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Synthesis, Characterization and Biological Application of Polymeric Complexes of Copper(I) With Substituted Benzaldehydethiosemicarbazone

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Abstract

$[Cu(CH_3CN)_4].PF_6$ reacted with 3-hydroxybenzaldehyde thiosemicarbazone (H^1L), 3-hydroxy benzaldehyde-N^1-Methyl thiosemicarbazone (H^2L), 4-hydroxybenzaldehyde thiosemicarbazones (H^3L), and 4-hydroxy benzaldehyde-N^1-Methyl thiosemicarbazone (H^4L) to form complexes of stiochiometry, $[Cu(L)_n].PF_6$ (L = ^1L(**1**); ^2L (**2**); ^3L (**3**); ^4L (**4**). The formation of these complexes was confirmed by elemental analysis and spectroscopic techniques (IR, ^1H NMR). All the four ligands and their complexes have shown anti-tubercular activity. Anti-TB activity of ligands get enhanced. All these complexes have shown Anti- TB activity.

Keywords: Thiosemicarbazones, anti-tubercular activity, complex, 3-hydroxybenzaldehyde, 4-hyroxybenzaldehyde

Introduction

Thiosemicarbazones {R^1R^2C=N-NH-C(=S)NR^3R^4, I} are well known derivative of imines [1]. Importance of thiosemicarbazones lie in their versatile coordination chemistry, analytical and biological applications like anticancer, antifungal, antiviral, anti-tumour, antibacterial, etc. [2-5]. Some thiosemicarbazones even use to expand their antitumour activity with their ability to forming a chelates with some particular type of metal ions. It is well known fact that biological activitities of thiosemicarbazones are closely related to parent ketone or aldehyde group [6-7]. Thiosemicarbazones are excellent ligands as they show variable bonding modes [8-18]. Number of copper(I) complexes with thiosemicarbazones as a neutral ligands are known [19-26]. Only few copper(I) complexes with anionic ligands are known for example hexameric complex,

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$[Cu_6L_6]$ (L = anionic form of 2-hydroxy benzaldehyde thiosemicarbazone) [27].

Present paper described synthesis of polymeric copper(I) complexes of 3-hydroxybenzaldehyde thiosemicarbazone (3-OHbtsc), 3-hydroxy benzaldehyde-N^1-Methyl thiosemicarbazone (3-OHbtsc-N^1-Me), 4- hydroxybenzaldehyde thiosemicarbazones (4-OHbtsc), and 4-hydroxy benzaldehyde-N^1-Methyl thiosemicarbazone (4-OHbtsc-N^1-Me) (Scheme 1). Characterization of compounds has been done using elemental analysis and spectroscopic techniques (IR and ^{1}H NMR). These complexes were also tested for their antitubercular activity.

Experimental:

Chemicals:

p-hydroxy benzaldehyde, m-hydroxy benzaldehyde, thiosemicarbazide, hexaflurophosphric acid and N-Me thiosemicarbazide are purchased from Qualikems Fine Chem Pvt are of analytical grade. SHIMADZU FTIR 8400S spectrophotometer was used to take Infrared spectra of ligands and their complexes. The base used to make pallets is KBr. Electrically heated Gallenkamp apparatus was used to check the melting point of compounds. ^{1}H NMR spectra of compounds were recorded on a Bruker AVANCE III 500 MHz (AV 500) in $CDCl_3$ and d^6- DMSO with TMS as the internal standard. Thermoelectron FLASHEA1112 CHNS analyzer was used for C,

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H and N analysis of complexes. XRD Spectra of synthesized complex were recorded in Bruker model- D8-Advance.

Synthesis:

Thiosemicarbazone ligands were prepared using literature method [19].

Synthesis of Cu_2O:

Dissolve Solid $CuSO_4.5H_2O$, 2g was in 400 ml of distilled water. To it was added 25 ml of 1M Sodium hydroxide solution drop wise. Change in the colour of the solution from blue to green occurred due to the formation of $Cu(OH)_2$. To this solution was add around 60ml of 1M glucose solution and the mixture was heated at moderate temperature. The reduction of $Cu(OH)_2$ resulted into formation of Cu_2O and appeared as yellow particles. The precipitates were left untouched for 2 hours and then washed thrice with water and then with ethanol. Precipitates were dried and collected.

Synthesis of Cuprous acetonitrile hexafluorophosphate $[Cu(CH_3CN)_4]PF_6$:

To Cu_2O (1g) was added acetonitrile (3ml) stirred properly until clear solution formed. To this solution was added 5-6 drops of Hexafluorophosphoric acid stirred for 15-20 minutes. After two days, white crystals were formed which were dried and collected. Yield, 65%, m.p. 190-195°C. Main IR peaks (KBr, cm^{-1}): $\nu_s(-CH_3)$, 2926m; $\nu(C\equiv N)$, 2360s; $\nu_d(CH_3)$, 1417m, 1365m; $\nu_r(-CH_3)$, 945s; ν(Cu-N), 484m.

Synthesis of $[Cu(3\text{-}OHbtsc)]_n \cdot PF_6$ 1.

Dissolve $[Cu(CH_3CN)_4]PF_6$ (0.1g, 0.3 mmol) in 15 ml acetonitrile. Add 3-OHbtsc, (0.052g, 0.264 mmol**)** and stirr for 30 minutes. Light yellow compound was formed. Yield, 62%, m. p. 245-247°C). Anal. Found: C, 23.6; H, 1.95; N, 10.41 %. Calcd. for $C_8H_8N_3SOCuPF_6$: C, 23.8; H, 1.98; N, 10.43 %. Main IR peaks (KBr cm^{-1}): ν(O-H), 3486m; ν(N-H), 33417m, ν(C=C) + ν(C=N) + $\delta(NH_2)$, 1651, 1583, 1509; ν(C=S), 834. ^{1}H NMR ($CDCl_3$, δ ppm): 9.94s (1H, -OH);

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7.24s (1H, C^4H); 7.09d (2H, C^8H, *J* = 8Hz); 7.35d (2H, C^6H, *J* = 7Hz); 7.43-7.40m (3H,C^7H).

Synthesis of $[Cu(3\text{-}OHbtsc\text{-}N\text{-}Me)]_n \cdot PF_6$ 2.

Dissolve $[Cu(CH_3CN)_4]PF_6$ (0.1g, 0.3 mmol) in 15ml acetonitrile. Add 3-OHbtsc-N^1-Me, (0.062g, 0.3 mmol) and stirr for 30 minutes. Light yellow compound was obtained after evaporation. Yield, 62%, m. p. 240-242°C. Anal. Found: C, 25.7; H, 2.36; N, 10.01 %. Calcd. for $C_8H_8N_3SOCuPF_6$: C, 25.9; H, 2.40; N, 10.08 %. Main IR peaks (KBr cm^{-1}): ν(O-H), 3463; ν(N-H), 3420; ν(C-H), 2957; ν(C=C) + ν(C=N) +δ(NH_2), 1651, 1590, 1493; ν(C=S), 843. ^{1}H NMR ($CDCl_3$, δ ppm): 10.61s (1H,-OH); 7.8s (1H,C^2H), 7.76s (1H,NH-Me), 7.417s (1H,C^4H), 7.302-7.286m (4H,$C^{6,7}H$), 6.61d (2H,C^8H, *J* = 8.5Hz) 2.97d (3H,-CH_3, *J* = 7.5Hz).

Synthesis of $[Cu(4\text{-}OHbtsc)]_n \cdot PF_6$ 3.

Dissolve $[Cu(CH_3CN)_4]PF_6$ (0.1g, 0.3 mmol) in 15ml acetonitrile. Add 4-OHbtsc, (0.052g, 0.3 mmol**)** and stir for 30 minutes.. Light orange compound was obtained after evaporation. Yield, 69%, m. p. 110-112°C). Anal. Found: C, 23.7; H, 1.93; N, 10.49 %. Calcd. for $C_8H_8N_3SOCuPF_6$: C, 23.8; H, 1.98; N, 10.43 %. Main IR peaks (KBr cm^{-1}): ν(O-H), 3523; ν(N-H), 3320; ν(C=C) + ν(C=N) +δ(NH_2), 1668, 1620, 1518; ν(C=S), 834. ^{1}H NMR ($CDCl_3$, δ ppm): 9.78s (1H,-OH); 12.08s (1H,N^2H); 7.75d (2H,$C^{5,7}H$, *J* = 8Hz); 6.92d (2H,$C^{4,8}H$, *J* = 8Hz).

Synthesis of $[Cu(4\text{-}OHbtsc\text{-}N\text{-}Me)]_n \cdot PF_6$ 4.

Dissolve $[Cu(CH_3CN)_4]PF_6$ (0.1g, 0.3 mmol) in 15ml acetonitrile. Add 4-OHbtsc-N^1-Me, (0.06g, 0.3 mmol)) and stirred for 30 minutes. Light orange compound was obtained after evaporation. Yield, 62%, m. p. 250-252°C. Anal. Found: C, 25.8; H, 2.39; N, 10.04 %. Calcd. for $C_8H_8N_3SOCuPF_6$: C, 25.9; H, 2.40; N, 10.08 %. Main IR peaks (KBr cm^{-1}): ν(O-H), 3473; ν(-NH-), 3153; ν(C-H), 2960; ν(C=C) + ν(C=N) +δ(NH_2), 1655, 1570, 1483; ν(C=S), 846. ^{1}H NMR ($CDCl_3$, δ ppm): 10.14s (1H,-OH); 7.7s (1H,C^2H), 7.73s (1H,NH-Me), 7.42s (1H,C^4H), 7.43-7.28m (4H,$C^{6,7}H$), 6.65d (2H,C^8H, *J* = 8Hz) 3.01d (3H,-CH_3, *J* = 7.5Hz).

Anti-*Tuberculosis* Activity:

The anti-mycobacterial activity of compounds (Ligands and their complexes) were using the

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method given in literature [28]

Result and Discussion:

Reaction of $[Cu(CH_3CN)_4].PF_6$ with 3-hydroxybenzaldehyde thiosemicarbazone (H^1L), 3-hydroxy benzaldehyde-N^1-Methyl thiosemicarbazone (H^2L), 4-hydroxybenzaldehyde thiosemicarbazones (H^3L), and 4-hydroxy benzaldehyde-N^1-Methyl thiosemicarbazone (H^4L) yielded complex of stiochiometry, $[Cu(L)_n].PF_6$ (L = ^1L(**1**); ^2L (**2**); ^3L (**3**); ^4L (**4**) (Scheme 2)

The ν(O-H) peak in complexes **1**-**4** appeared in the range of 3450-3550 cm^{-1}. The ν(N-H) peaks of free ligands appeared in the range of 3435-3296 cm^{-1}.This peak show shift to lower energy in their respective complexes. Absence of ν(-NH-) band in complexes **1**-**4**, which otherwise appeared in ligands in the range, 3126-3163 cm^{-1} suggested that thiosemicarbazone ligands are binding to metal centre in anionic form. The characteristic ν(C=S) peaks in free ligand appeared in the range, 869-880 cm^{-1}. Low energy shift of this band in complexes **1**-**4** (in the range, 834-843 cm^{-1} indicates that ligand is binding through sulfur in thiolate form.

Absence of $–N^2H$ proton in complexes **1**-**4**, which otherwise appear in the free ligands in the range δ 8.9-δ 10.57 ppm ensured deprotonation of ligand and binding of ligand to metal centre in anionic form. The hydroxyl proton appeared in the range, δ 9.78- δ 10.61 ppm in complexes **1**-**4**. The methyl proton at N^1 atom appeared at δ2.97 ppm (**2**) and δ 3.01 ppm (**4**).

Anti-Tubercular activities:

Table 1. contains MIC value of H^1L-H^4L and their complexes **1**-**4** .Anti-tubercular activity of 4-Ohbtsc-N-Me (MIC, 50μg/ml) is less as compare to 4-Ohbtsc (MIC, 25μg/ml) due to the presence of methyl group. Anti-tubercular activity of 3-OHbtsc (H^1L) and 3-OHbtsc-N-Me (H^3L) is similar to 4-OHbtsc. It has been observed that anti tubercular activity of all the ligands get enhanced on complexation with Cu(I). This enhancement in the activity is more pronounced

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(MIC, 6.25μg/ml) in complexes $[Cu(4\text{-}OHbtsc)]_n.PF_6$ (**2**), and $[Cu(3OHbtsc\text{-}N\text{-}Me)]_n.PF_6$ (**4**), which is similar to the Streptomycin drugs commercially available (MIC. 6.25μg/ml).

Table 1. Anti-Tubercular activities of ligands (**H^1L-H^4L**) and complexes (**1-4**)

Compound	**H37RV Strain MIC(μg/ml)**							
	100	**50**	**25**	**12.5**	**6.25**	**3.12**	**1.6**	**0.8**
H^1L	S	S	S	NS	NS	NS	NS	NS
1	S	S	S	S	NS	NS	NS	NS
H^2L	S	S	S	NS	NS	NS	NS	NS
2	S	S	S	S	NS	NS	NS	NS
H^3L	S	S	S	NS	NS	NS	NS	NS
3	S	S	S	S	S	NS	NS	NS
H^4L	S	S	NS	NS	NS	NS	NS	NS
4	S	S	S	S	S	NS	NS	NS

S = Sensitive, NS = Not sensitive

Conclusion and Discussion:

Polymeric complexes $[Cu(3\text{-}OHbtsc)]_n{\cdot}PF_6$ **1**, $[Cu(4\text{-}OHbtsc)]_n{\cdot}PF_6$ **2**, $[Cu(3\text{-}OHbtsc\text{-}N\text{-}Me)]_n{\cdot}PF_6$ **3**, and $[Cu(4\text{-}OHbtsc\text{-}N\text{-}Me)]_n{\cdot}PF_6$ has been formed. The formation of these complexes was confirmed by elemental analysis and spectroscopic techniques (IR, ^1H NMR). All the four ligands and their complexes have shown anti-tubercular activity. Anti-TB activity of ligands get enhanced. All these complexes have shown Anti- TB activity.

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