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Structure and spectroscopic investigations of a bi-dentate *N′*-[(4-ethylphenyl)methylidene]-4-hydroxybenzohydrazide and its Co(II), Ni(II), Cu(II) and Cd(II) complexes: Insights relevant to biological properties

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ABSTRACT

The present paper describes the synthesis of novel ligand, *N′*-[(4-ethylphenyl)methylidene]-4-hydroxy benzohydrazide (HL) and its Co(II), Ni(II), Cu(II) and Cd(II) complexes. The ligand (HL) crystallizes in orthorhombic lattice in $P2_12_12_1$ space group with a = 7.9941 (7) Å, b = 11.6154 (10) Å, c = 15.2278 (13) Å, $\alpha = \beta = \gamma = 90^{\circ}$. Spectroscopic data gives the strong evidence that ligand is coordinated through azomethine nitrogen and enolic oxygen with metal ion. The DNA binding studies revealed that the complexes bind to CT-DNA via intercalation/electrostatic interaction. All the targeted compounds showed more pronounced DNA cleavage activity in the presence of H_2O_2 and also inhibit the growth of in vitro antibacterial activity against Gram-positive and Gram-negative bacteria.

1. Introduction

The design as well as identification of small molecules to bind DNA is important to the development of DNA molecular probes and new therapeutic reagents. Among Schiff bases, hydrazones, a versatile class of organic compounds constitutes one of the most active classes of compounds possessing diversified biological activities [1]. Literature survey reveals that hydrazone derivatives have been incorporated into a large number of compounds with potential medicinal values such as anti-inflammatory, analgesic, anticonvulsant, antituberculous, antitumor, anti-HIV and antimicrobial activity [2–6]. In addition to biological properties, hydrazones and their metal complexes have interest as possible ligands for metal complexes, organocatalysis and also for the syntheses of heterocyclic compounds [7–13]. It has also been shown that the azomethine N, which has a lone pair of electrons in a sp^2 hybridised orbital, is biologically important [14].

The ease of preparation, increased hydrolytic stability relative to imines, and tendency toward crystallinity are all desirable characteristics of hydrazones. Due to these positive traits, hydrazones have been under study for a long time, but much of their basic chemistry remains unexplored.

Hydrazones and their analogs act as either mono- or di-negative ligands towards transition metal ions [15]. These ligands coordinate in four different modes: such as (i) monodentate by the deprotonated amide nitrogen-donor [16]; (ii) bidentate by the imine nitrogen and deprotonated amide nitrogen-donor [17]; (iii) tridentate by phenoxy oxygen, imine nitrogen and deprotonated enolimine oxygen/protonated amide oxygen-donor [18,19]; (iv) tetradentate by phenoxy oxygen, imine nitrogen, deprotonated enolimine oxygen and deprotonated enolimine nitrogen donor [20–22].

In the light of the above and in continuation of our interest in the chemistry and biology of transition metal azomethine, N chelates [23–28], we now carry out another systematic study of their

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synthesis and biological activity of the novel *N′*-[(4-ethylphenyl) methylidene]-4-hydroxy benzohydrazide (Scheme 1) as well as their complexes with Co(II), Ni(II), Cu(II) and Cd(II) ions.

2. Experimental

2.1. Materials and methodology

All starting precursors were of analytical grade, and double-distilled water was used throughout the experiments. The reagents and solvents were purchased commercially and used without further purification unless otherwise noted. 4-hydroxybenzhydrazide, 4-ethylbenzaldehyde and calf thymus DNA (CT-DNA) were purchased from Sigma-Aldrich and used as received. The purity of the synthesized compounds was ascertained by thin layer chromatography on silica gel in various solvent system using iodine vapors as detecting agent. The ligand and its complexes were analyzed for their elemental analysis on a Perkin Elmer CHN 2400 analyzer. Melting points were determined in evacuated capillaries. Electronic spectra were recorded on an Elico-150 in DMSO solvent. The diffuse electronic spectra were recorded by Specord 210 (made in Germany). Infrared spectra were recorded in the 4000–400 cm^{-1} region (KBr disc) on a Nicolet protage 460 FT-IR spectrophotometer. ^1H- and $^{13}C\{^1H\}$-NMR spectra were obtained in DMSO-d_6 using tetra methyl silane (TMS) as an internal reference on advanced 200.12 and 50.32 MHz NMR spectrometer. Mass spectra were recorded on LC-MS. Magnetic susceptibility measurements were carried at room temperature on a magnetic susceptibility balance (Sherwood Scientific, Cambridge, England) using $CuSO_4 \cdot 5H_2O$ as standard. The single crystal X-ray diffraction (XRD) analysis was carried out using an Oxford X Calibur, Gemini diffractometer. EPR spectra were recorded on various E-112 X-band spectrophotometers at liquid nitrogen temperature in DMSO solvent.

2.2. Preparations of *N′*-[(4-ethylphenyl)methylidene]-4-hydroxybenzohydrazide ligand (HL)

Ligand, HL was prepared according to the literature procedure [29]. Equimolar amounts of 4-hydroxybenzhydrazide (3.33 g, 21.87 mmol) and appropriate 4-ethylbenzaldehyde (2.937 g, 21.87 mmol) were refluxed in ethanol (50 mL) for 2–3 h. After cooling over night, a white crystalline product was collected by filtration and recrystallized from ethanol. Single crystals suitable for X-ray diffraction were formed by slow evaporation of the ethanol solution of the ligand. Analytical data for $C_{16}H_{16}N_2O_2$: Yield, 77.73%. Melting point 200–202 °C, Elemental analysis, Calculated: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.56; H, 5.89; N, 10.39%. ^1H NMR, δ ppm (DMSO-d^6): 1.2 (3H, t), 2.65 (2H, q), 6.89–7.30 (aromatic), 11.6 (1H, s), 10.9 (1H, s); $^{13}C\{^1H\}$ NMR, δ ppm (DMSO-d^6): 160.42 (−C(O)−N), 145.83(−C=N), 131.54, 129.36, 127.61, 126.96, 123.80, 114.72 (aromatic carbons), 28.21 ($-CH_2$) and 14.93 ($-CH_3$) ppm.

2.3. Procedure for the preparation of complexes

2.3.1. Synthesis of $Co(L)_2$ (I)

A warm ethanol solution containing hydrazone ligand (1.0 g, 3.72 mmol) was added to an ethanol solution (20 mL) of $CoCl_2 \cdot 6H_2O$ (0.443 g, 1.86 mmol). The reaction mixture was then stirred for 2 h at room temperature and the rose colored solid compound formed was filtered off, washed with cold ethanol, and dried in a desiccators over anhydrous $CaCl_2$. Analytical data for $Co(C_{16}H_{15}N_2O_2)_2$: Yield, 75.54%. Melting point, >300 °C. Elemental analysis, Calculated: C, 64.75; H, 5.09; N, 9.44. Found: C, 64.71; H, 5.01; N, 9.31%. $\mu_{eff} = 0.996$ BM.

2.3.2. Synthesis of $Ni(L)_2$ (II)

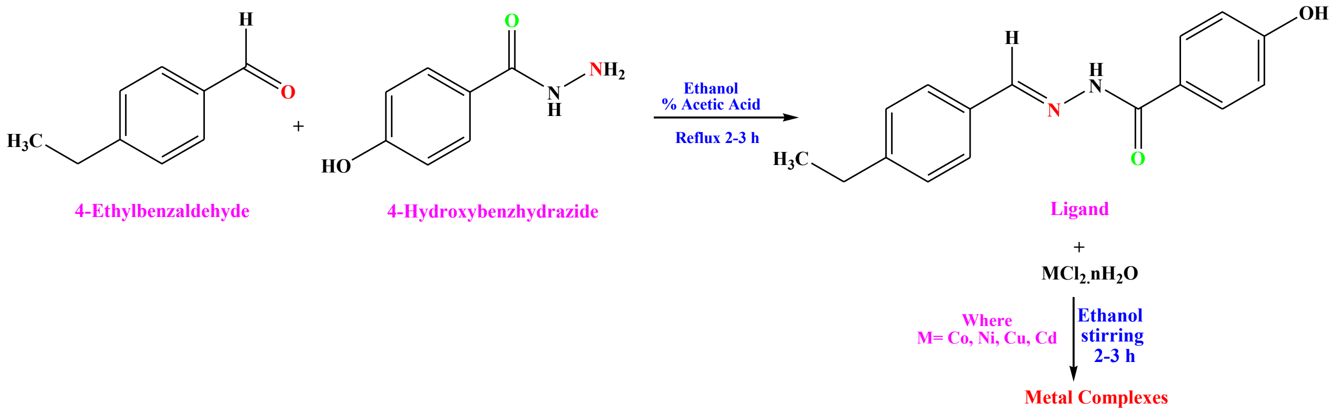
A solution of 3.72 mmol (1.0 g) of hydrazone ligand in 20 mL of ethanol solution was added to 1.86 mmol (0.442 g) of $NiCl_2 \cdot 6H_2O$. The mixture was stirred about 2 h at room temperature and the light blue solid compound formed was filtered off, washed with cold ethanol, and dried in a desiccators over anhydrous $CaCl_2$. Analytical data for $Ni(C_{16}H_{15}N_2O_2)_2$: Yield, 80.65%. Melting point, >300 °C. Elemental analysis, Calculated: C, 64.78; H, 5.10; N, 9.44. Found: C, 64.73; H, 4.98; N, 9.23%. $\mu_{eff} = 0.771$ BM.

2.3.3. Synthesis of $Cu(L)_2$ (III)

A hot ethanol solution of hydrazone ligand (1.0 g, 3.72 mmol) was mixed to the alcoholic solution of $CuCl_2 \cdot 2H_2O$ (0.317 g, 1.86 mmol), with constant stirring by the help of mechanical stirrer for about 2 h at room temperature and the yellow solid compound formed was filtered off, washed with cold ethanol, and dried in a desiccator over anhydrous $CaCl_2$. Analytical data for $Cu(C_{16}H_{15}N_2O_2)_2$: Yield, 68.05%. Melting point, 220 °C. Elemental analysis, Calculated: C, 64.26; H, 5.06; N, 9.37. Found: C, 64.21; H, 5.00; N, 9.36%. $\mu_{eff} = 1.11$ BM.

2.3.4. Synthesis of $Cd(L)_2$ (IV)

Cadmium complex of hydrazone ligand was synthesized by reacting aqueous ethanolic solutions 1.86 mmol of $CdCl_2 \cdot H_2O$ (0.375 g) with ligand (3.72 mmol) solutions in 50 mL aqueous



Scheme 1. Synthesis of ligand and its complexes.