Synthesis and Characterization of Biological active Phenethylamine Dithio carbamate metal Complexes-Biological studies

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Abstract

Dithiocarbamates are a class of sulphur-based metal-chelating compounds with various applications in medicine. In the present investigation, a series of novel Phenethylamine dithiocarbamates have been synthesized. The synthesized compounds were characterized by IR, ^{1}HNMR, followed by antimicrobial screening. A new series of new transition metal [Cu(II), and Fe (II)] complexes of Dithiocarbamates were synthesized from Phenethylamine and Carbon disulphide and further characterized. The investigation of these complexes confirmed that the stability of metal–ligands coordination through, S & S,N atoms as bidentate chelates.

Key words: Phenethylamine Metal Complexes, dithiocarbamates,

Introduction:

The field of dithiocarbamates metal complexes are vast and fast developing on account of their spectacular applications in various fields, also owing to the varieties of structural forms of the ligands. The ever-increasing applications of transition metal complexes in different fields of sciences are the driving force for the present research. The dithiocarbamates are organo sulphur compounds considered to be versatile organic ligands which form complexes with many transition metals like Cu, Fe, Ni, Mn and Zn leading to the stabilization of a wide range of oxidation states.

The complexing ability of dithiocarbamate is well established and this is due to two sulphur atoms, which are capable to donate a lone pair of electrons to the central metal atom to form the stable metal complexes. These are known to stabilize unusual oxidation states of metal complexes, because of the delocalization of positive charge from the metal to nitrogen. Besides, dithiocarbamates ligand and its metal complexes exhibit their striking and diversified applications in many fields like Medicine, Agriculture Industry, Polymer technology, Inorganic and Environmental trace analysis.

Dithiocarbamates ligands are soft bases. They had been found to act almost as uni negative bi dentate ligands coordinating through sulphur atoms, and also both tetra and hexa co-ordinate complex of many transitional metal ions have been isolated. They exhibit various applications in different fields especially in the production of petroleum derivatives, lubricants, as accelerators for vulcanization in Polymer Industry, as antioxidants and anti humidity agents. They are also having fungicidal, bactericidal, insecticidal, anticancer, and photochemical activities. Dithiocarbamates ligands itself acts as a good antibacterial and antifungal activity and are used as biocides (vapam, nabam).

Owing to wide applicability of sulphur bearing ligands in biological and industrial field, a bulk of literature is available on the dithiocarbamates ligands and its complexes of transition and non-transition metals. A large number of transition metal complexes with various aliphatic and aromatic dithiocarbamate ligands have been reported. Though a number of dithiocarbamates have been prepared in the literature, there is no attempt in preparation of Phenethylamine.

Phenethylamine (PEA) is an organic compound, natural monoamine alkaloid, and trace primary amine, which acts as a central nervous system stimulant in humans. In the brain, phenethylamine regulates monoamine neurotransmission by binding to trace amine-associated receptor 1 (TAAR1) and inhibiting vesicular monoamine transporter 2 (VMAT2) in monoamine neurons to a lesser extent, it also acts as a neurotransmitter in the human central nervous system.In mammals, phenethylamine is produced from the amino acid L-phenylalanine by the enzyme aromatic L-amino acid decarboxylase via enzymatic decarboxylation. In addition to its presence in mammals, phenethylamine is found in many other organisms and foods, such as chocolate, especially after microbial fermentation.

Phenethylamines, or more properly, substituted phenethylamines, are the group of phenethylamine derivatives that contain phenethylamine as a "backbone"; in other words, this chemical class includes derivative compounds that are formed by replacing one or more hydrogen atoms in the phenethylamine core structure with substituents. The class of substituted phenethylamines includes all substituted amphetamines, and substituted methylenedioxyphenethylamines (MDxx),and contains many drugs which act as empathogens, stimulants, psychedelics, anorectics, bronchodilators, decongestants, and antidepressants, among others.

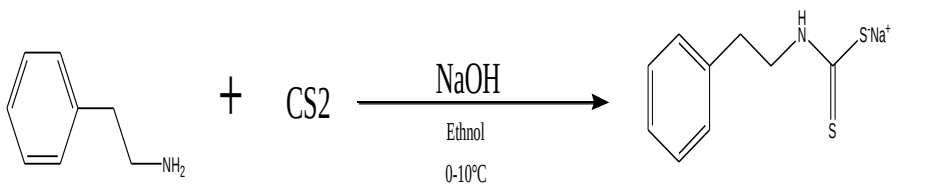
The present work has been extended to know antibacterial activity, anti inflammatory activity and antifungal activity of the dithiocarbamates metal complexes.

The main thrust of the study is to prepare as such new dithiocarbamates ligand from an amine having considerable amount of applications on its own with the hope that the resultant dithiocarbamates may possess much more applications and find a place in major fields of interest.

MATERIALS AND METHODS

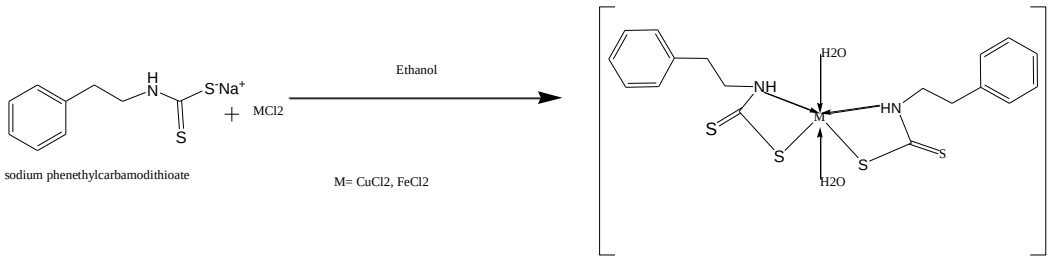
Experimental Section

Copper chloride anhydrous was obtained from Fluka, Pramipexole and carbon disulfide were purchased from Aldrich. Other chemicals used were of analytical reagent or higher purity grade. Solvents used were of reagent grade and purified before use by the standard methods. Conductivity measurement was carried out by a Systronics conductivity bridge 305, using a conductivity cell of cell constant 1.0 double distilled water was used as solvent. Electronic absorption spectra on JAS.CO UV/VIS-7850 recording spectrophotometer. Infrared spectra was recorded on a JAS.Co-460 plus FT-IR spectrophotometer in the range of 4000-400 cm^{-1} in KBr pellets. Micro chemical analysis of carbon, hydrogen and nitrogen for the complexes were carried out on a Herause CHNO-Rapid elemental analyzer.^{1}H NMR spectra were recorded on a Brucker DRX-500 Advance spectrometer at 500MHz in DMSO-discussing tetra methyl silane as internal reference standard. Melting points were measured on a unimelt capillary melting Point apparatus and reported uncorrected.



2-phenylethanamine

Sodium salt of Phenethylamine carbamate



Preparation of Sodium salt of Dithiocarbamate ligands

0.05 mol of amine was dissolved in 30 ml of absolute alcohol in a clean beaker which was placed in ice bath. To this cold solution add 5 ml of Sodium hydroxide (10N) solution, and then add Pure carbon disulphide (0.05ml) in drop wise with constant stirring. The contents were stirred mechanically for about 30 min, sodium salt of Dithiocarbamate precipitated out. It was dried over and recrystallized from ethanol.

Preparation of Cu (II) and Ru (II) Complexes

Synthesis of [Cu ((PEADCT))$_2$)Cl$_2$]

The aqueous solution of 0.05 mol of Cupper Chloride was added with constant stirring to an aqueous solution of 0.01 mol of Sodium salt of Phenethylamine ligand. The reaction mixture was stirred at room temperature for 2 hours. The coloured (black) precipitates were obtained. The precipitates were filtered and washed with water and then with methanol and dried over calcium chloride in desiccator's Yield:78% and decomposes at 110 C.

Anal. Calcd. For C19H24CuN2O2S4

Calculated: C, 45.26; H, 4.80; Cu, 12.60; N, 5.56; O, 6.35; S, 25.44 ; Found: C, 46.26; H, 5.80; Cu, 12.60; N, 6.56; O, 7.35; S, 26.44.

Synthesis of [Fe (PEADCT)Cl$_2$]

The aqueous solution of 0.05 mol of Iron Chloride was added with constant stirring to an aqueous solution of 0.01 mol of Sodium salt of Phenethylamine Dithiocarbamate ligand in the presence of small quantity of triethylamine. The reaction mixture was stirred at room temperature for 2 hours. The coloured (gray) precipitates were obtained. The precipitates were filtered and washed with water and then with methanol and dried over calcium chloride in a desiccator Yield: 80% and decomposes at 110^{0}C. Anal. Calcd. For C19H24FeN2O2S4

C, 45.96; H, 4.87; Fe, 11.25; N, 5.64; O, 6.44; S, 25.83 Found: C, 46.96; H, 5.87; Fe, 13.25; N, 6.64; O, 7.44; S, 26.83

RESULTS AND DISCUSSION

Solid reflectance spectra data for the Cu and Fe of Phenethylamine metal complexes. The complexes [Cu(PEADCT)$_2$)Cl$_2$] and [Fe(PEADCT)$_2$Cl$_2$] complexes exhibit magnetic property and has an electronic spectrum which can be assigned to low spin Cu (II) and Fe (II) in an Octahedral Environment. Intra ligand electronic transition in then…C…S…S and S…C…S chronophers of the Dithiocarbamate moiety. Thus, the peak at 646 nm and the

shoulder at 499 nm arise from 1A1g_1T1g and 1A1g_ 1T2g transitions, respectively. The other lower peaks are probably charge-transfer in origin.

Infrared Spectrum

Two regions of the IR spectrum of the $[Cu(PEADCT)_2)Cl_2]$ and $[Fe(PEADCT)_2Cl_2]$ complex have proven valuable in arguments concerning the electronic and structural characteristics of this compound. The presence of the thiouride band between 1449.7-1493.1 cm^{-1} and 1449.7-1505.8cm^{-1}suggest a considerable double bond character in the C…N bond vibration of the S_2C-NR_2 group. The band present in the 940 cm^{-1} range is attributed to the prevailing contribution of (C…S) Vibrations in these ranges have been used defectively in differentiating between monodentate, bidentate dithiocarbamate ligands. The presence of only one strong band supports bidentate coordination of the dithio ligands, where as a doublet is expected in the case of monodentate coordination. (C…S) and (C..N) Stretching frequencies fall in the 1018.7 cm^{-1} (1001 cm^{-1} for the free ligand) and 1023.1cm^{-1} respectively.

H^1-NMR Spectra

The NMR spectrum of the $[Cu(PEADCT)_2)Cl_2]$ and $[Fe(PEADCT)_2Cl_2]$ complexes showed at he peak at 7.9-7.98 attributed to NH protons of thiouraide nitrogens in both complexes. In other signals is also appeared in the region 0.98, 1.5, 3.8 ppm.

Antimicrobial Activity

Antimicrobial test was performed on four bacterias (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa,*) and two fungi (*Candida albicans and Candida tropicalis*). The media used were prepared by dissolving separately 2g of nutrient broth powder and 38g of the Mueller-Hinton agar powder in 250 ml and 1 L of deionized water, respectively. Two media were sterilized in an autoclave at 121^0C for 15 minutes and then stored overnight in a refrigerator after cooling. Cultures of the microorganisms were prepared in sterile nutrient broth and incubated for 24 hours at 37^0C for the bacteria and 27^0C for the fungi. 0.1 ml of each of the overnight cultures in sterile test tubes with caps were made up to 10 ml with 9.9 ml of sterile deionized water

Growth inhibition zone in millimetre(mm)						
Bacteria					**Fungus**	
	Gram +Ve		**Gram -Ve**			
	S.aur	**B.Subt**	**E.Coli**	**P.aerug**	**C.alb**	**C.trop**
[Cu ((PEADCT))$_2$)	15	16	16	14	13	16
[Fe ((PEADCT))$_2$)	13	15	14	11.5	15	15
FLU	---	---	----	----	16	13
DMSO	12	14	15	16	-----	------

To give 1:100 or 10-2 dilution of the microorganisms. The technique used for the study was agar-well diffusion. Solutions of concentration 10 mg/ml of the compounds were made in dimethyl sulphoxide (DMSO).

DMSO was also used as the negative control. Positive controls for bacteria and fungi were discs of commercial antibiotics manufactured by Abtek Biological Limited and Fluconazole dissolved in DMSO. The discs were carefully placed on the inoculated media with the aid of sterile forceps. Plates inoculated with bacteria were incubated at 37^0C for 24 hours, and those inoculated with fungi were incubated at 27^0C for 72 hours. Afterwards, the zones of inhibition of microbial growth that appeared around the wells of the compounds were examined and the diameters measured and recorded in millimetres (mm). Antimicrobial activity of the Cu (II) and Fe (II) complexes was evaluated *in vitro* against Gram positive bacteria-*Staphylococcus aureus* and *Bacillus subtilis*, Gram negative bacteria- *Escherichia coli*, *Pseudomonas aeruginosa* and fungi, *Candida albicans*, *Candida tropicalis.* The results for the complexes and commercial antibiotics used as positive controls are listed in (Table 1).

Conclusion:

Cu (II) and Fe(II) complexes of Phenethylamine Dithiocarbamate Ligand with have been synthesized and characterized. The ligand moiety exhibits a bidentate coordination mode in the Cu (II) and Fe (II) complexes. Solid reflectance spectra and magnetic data indicate that the complexes are Paramagnetic and Octahedral. The complexes show selective activity towards some of the test microorganisms.

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