)): 1.75 (CH_3); 5.00 (NH_2); 6.07 (s, 1H), 6.62 (d, 1H, *J* = 7.5), 6.94 (d, 1H, *J* = 7.5), 7.36–7.79 (azomethine + PPh_3). IR (cm^{-1}): 1624, 1597, 1577, 1551, 1500, 1462, 1450, 1433, 1215, 1180, 1130, 752, 694, 515.

2.2.1.3. $[Pt(PPh_3)(L\text{-}H)]$. Yield: 63%. *Anal.* Calc. for $C_{26}H_{22}N_3PSPt$: C, 49.21; H, 3.47; N, 6.62. Found: C, 49.17; H, 3.46; N, 6.63%. ^1H NMR (300 MHz; $CDCl_3$) δ (ppm) (*J* (Hz)): 5.04 (NH_2); 6.31 (d, 1H, 7.5), 6.49 (d, 1H, *J* = 7.0), 7.03 (d, 1H, *J* = 7.1), 7.39–7.81 (azomethine + PPh_3). IR (cm^{-1}): 1625, 1598, 1579, 1550, 1505, 1463, 1453, 1431, 1214, 1182, 1133, 750, 694, 516.

2.2.1.4. $[Pt(PPh_3)(L\text{-}Cl)]$. Yield: 57%. *Anal.* Calc. for $C_{26}H_{21}N_3PSClPt$: C, 46.67; H, 3.14; N, 6.28. Found: C, 46.57; H, 3.13; N, 6.27%. ^1H NMR (300 MHz; $CDCl_3$) δ (ppm) (*J* (Hz)): 5.08 (NH_2); 6.24 (s, 1H), 6.79 (d, 1H, *J* = 7.8), 6.96 (d, 1H, *J* = 7.8), 7.42–7.68 (azomethine + PPh_3). IR (cm^{-1}): 1624, 1596, 1577, 1552, 1501, 1460, 1450, 1433, 1211, 1184, 1130, 754, 696, 515.

2.2.1.5. $[Pt(PPh_3)(L\text{-}NO_2)]$. Yield: 62%. *Anal.* Calc. for $C_{26}H_{21}N_4O_2PSPt$: C, 45.95; H, 3.09; N, 8.25. Found: C, 45.89; H, 3.08; N, 8.26%. ^1H NMR (300 MHz; $CDCl_3$) δ (ppm): 6.84 (NH_2); 7.34–7.83 (azomethine + 3H + PPh_3).[1] IR (cm^{-1}): 1626, 1599, 1579, 1556, 1502, 1461, 1456, 1435, 1213, 1188, 1126, 755, 694, 514.

2.2.2. $[Pt(HL\text{-}R)_2]$ complexes

2.2.2.1. $[Pt(HL\text{-}OCH_3)_2]$. 4-Methoxybenzaldehyde thiosemicarbazone (101 mg, 0.48 mmol) was dissolved in methanol (30 mL) and $K_2[PtCl_4]$ (100 mg, 0.24 mmol) was added to this solution followed by triethylamine (49 mg, 0.49 mmol). The solution was then stirred for 24 h, whereby $[Pt(HL\text{-}OCH_3)_2]$ separated out as a yellow crystalline precipitate, which was collected by filtration, washed with cold methanol, and dried in air. Yield: 70%. *Anal.* Calc. for $C_{18}H_{20}N_6O_2S_2Pt$: C, 35.35; H, 3.27; N, 13.75. Found: C, 35.26; H, 3.28; N, 13.76%. ^1H NMR (300 MHz; $CDCl_3$) δ (ppm) (*J* (Hz)): 3.85 (OCH_3); 6.29 (NH_2); 6.91 (d, 2H, *J* = 6.3), 7.59 (d, 2H, *J* = 8.8), 7.77 (s, 2H). IR (cm^{-1}): 1605, 1524, 1368, 1292, 1181, 810.

2.2.2.2. $[Pt(HL\text{-}CH_3)_2]$. 4-Methylbenzaldehyde thiosemicarbazone (95 mg, 0.49 mmol) was dissolved in methanol (30 mL) and $K_2[PtCl_4]$ (100 mg, 0.24 mmol) was added to this solution followed by triethylamine (49 mg, 0.49 mmol). The solution was then stirred for 24 h producing a yellow solution. Evaporation of this solution gave a yellow solid, which was subjected to purification by thin layer chromatography on a silica plate. With benzene–acetonitrile (10:1) as the eluant a yellow band separated, which was extracted with acetonitrile and evaporation of this extract gave $[Pt(HL\text{-}CH_3)_2]$ as a yellow crystalline solid. Yield: 68%. *Anal.* Calc. for $C_{18}H_{20}N_6S_2Pt$: C, 37.31; H, 3.45; N, 14.51. Found: C, 37.39; H, 3.46; N, 14.52%. ^1H NMR (300 MHz; $CDCl_3$) δ (ppm) (*J* (Hz)): 2.25 (CH_3); 6.16 (NH_2); 7.01 (d, 2H, *J* = 7.4), 7.40 (d, 2H, *J* = 8.0), 7.63 (s, 2H). IR (cm^{-1}): 1605, 1524, 1367, 1292, 1180, 810.

2.2.2.3. $[Pt(HL\text{-}H)_2]$. The $[Pt(HL\text{-}H)_2]$ complex was prepared by following the same above procedure using H_2L-H instead of H_2L-CH_3. Yield: 71%. *Anal.* Calc. for $C_{16}H_{16}N_6S_2Pt$: C, 34.85; H, 2.90; N,

[1] All aromatic and PPh_3 proton signal are observed in the region 7.47–7.91 and could not be seen distinctly due to their overlap in this region.