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Synthesis, characterization and bio-activity of nickel(II) and copper(II) complexes of a bidentate NS Schiff base of S-benzyl dithiocarbazate

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ABSTRACT

The reaction of S-benzyldithiocarbazate (SBDTC) with 3-hydroxyacetophenone afforded a bidentate NS Schiff base HL (HL = benzyl-3-(3-hydroxyphenyl methyl ethylene)hydrazine carbodithioate) which on further reaction with nickel(II) and copper(II) salt yielded bis-chelated inner complexes, NiL_2 and CuL_2, respectively with deprotonated L ligand. The ligand and its complexes were characterized by physico-chemical techniques, viz., molar conductance, magnetic susceptibility measurement, IR, NMR, UV–Vis spectroscopy and mass spectroscopic techniques. The crystal structure of all the compounds was also characterized by single crystal X-ray crystallography. The ligand exists in its thione tautomeric form both in solution and in the solid state. In the complexes the two deprotonated ligands chelate the metal through the azomethine nitrogen and the thione sulfur atom with *cis* arrangement generating a tetrahedrally distorted square planar geometry around the metal center. Only complex CuL_2 showed moderate analgesic activity at 60 min compared to Diclofenac sodium, while all the test compounds exhibited good anti-inflammatory activity as compared to standard drug Indomethacin.

1. Introduction

S-alkyl or aryl dithiocarbazates constitute one of the most important classes of mixed hard-soft nitrogen–sulfur donor ligands [1,2], having four potential donor atoms of which two are sterically available at a time to chelate metal ions. In fact the presence of hard nitrogen and soft sulfur atoms enable these ligands to react with both transition and main group metals [3]. In principle both NS and SS complexes are feasible [4]. However, the free dithiocarbazic acid and its S-alkyl/aryl esters behave typically through the NS donors with formation of a five-membered chelate ring [3–5]. Generally bidentate NS Schiff bases of S-alkyl/aryl dithiocarbazates generate four coordinate complexes with nickel(II) and copper(II) ions either in *cis*- or in *trans*-planar geometry [6–11], and the different configuration can affect the bioactivity of these derivatives. [12]. In fact bis-chelated nickel(II) and copper(II) complexes have been synthesized for their potential use and tested in various medicinal applications such as antibacterial [13–15], antifungal [14], and cytotoxic activities. [14,15] Although considerable work has been done with S-alkyl or aryl dithiocarbazate Schiff bases and on their biological activities, this field of investigation represents a current area of interest. As an additional contribution, the present work reports the coordination behavior of a bidentate Schiff base derived from the condensation of S-benzyl dithiocarbazate with 3-hydroxyacetophenone with nickel(II) and copper(II) and the study of their analgesic and anti-inflammatory activity.

2. Experimental

2.1. Materials and instrumentation

All the chemicals and solvents were of reagent grade and used without further purification. Chemicals such as hydrazine hydrate (90%), carbon disulfide and potassium hydroxide were purchased from (Merck, India), while benzyl chloride and 3-hydroxy acetophenone were obtained from Sisco Research Laboratories (SRL) Pvt. Ltd, India. The metal salts nickel(II) acetate tetrahydrate and

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copper(II) acetate monohydrate were obtained from Fluka Chemica (Switzerland). Solvents chloroform, ethanol and DMSO were obtained from Active Fine (Bangladesh), Diclofenac sodium USP and Indomethacin from Watson Pharma (USA) and Sigma–Aldrich (USA), respectively. IR spectra (4000–400 cm^{-1}) were obtained as KBr pellet using a FTIR-8400/8900 Shimadzu spectrophotometer at BCSIR laboratories, Rajshahi. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JNM-A400 spectrometer in $CDCl_3$ (and in some cases d_6-DMSO) using TMS as internal standard and C, H, N and S microanalyses were performed on a Yanaco JMS-D300 spectrometer at the Department of Applied Chemistry, University of Toyama, Japan. Mass spectra were obtained on a JEOL-JMS-D300 mass spectrometer from Water Quality Management Centre, University of Toyama, Japan. Magnetic susceptibility and molar conductance measurements were made on a magnetic susceptibility balance (Sherwood Scientific, UK) and a heavy-duty conductivity/temperature meter (Extech Instruments, USA, model No. 407303), respectively, while the UV–Vis absorptions were scanned on a T60 UV–Vis spectrophotometer (PG Instruments, UK) between 200 and 800 nm using 10^{-5} M solution in chloroform at the Department of Chemistry, Rajshahi University of Engineering & Technology.

2.2. X-ray crystal structure determination

Intensity measurements for the structures reported were carried out at a temperature of 173(1) K on a Rigaku R-AXIS RAPID diffractometer (Water Quality Management Center, University of Toyama, Japan) by using filtered Cu Ka radiation (λ = 1.54187 Å). All the structures were solved by direct methods [16] and successive Fourier syntheses and refined by the full-matrix least-squares method based on F^2 with all observed reflections [17]. Hydrogen atoms were geometrically located and refined using the riding model. All calculations were performed using the Crystal Structure package [18] except for the refinements for which SHELXL-97 was used [17]. Crystal data and details of refinements of the structures reported are summarized in Table 1.

2.3. Synthesis of the HL Schiff base

The ligand precursor, S-benzyl dithiocarbazate (SBDTC) as well as the Schiff base was prepared by literature method [19]: SBDTC (1.98 g, 10 mmol) was dissolved in absolute ethanol (40 mL) under reflux. To this solution, 3-hydroxy acetophenone (1.36 g, 10 mmol) in absolute ethanol (10 mL) was added and the mixture was refluxed for 2 h. The aliquot was cooled to 5 °C in refrigerator for about 72 h. The light yellow precipitate, which formed was separated and dried *in vacuum over* anhydrous $CaCl_2$ (Yield: 2.91 g, 88.92%). The product was recrystallized from absolute ethanol. Colorless needle shaped single crystals were obtained after crystallization of 0.15 g of the recrystallized product from chloroform (25 mL) over 7 days.

Characterization of HL: (2.91 g, 88.92%); m.p. 162 °C. *Anal.* Calc. for $C_{16}H_{16}N_2OS_2$: C, 60.73; H, 5.10; N, 8.85; S, 20.27. Found: C, 60.80; H, 5.19; N, 8.90; S, 20.30%. Selected IR data (KBr pellet, cm^{-1}): 3464 m ν(O–H), 3184s ν(N–H), 1607 m ν(C=N), 1462 m ν(C=C), 943 m ν(C=S), 1053 m ν(N–N). ^1H NMR (500 MHz, $CDCl_3$, ppm) δ: 0.88 (s, CH_3), 4.02 (s, 2H, SCH_2), 7.24–7.45 (m, 9H, 2 × ph), 10.02 (bs, 1H, NH), 9.10 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ: 183.75 (C=S), 169.92 (C=N), 129.01, 128.90, 128.71, 128.37, 128.15, 128.11, 126.93, 106.31 (ring), 39.09 (SCH_2); UV–Vis λ_{max}($CHCl_3$)/nm (log ε): 258 (4.03), 290 (4.26), 327 (4.77), 333(4.83), 350 (4.71). LRMS (FAB, 70 eV,%) *m*/*z*: 316 (M^+, 1.73%), 281 (M-H_3S, 8.18%), 230 (M-$C_2H_2N_2S$, 9.79%), 182 (M-C_8H_8NO, 1.89%), 169 (M-$C_8H_7N_2O$, 18.43%), 131 (M-$C_7H_9N_2S_2$, 20.62%), 119 (M-$C_8H_9N_2S_2$, 22.35%), 91 (M-$C_9H_9N_2OS_2$, 100%), 69 (M-$C_{11}H_7N_2OS_2$, 59.36%).

2.4. Synthesis of the NiL_2 complex

Nickel(II) acetate tetrahydrate (0.124 g, 0.5 mmol) dissolved in ethanol (15 mL) was added to a hot solution of the ligand (0.316 g, 1 mmol) in ethanol (40 mL) and the resulting bluish green solution was refluxed for 1 h. The volume was reduced to half and kept in refrigerator for about 24 h. The bluish green precipitate which formed was separated out, washed with ethanol and dried

Table 1
Crystallographic data of the Schiff base HL and its NiL_2 and CuL_2 complexes.

	HL	NiL_2	CuL_2
Empirical formula	$C_{16}H_{16}N_2OS_2$	$C_{32}H_{30}NiN_4O_2S_4$	$C_{32}H_{30}CuN_4O_2S_4$
Formula weight	316.44	789.55	694.40
Crystal color, habit	colorless, prism	green, prism	red, prism
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	*Pbca*	*C*2/*c*	*C*2/*c*
a (Å)	15.3008(2)	24.9982(5)	24.9825(5)
b (Å)	7.47728(10)	8.44322(15)	8.40001(15)
c (Å)	27.5926(5)	15.8497(3)	15.8690(3)
β (°)	90.00	111.3993(7)	111.0849(7)
V (Å^3)	3156.82(9)	3114.69(10)	3107.20(10)
Z	8	4	4
D_{calc} (g cm^{-3})	1.331	1.470	1.484
Crystal size (mm)	0.69 × 0.40 × 0.25	0.47 × 0.36 × 0.29	0.20 × 0.15 × 0.04
μ (Cu Kα), mm^{-1}	3.050	3.702	3.802
F(000)	1328	1432	1436
θ max (°)	68.22	68.23	68.24
No. of reflections collected	33759	16889	17504
R_{int}	0.0760	0.0746	0.0566
T_{min}, T_{max}	0.367, 0.467	0.290, 0.342	0.703, 0.859
No. of independent reflections	2882	2836	2841
No. of observed reflections ($I > 2\sigma(I)$)	2751	2668	2649
No. of refined parameters	194	195	196
Goodness-of-fit, *S* (F^2)	1.073	1.070	1.084
R_1, wR_2 ($I > 2\sigma(I)$)	0.0398, 0.1078	0.0472, 0.1376	0.0436, 0.1222
Residuals (e Å^{-3})	0.60, −0.35	0.95, −0.33	1.39, −0.39