

**Complexes of Fe(III), Co(II), Cu(II) and Zn(II)
With Thiocarbamylthiocarbamate and
their Antibacterial Activity**

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Summary: A number of coordination compounds of a new ligand thiocarbamylthiocarbamate (tcdtc) with Fe^{3+} , Co^{2+} , Cu^{2+} , and Zn^{2+} ions have been synthesised. The ligand is unstable and cannot be isolated from its reaction mixture, however it readily forms air stable complexes with these metals. These compounds have been characterized by elemental analysis, conductance measurements, absorption and infra-red spectral studies. The compounds $[\text{Fe}(\text{tcdtc})_2\text{Cl}\cdot\text{H}_2\text{O}]$, $[\text{Co}(\text{tcdtc})_2(\text{H}_2\text{O})_2]\text{H}_2\text{O}$ and $[\text{Cu}(\text{tcdtc})_2(\text{H}_2\text{O})_2]$ have an octahedral structure with tcdtc coordinating through its S_1, S_3 atoms forming six membered chelates. The complex $[\text{Zn}(\text{tcdtc})_2]\text{H}_2\text{O}$ has a tetrahedral arrangement of ligands around the metal atom. The complexes $[\text{Co}(\text{tcdtc})_2\cdot(\text{H}_2\text{O})_2]\text{H}_2\text{O}$ and $[\text{Cu}(\text{tcdtc})_2(\text{H}_2\text{O})_2]$ show antibacterial activity against B.subtilis, V.Cholrea and E.coli while $[\text{Fe}(\text{tcdtc})_2\text{Cl}\cdot\text{H}_2\text{O}]$ shows very little activity against E.coli and B.subtilis.

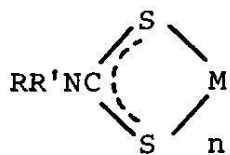
Introduction

Metallic derivatives of a variety of dithiocarbamates (I) have been under investigation for quite some time. The dithiocarbamate moiety interacts with transition metal ions through its two sulphur atoms forming planar four membered chelates. These chelates present some interesting problems of structure, stability and kinetics for investigation [1-8].

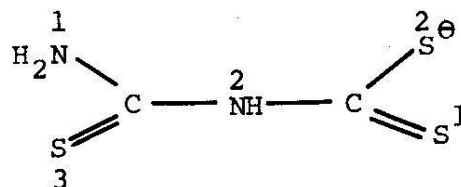
These derivatives have found their utility in chemical analysis, in the rubber industry as vulcanization accelerators and antioxidants. Their antifungal activity has also been thoroughly investigated [9]. However, only a few reports have been published on the medicinal properties of such compounds.

We report a few metal complexes of a new ligand, thiocarbamylthiocarbamate (II) prepared by interaction of thiourea with carbon disulphide in alkaline medium, capable of coordinating either through two sulphur atoms in different positions (III) or through a nitrogen and a sulphur atom (IV) forming six membered chelates. These expanded chelates are expected to be more stable than simple dithiocarbamates, interesting from structural and isomerism considerations.

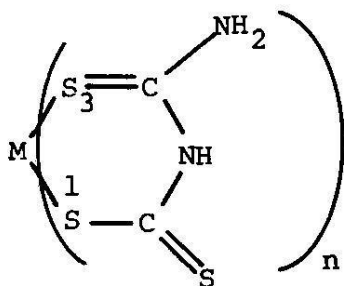
The free ligand, being unstable, could not be isolated from its reaction mixture. However, its complexes were readily precipitated out by adding respective metal halides to the freshly prepared ligand reaction solution.



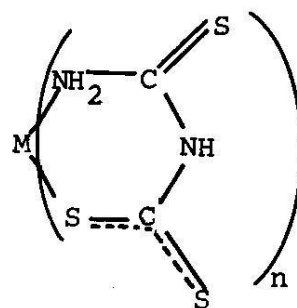
(I)



(II)



(III)



(IV)

These compounds were characterized by elemental analysis, conductance measurements and spectral studies. The complexes $[\text{Fe}(\text{tcdbc})_2 \cdot \text{Cl} \cdot \text{H}_2\text{O}]$, $[\text{Co}(\text{tcdbc})_2 (\text{H}_2\text{O})_2] \cdot \text{H}_2\text{O}$ and $[\text{Cu}(\text{tcdbc})_2 (\text{H}_2\text{O})_2]$ have octahedral environment around the metal ions with tcdbc acting as bidentate and two ambidentate ligands in trans positions, while $[\text{Zn}(\text{tcdbc})_2] \cdot \text{H}_2\text{O}$ has a tetrahedral arrangement of ligands around the Zn^{2+} ion. Antibacterial activity of Fe(III), Co(II) and Cu(II) complexes were checked against a number of bacteria such as *Bacillus subtilis*, *Staphylococcus aureus*, *Vibrio cholera* and *Escherichia coli*. The Co(II) and Cu(II) complexes are active against *B. subtilis*, *V. cholera* and *E. coli* while Fe(III) complex has feeble activity only against *B. subtilis* and *E. coli*.

Experimental

All the reagents were of "Analar" or reagent grade and were used without further purification.

i) Synthesis of Thiocarbamyl dithiocarbamate

The ligand was prepared by a general procedure reported for synthesis of dithiocarbamates [9]. For this purpose 6.5 ml (0.075 mole) triethylamine, 4.5 ml CS_2 (0.075 mole) and 30 ml methanol were placed in a 250 ml round bottom flask. The solution was stirred well for 10-15 minutes. 1.52 g (0.02 mole) of thiourea dissolved in 50 ml methanol was added dropwise to the basic CS_2 solution. The temperature of the reaction mixture was maintained between 5-10° during this addition. The reaction solution turned yellow after complete addition of thiourea. Attempts to recover solid product from the reaction solution were unsuccessful. Therefore, the reaction solution was promptly reacted with a methanol solution of the metal ion for complexation.

ii) Synthesis of Complexes

The chelates of Fe(III), Co(II), Cu(II) and Zn(II) ions with thiocarbamate

myldithiocarbamate were synthesised by a general procedure using methanol solutions of the respective metal chlorides. A methanol solution of metal chloride (0.004 mole) in 100 ml solvent was dropwise added to 25 ml of freshly prepared ligand (0.008 mole) solution in the same solvent. The complexes instantaneously precipitated, they were filtered and dried at 60-70° in a drying cabinet. These were finally dried in a vacuum oven at 40°.

iii) Analysis of Complexes

The complexes were analysed for metals, nitrogen and sulphur contents. The metal content of the complexes were estimated by atomic absorption spectrophotometer Hitachi Model 170-10. An accurately weighed samples of the complex was decomposed by digesting with 3:1 mixture of concentrated HNO₃ and H₂SO₄. The mixture was heated to dryness. To the residue acid mixture was again added and heated to dryness. The residue was dissolved in water and diluted to a known volume. The absorbance of these solutions alongwith a set of standard solutions of the appropriate metal ions were measured at specific wavelengths on the atomic absorption spectrophotometer.

The amount of sulphur in the complexes was determined by oxidizing organic sulphur to sulphate ion by means of sodium peroxide and then precipitating it as barium sulphate. The percentage of nitrogen was estimated by a conductometric titration of the complex ion solution with perchloric acid in acetic acid medium [10].

iv) Antibacterial activity of the complexes

It was determined on nutrient Agar medium. This medium was prepared by dissolving agar (0.7%) in water,

then sterilizing it in an autoclave and uniformly pouring in a petri dish. Finally the medium was allowed to solidify and incubated at 37° for 24 hours. Cultures of appropriate bacteria were spread all over the surface of the medium with the help of a wire loop, aseptically. Sterile discs of 3-4 mm diameter (prepared from Whatman filter paper No.1) already soaked with solutions of metal complexes were placed over the surface of medium and lightly pressed. These plates were then incubated at 37° and kept under observation for 24-48 hours. Antibacterial activity was indicated by a clear zone encircling the discs where no growth was found, beyond that a homogenous confluent lawn of bacterial growth was produced.

Antibacterial activity of [Fe(tedtc)₂Cl.H₂O], [Co(tedtc)₂(H₂O)₂], H₂O and [Cu(tedtc)₂(H₂O)₂] was tested using 50 ppm solutions of complexes in ethyl acetoacetate. These solutions were further diluted to 5, 0.5 and 0.05 ppm using 10% aqueous ethanol as solvent. The activity was tested against Escherichia coli, Bacillus subtilis, Vibrio cholera and Staphylococcus aureus.

v) Instrumentation

These complexes were characterized by means of a number of instrumental techniques. The melting points were determined on melting point apparatus using capillary method. Solution spectra in the UV-Visible region of the complexes were obtained on Hitachi model 100-50 spectrophotometer. The complexes were dissolved in ethyl acetoacetate. The concentrations of these solutions were between 10⁻² -10⁻³ M. A matched pair of quartz cuvettes of 1 cm thickness were used for recording the spectra. The infra-

Table-1: Properties, Analytical data, Conductance and Absorption Spectra of Thiocarbamylthiocarbamate Complexes.

Complex	Colour	m.p./ d.p. °C	Metal (%)		Nitrogen (%)		Sulphur (%)		Molar Conductance mho- Mole ⁻¹ cm ²	Absorption in Ethyl aceto- actate cm ⁻¹
			Found	Calc.	Found	Calc	Found	Calc.		
[Fe(C ₂ H ₃ N ₂ S ₂) ₂ Cl.H ₂ O]	Brown amorphous Solid	180	13.70	13.58	13.14	13.58	46.82	46.68	22	30,120
[Co(C ₂ H ₃ N ₂ S ₂) ₂ (H ₂ O) ₂ .H ₂ O]	Dark green	185	13.66	14.21	13.24	13.49	47.3	46.26	24	16,110 (28*) 16,610(sh)
[Cu(C ₂ H ₃ N ₂ S ₂) ₂ (H ₂ O) ₂]	Green	200	16.70	15.82	13.50	13.94	47.67	47.81	28	15,000(34*) 13,477(sh) 17,152(sh)
[Zn(C ₂ H ₃ N ₂ S ₂) ₂ .H ₂ O]	Colourless	230	17.01	16.91	13.80	14.55	50.50	49.87	47	--

* Extinction Coefficient, Sh = Shoulder

red spectra in the region 4000-300 cm^{-1} of solid complexes in KBr discs were recorded on Beckman model IR-20A spectrophotometer. These spectra were calibrated with a standard polystyrene film. Conductance of ethyl acetoacetate solutions was measured on a conductance bridge model YSI-31. The cell constant was determined using a set of aqueous solutions of KCl of known strength.

Results and Discussion

The ligand, thiocarbamyldithiocarbamate could not be isolated from its reaction mixture and is unstable just like its other analogues derived from monoalkyl amines. However coordination compounds of this ligand with metal ions such as Fe^{3+} , Co^{2+} , Ni^{2+} and Zn^{2+} were readily precipitated out from the methanolic ligand reaction mixture by adding solutions of appropriate metal halides in the same solvent. These complexes are brown to dark green amorphous solids except $[\text{Zn}(\text{tc}(\text{dtc})_2)_2 \text{H}_2\text{O}]$ (colorless) and decompose between 180-230°. The compounds are insoluble in water and many organic solvents. However, they readily dissolve in ethyl acetoacetate. These compounds were characterized by elemental analysis, conductance, and spectral studies in UV-Vis and infra-red region. The colours, decomposition points, analytical data, conductance and absorption band data of these complexes are reported in Table 1. The elemental analysis reveals that two $\text{tc}(\text{dtc})_2$ ligands are attached to each metal ion. The ferric complex has a chloride ion attached to the metal ion. In addition, these complexes are associated with 1-3 water molecules. Solutions of these compounds in ethyl acetoacetate have molar conductances in the range 22-47 mho/mole which is substantially lower than

that expected for 1:1 electrolytes. Therefore these complexes are non-electrolytes and exist as neutral species in solution. It seems that $\text{tc}(\text{dtc})_2$ just like other dithiocarbamates, is acting as a bidentate ligand in these complexes. The complexes $[\text{Fe}(\text{tc}(\text{dtc})_2)_2 \text{Cl} \cdot \text{H}_2\text{O}]$, $[\text{Cu}(\text{tc}(\text{dtc})_2)_2 (\text{H}_2\text{O})_2]$ and $[\text{Co}(\text{tc}(\text{dtc})_2)_2 (\text{H}_2\text{O})_2] \text{H}_2\text{O}$ should have an octahedral geometry around the metal atoms with two water or chloride and a water molecule probably occupying trans positions. The complex $[\text{Zn}(\text{tc}(\text{dtc})_2)_2 \text{H}_2\text{O}]$ may be considered as four coordinated tetrahedral molecule.

The solution spectrum of the Co(II) complex consists of an asymmetric band centered at 16,110 cm^{-1} ($\epsilon=28$) and a shoulder near 16,610 cm^{-1} on the higher energy side. The position and intensity of these bands is typical of octahedral complexes. Ferguson et al. [11] have analysed the absorption spectrum of octahedral Co(II) complexes and assigned a band near 20,000 cm^{-1} ($\epsilon=5-40$) to the electronic transition $4T_{1g} \longrightarrow 4A_{2g}$ (P). The band observed at 16,110 cm^{-1} in the solution spectrum of $[\text{Co}(\text{tc}(\text{dtc})_2)_2 (\text{H}_2\text{O})_2] \text{H}_2\text{O}$ can be assigned to this electronic transition. The asymmetric nature of the band may be arising from lower symmetry of the molecule due to which triplet states split to give non-degenerate energy states. The shoulder at 16,610 cm^{-1} is probably due to a spin forbidden transition which was also observed by Ferguson. The solution spectrum of $[\text{Cu}(\text{tc}(\text{dtc})_2)_2 (\text{H}_2\text{O})_2]$ consists of a broad band centred at 15,000 cm^{-1} ($\epsilon=34$) with a tail in the near infrared

region which is reminiscent of tetragonally distorted complexes [12]. This absorption band is so broad that it covers nearly the whole visible region with slight shoulders at 13477 and 17152 cm^{-1} . This band seems to belong to ${}^2E_g \longrightarrow {}^2T_{2g}$ transition. However the shoulders and broad nature of the band indicates lower symmetry of the complex achieved through the ligands and distortion of the molecule. Therefore it is suggested that $[\text{Cu}(\text{tedtc})_2(\text{H}_2\text{O})_2]$ is a tetragonally distorted molecule with two water molecules in trans position. The $[\text{Fe}(\text{tedtc})_2 \cdot \text{Cl} \cdot \text{H}_2\text{O}]$ has no absorption in the visible region of spectrum. However it has a sharp, intense band centred at 30, 120 cm^{-1} due to a charge transfer transition. The high spin ferric complexes have A_{1g} ground state term and do not have any higher terms with the same spin. Therefore ferric complexes do not have spin allowed transitions and their absorption spectrum in the visible region usually consists of extremely weak and sharp bands due to forbidden transitions.

Since the ligand is unstable and could not be isolated, its infrared spectrum for comparison with that of complexes was not available. However infrared spectra of solid complexes were obtained and prominent bands along with their assignments are reproduced in Table 2. These spectra clearly show the existence of the thiocarbamyldithiocarbamate moiety in the complexes. Infrared spectra of these complexes are comparable to those of extensively studied complexes of dithiocarbamates. It is possible to assign some of the observed bands with certainty. The NH_2 stretching bands are observed in 3200-3400 cm^{-1} region

as broad strong peaks commonly found for primary amines. The NH bending is observed between 1600-1640 cm^{-1} . These bands fit very well in the expected range of free primary amines. Similarly the thiouride band near 1400 cm^{-1} is characteristic of dithiocarbamates and indicates considerable double bond character in $\text{N}=\text{C}=\text{S}$ bond [13]. All these complexes exhibit strong C=N stretching vibrations in 1600-1450 cm^{-1} region.

Bonati and Ugo [14] have analysed the (C=S) band observed near 1000 cm^{-1} for determining the mode of bonding of dithiocarbamates with metals. These workers have observed a single band near 1000 cm^{-1} for a bidentate bonded ($-\text{C} \begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{array} \text{M}$) dithiocarbamate and a doublet band in the same region for an ambidentate bonded ($-\text{C} \begin{array}{c} \text{S} \\ \diagdown \\ \text{S} \end{array} \text{M}$) ligand. The infra-red spectra of these complexes invariably exhibit a doublet band in 1010-1090 cm^{-1} indicating that one of the sulphur atoms (i.e. S_1 or S_2) of the dithiocarbamate group is not coordinated with the metal atom. Since metal-ligand vibrations are observed in the far infra-red region, this region of the spectra should provide more information about bond sites. The M-N stretching vibrations are commonly observed in 500-600 cm^{-1} region [15] whereas M-S vibrations are found in 300-400 cm^{-1} [13]. The ligand (tedtc) could coordinate through its S_1, S_3 or N_1, S_1 donor atoms forming six membered chelates. The far infra-red spectra of S_1, S_3 bonded thiocarbamyldithiocarbamate complexes should consist of bands in 300-400 cm^{-1} region whereas that of N_1, S_1 bonded com-

Table-2: Prominent Infra-red bands of Thioarbamyldithiocarbamate Complexes*

[Fe(tcdbc) ₂ Cl.H ₂ O]	[Co(tcdbc) ₂ (H ₂ O) ₂ .H ₂ O]	[Cu(tcdbc) ₂ -(H ₂ O) ₂]	[Zn(tcdbc) ₂ .H ₂ O]	Band Assignment
3400-3200(b)	3450-3200(b)	3300	3400-3100	N-H Stretch
1600	1620	1640	1610	NH ₂ deformation + C-N Stretch
1425	1400	1560	1450	C-N Stretch
1390	1370	1360	1390	C = S Stretch in N-C=S group
1110	1130	1140	1130	C-N Stretch (aliphatic)
1010(d)	1080(d)	1090(d)	1020(d)	C----S
770	820	800	780	-
405	360	400	380	M-S Stretch

* All bands are reported in cm⁻¹. b = broad, d = doublet.

pound should exhibit at least two bands due to M-S and M-N stretching vibrations in different regions. The newly synthesised complexes are found to be transparent in the 500-600 cm⁻¹ region, indicating that primary amine is not in a bonding position with the metals. This is also indicated from the observed stretching and bending vibrations of primary amine in these complexes. However single bands in the region 360-405 cm⁻¹, as expected for M-S vibrations, have been observed in all of these complexes.

These infra-red band assignments indicate that, tcdbc is coordinated to metals through two sulphur atoms (S₁, S₃) forming six membered chelates. Dithiocarbamates usually coordinate through two sulphur atoms of -CSS part forming planar four membered chelates which are not very stable. The ligand (tcdbc) has another equivalent sulphur atom in proper position to form six membered chelates with some pi-bonding in the ring. Such systems are expected to be more stable than dithiocarbamate chelates. In the light of the preceding discussion, it

Table-3: Antibacterial activity of Thiocarbamyl dithiocarbamate Complexes

Complex	Concentration (ppM)	Organism			
		<u>E.coli</u>	<u>B.subtilus</u>	<u>S.aureus</u>	<u>V.cholrea</u>
[Co(tcdtc) ₂ (H ₂ O) ₂]H ₂ O	50	+	+	±	+
	5	+	±	-	+
	0.5	-	-	-	±
	0.05	-	-	-	-
[Fe(tcdtc) ₂ Cl.H ₂ O]	50	±	±	-	-
	5	-	-	-	-
	0.5	-	-	-	-
[Cu(tcdtc) ₂ (H ₂ O) ₂]	50	±	+	±	+
	5	-	±	-	+
	0.5	-	-	-	±
	0.05	-	-	-	-

+ Antibacterial activity present.

± Antibacterial activity doubtful.

- Antibacterial activity absent.

is proposed that tcdtc is coordinated to the metal ions through its S₁, S₃ atoms (III). The complexes [Co(tcdtc)₂(H₂O)₂]H₂O,

[Fe(tcdtc)₂Cl.H₂O] and [Cu(tcdtc)₂(H₂O)₂] have an octahedral environment around the metals. The ligand is acting as a bidentate through its S₁, S₃ atoms. The remaining two coordination positions are occupied by water or chloride and water. Perhaps the two ambidentate ligands occupy

trans positions on the octahedron leading to a more stable complex. The complex [Zn(tcdtc)₂]H₂O is a 4-coordinated tetrahedral complex.

Antibacterial Activity

The antibacterial activity of complexes [Fe(tcdtc)₂Cl.H₂O], [Co(tcdtc)₂(H₂O)₂]H₂O and [Cu(tcdtc)₂(H₂O)₂] on agar medium was studied against Escherichia coli,

Bacillus subtilis, Staphylococcus aureus, and Vibrio cholera. The results are collected in Table 3. It is observed that the Co(II) complex is quite effective against Escherichia coli, Bacillus subtilis and Vibrio cholera in more concentrated solutions. This complex is ineffective against any bacteria below 5 ppm concentration. $[\text{Cu}(\text{tcdtc})_2(\text{H}_2\text{O})_2]$ shows activity against Bacillus subtilis, and Vibrio cholera in samples of maximum concentration. Its antibacterial activity is doubtful for Escherichia coli and Staphylococcus aureus. On the contrary, $[\text{Fe}(\text{tcdtc})_2\text{Cl}\cdot\text{H}_2\text{O}]$ is found ineffective against any of the bacteria under investigation. An ethyleneglycol solution of Cu(II) complex when treated with white yeast and incubated for 24 hours, caused some red pigmentation in their culture. This red pigment is difficult to identify.

These studies clearly demonstrate that complexes of thiocarbonyldithiocarbamate have some antibacterial activity.

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