



## STRUCTURAL ELUCIDATION OF TRANSITION METAL COMPLEXES OF MODIFIED DIAMINE ALONG WITH BIOASSAY STUDIES

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A number of complexes of modified diamine (3,7-dimethyl-1,5-dithia-3,7-diazacyclooctane), were prepared with first row divalent transition metals, i.e., Cu(II) and Zn(II). The structures of these complexes were elucidated on the basis of various physical techniques such as mass spectrometry, NMR, IR, UV-Visible spectroscopies, magnetic and conductance measurements. Bioassay of these complexes has also been carried out. The physical measurements confirm distorted tetrahedral structure for these complexes.

**Keywords :** Transition metals, Modified diamine, DTACO, Tetrahedral geometry, Bioassay

### 1. Introduction

The chelating characteristics of acyclic/cyclic diamines and amidines have been investigated in detail and a number of studies on metal complexes of these chelating agents have already been reported [1-3]. Medium-ring diamines (Mesocyclic) are versatile chelating agents and often confer various geometries on metal complexes, providing a link between acyclic and macrocyclic chelating agents for the trend in enforcing various geometries to coordination compounds. The molecular properties of the complexes formed by the mesocyclic are often controlled by their unique steric requirements and are different from the complexes of acyclic ligands.

In the last one and a half decade, extensive research work has been done on the coordination compounds of diamine, where  $\text{H}_2\text{N-NH}_2$  (hydrazine) is the basic unit. Several workers extended scientific work to the cyclic dithioethers (dithiocyclooctane) while modifying them by replacing amines with sulfur-donating moiety. The ability to impart several geometries as well as enhancing stabilities of the complexes by these diamines is due to specific steric requirements and their unusual chelate-bite angle. The maximum metal-ligand stability was achieved through multiple- (five or six) membered ring formation and/or due to effective shielding of axial positions of the central metal ions where eight-membered ring functions as a chelating agent in chair/boat

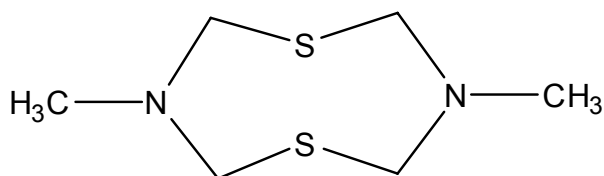
conformation. Two carbon chains can be on the same side of the plane (*cis*) formed by the four nitrogen atoms or they may be on the opposite sides of the plane (*trans*). Any twisting or change in conformation which opens the axial positions, increases inter- or intra-ligand interaction of the molecule. The daco (diazacyclooctane) where the axial positions are blocked, no octahedral complexes are obtained with nickel(II), copper(II) and cobalt(II). By altering this conformation, complexes of these metals with different structures were obtained. Many papers are available in literature and the researchers have exploited this factor by modifying these diamines [4,5]. The complexes prepared, so far, of these ligands are either pure diamines or dithioethers.

The modification of cyclic diamines continued to restrict the freedom of  $\text{C}_3$  and  $\text{C}_7$  of diazacyclooctane to make the space available for further coordination [6,7]. These various diamines (cyclic or acyclic) give unusual geometries to the metal ions, viz., tetrahedral, square planar or octahedral depending on the structure of diamine [8-13].

In the present work, we synthesized a chelating species retaining both thioether as well as diamine segments. We thought it of interest to synthesize and study the coordination compounds of modified diamine-3, 7-dimethyl-1, 5-dithia-3, 7-diazacyclooctane (DTACO). It can be viewed as eight-membered diazacyclooctane having thio groups.

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Sulphur atoms make it a tetradentate ligand.



3,7-dimethyl-1,5-dithia-3,7-diazacyclooctane

(DTACO)

## 2. Experimental

### 2.1. Materials and methods

All chemicals and solvents used were of AnalaR grade. Metal (II) salts of Cu and Zn were used as chlorides and bromides. Solvents were distilled at least twice before use. Elemental analyses were conducted at HEJ Research Laboratories, Karachi. Melting points of all complexes were recorded on Gallenkamp apparatus and were reported without correction.

### 2.2. Preparation of DTACO

The ligand DTACO was prepared according to the reported procedure [14]. Thirty percent aqueous methylamine (31 mL) solution was saturated with H<sub>2</sub>S at 0 °C and was added very slowly to a stirred mixture of 40% formaldehyde (14 mL) and water. After an hour, white precipitate was formed which was washed with water and dried in air. The precipitate was recrystallized from acetone. Needle-like crystals with melting point of 127-129 °C were obtained.

### 2.3. General procedure for the preparation of metal complexes

All complexes with DTACO were prepared using the same general procedure. The required amount of dehydrated salts was dissolved in a minimum amount of anhydrous ethanol or methanol. Dehydration of the metal salts was achieved using 2, 2-dimethoxy propane as dehydrating agent. The solution was stirred for about half an hour in order to ensure complete dehydration. Ligand solution (2:1 mole ratio) was added slowly to the metal salt solution with constant stirring. The solid complex was obtained immediately on mixing or by reducing the volume of the solution on rotary evaporator. The products were filtered through sintered glass crucible, washed several times with n-hexane or dry ethanol and then dried under vacuum.

### 2.4. Instrumentation

The <sup>1</sup>H and <sup>13</sup>C NMR in CCl<sub>4</sub> for ligand are obtained with Bruker (AM 400) using TMS as an internal standard. Infrared spectra were taken in the range of 4000-600 cm<sup>-1</sup> on PYE UNICAM Infrared Spectrophotometer as KBr disc. The far IR spectra were also examined as KBr discs in the region of 400- 200 cm<sup>-1</sup> (FT-IR SHIMADZU). The absorption spectra of solution of complexes in the range of 200-900 nm using different solvents, were obtained on Jasco DEC-1 Spectrophotometer with 1 cm matched quartz cells. Mass spectrum was recorded with MAT 312 mass spectrophotometer. Molar conductance of the solution of the metal complexes was performed with a conductivity meter type HI 8333. All measurements were taken at room temperature on freshly prepared solutions. Magnetic susceptibilities were measured by Gouy's method at ambient temperature using Hg[Co(SCN)<sub>4</sub>] as standard [15]. The magnetic moments were calculated. The cations and anions were estimated by using standard analytical procedures.

### 2.5. Biological activities

The biological activities of the complexes are also carried out and the results are reported in Table 5. The complexes were screened for antibacterial and antifungal activities against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, *Enterobacter aerogenes*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Candida albicans*.

In order to check the antibacterial/antifungal activity, discs of 100µg of compounds were made in distilled water. Two to eight hours old bacterial inoculums containing 10<sup>4</sup> – 10<sup>6</sup> colony forming units (CFU)/ml were used in these assays. The wells were dug in the agar media using a sterile metallic borer with centers at least 24 mm. Recommended concentration (100 µL) of the test sample (1 mg/mL in DMSO) was introduced into the respective wells [22]. Other wells were supplemented with DMSO and reference antibacterial drug, imipenem, served as negative and positive controls respectively. These discs/plates were placed in incubator for 24 hours at 37 °C for drying. After that, sensitivity tests were conducted. Media for different types of bacteria used were blood, agar and nutrient agar. The zone inhibition was then measured (in diameter) around the discs.

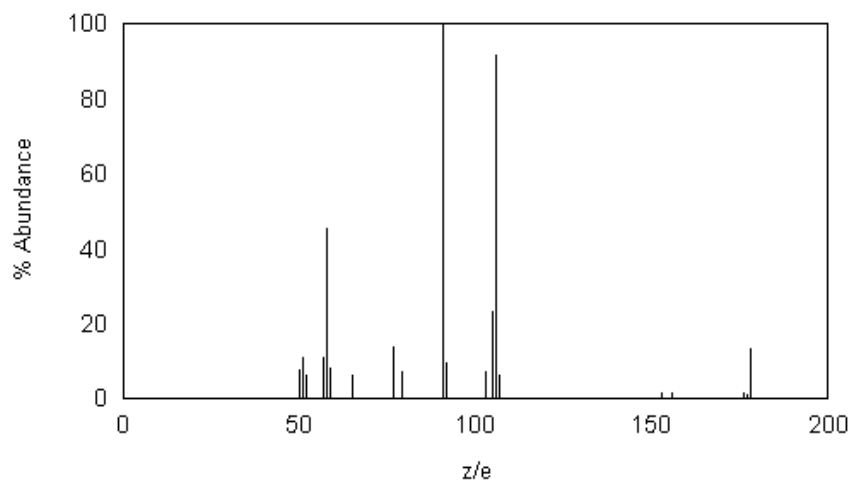


Figure 1. Mass spectrum of DTACO

Table 1. Analytical data of DTACO and its complexes.

Complexes	Color	M.Pt. °C	C (%)	H (%)	N (%)	S (%)	Cation (%)	Anion (%)
(DTACO)	White	127-129	40.5 (40.4)	8.1 (7.9)	15.8 (15.7)	35.8 (35.9)	---	---
[Cu(DTACO)Cl <sub>2</sub> ]	Brown	120	24.4 (23.0)	3.7 (4.5)	8.7 (8.9)	20.8 (20.5)	20.8 (20.3)	23.1 (22.7)
[Cu(DTACO)Br <sub>2</sub> ]	Brown	100	18.2 (17.9)	3.7 (3.5)	7.2 (7.0)	15.8 (15.9)	16.5 (15.9)	40.5 (39.8)
[Cu(DTACO)(NO <sub>3</sub> ) <sub>2</sub> ]	Brown	130	19.5 (19.7)	3.6 (3.8)	15.2 (15.5)	17.0 (17.5)	15.0 (17.3)	---
[Zn(DTACO)Cl <sub>2</sub> ]	White	250	29.5 (29.8)	4.1 (4.5)	6.6 (8.8)	21.7 (20.4)	22.0 (22.8)	23.6 (22.5)
[Zn(DTACO)Br <sub>2</sub> ]	White	260	18.2 (17.9)	2.2 (3.5)	7.2 (6.9)	15.6 (15.8)	17.5 (16.2)	39.3 (39.6)
[Zn(DTACO)(NO <sub>3</sub> ) <sub>2</sub> ]	White	>300	19.8 (19.6)	3.5 (3.8)	15.2 (15.2)	17.3 (17.4)	17.2 (17.8)	---

Calculated values are given in parentheses.

The nitrate could not be determined for the lack of facility

### 3. Results and Discussion

#### 3.1. Ligand

The DTACO ligand was characterized by elemental analyses, mass spectrum and NMR (<sup>1</sup>H and <sup>13</sup>C). The elemental analyses of carbon, hydrogen and nitrogen along with cations and anions are well in agreement with the calculated values. The M<sup>+</sup> peak for the DTACO appears at z/e 178 as shown in Fig. 1.

The <sup>1</sup>H-NMR shows two peaks at 2.3 and 5.2 ppm corresponding to the hydrogens of methyl attached to amine and that of methylene of the

diazacyclic ring, respectively. The intensity ratios and coupling constants are in agreement with their population. The <sup>13</sup>C NMR spectrum shows two single peaks at 43 and 62 ppm. The former peak corresponds to methyl carbons and the latter to methylene carbons. The elemental analyses data of DTACO and its complexes are presented in Table 1. The ligand DTACO behaves as a bidentate ligand and bears resemblance to various diamines and their derivatives. Molar conductance and magnetic moment values are listed in Table 2. The molar conductance values indicate that the complexes are non-electrolytic. The infrared study of the complexes reveals that there is shift and

Table 2. Conductance and magnetic moments data of complexes.

Complex	Solvent	Molar Conductance (S/cm)	Cor x M x 10 <sup>-6</sup> (c.g.s)	$\mu_{\text{eff}}$ (B.M.)
[Cu(DTACO)Cl <sub>2</sub> ]	DMF	2.84	376.0	1.25
[Cu(DTACO)Br <sub>2</sub> ]	DMF	56.6	291.7	1.33
[Cu(DTACO)(NO <sub>3</sub> ) <sub>2</sub> ]	DMF	56.6	212.4	1.34
[Zn(DTACO)Cl <sub>2</sub> ]	DMF	4.23	180.4	Dia-magnetic
[Zn(DTACO)Br <sub>2</sub> ]	DMF	6.31	207.6	Dia-magnetic
[Zn(DTACO)(NO <sub>3</sub> ) <sub>2</sub> ]	DMF	8.16	174.3	Dia-magnetic

DMF = Dimethyl formamide

Table 3. IR Spectra for DTACO and its complexes (cm<sup>-1</sup>) of selected region.

Complex	N-C Stretching frequency	C-S Stretching frequency	Other bands	M-X
DTACO	1330 sh	670 m	1260, 960, 725	400s
[Cu(DTACO)Cl <sub>2</sub> ]	1370 bd	670 bd	1105, 1120, 725	400s
[Cu(DTACO)Br <sub>2</sub> ]	1365 bd	670 m	1100, 1120, 1040, 725	400s
[Cu(DTACO)(NO <sub>3</sub> ) <sub>2</sub> ]	1390 bd	670 m	1270, 1210, 725	400s
[Zn(DTACO)Cl <sub>2</sub> ]	1375 bd	670 m	1110, 1070, 1040, 725	400s
[Zn(DTACO)Br <sub>2</sub> ]	1370 bd	670 m	1110, 790, 725	400s
[Zn(DTACO)(NO <sub>3</sub> ) <sub>2</sub> ]	1375 bd	670 m	1110, 1040, 725	400s

sh = sharp    m = medium    s = small    bd = broad    M-X where M= Cu(II), Zn(II) and X= Cl<sup>-</sup>, Br<sup>-</sup>, NO<sub>3</sub><sup>-</sup>

change in broadness of C-N frequency around 1330 cm<sup>-1</sup> whereas that of C-S frequency at 670 cm<sup>-1</sup> remains unaltered, showing non-involvement of sulphur in coordination. The far IR spectra show the M-X (metal-anion) bonding. The relevant data are given in Table 3.

### 3.2. Copper complexes

The Cu (II) complexes exhibit absorption bands in the region 10000-19000 cm<sup>-1</sup>. The envelopes of these bands are generally unsymmetrical seeming to encompass several overlapping transitions. The spectra of these complexes are characteristically different from those of square planar complexes of 1,4-diazacycloheptane (DACH) and 1,5-diazacyclooctane (DACO) (3,4). The absorption band for the copper coordinated complex by

DTACO is similar to the band observed for the complex of 1,5-diazacyclooctane diacetate [Cu(daco-diac)<sub>2</sub>X<sub>2</sub>] [14]. The visible spectrum of copper DTACO complexes is shown in Fig. 2. The magnetic moment is around 1.25-1.34 B.M. which is very close to the spin-only value for the unpaired electron. The conductance behavior hints at non-electrolytic nature of the complexes. On the basis of spectral measurements, a distorted tetrahedral structure may be assigned.

### 3.3. Zinc complexes

The conductance data of Zn(II) complexes indicate the non-ionic species. As the complexes of the cyclic diamines have not been reported so far, however, they can be compared with cyclic amidines. In view of the well-known tendencies of

Table 4. Electronic absorption data of DTACO complexes.

Complex	Solvent	$\lambda_{\text{max}}$	$\nu_{\text{cm}^{-1}}$	Comments
[Cu(DTACO)Cl <sub>2</sub> ]	DMF	530 755 910	18800 13200 10900	d→d
[Cu(DTACO)Br <sub>2</sub> ]	DMF	530 680 740	18800 14700 13500	d→d
[Cu(DTACO)(NO <sub>3</sub> ) <sub>2</sub> ]	DMF	530 700 800	18800 14200 12500	d→d

Table 5. Biological activities of complexes.

Compound	<i>Escherichia coli</i> (mm)	<i>Staphylococcus aureus</i> (mm)	<i>Salmonella typhi</i> (mm)	<i>Enterobacter aerogenes</i> (mm)	<i>Proteus vulgaris</i> (mm)	<i>Pseudomonas aeruginosa</i> (mm)	<i>Candida albicans</i> (mm)
DTACO	5	0	0	10	0	0	0
[Cu(DTACO)Cl <sub>2</sub> ]	17	26	16	17	19	19	19
[Cu(DTACO)Br <sub>2</sub> ]	16	20	0	0	20	13	12
[Cu(DTACO)(NO <sub>3</sub> ) <sub>2</sub> ]	23	21	14	12	10	12	18
[Zn(DTACO)Cl <sub>2</sub> ]	15	20	16	15	14	22	15
[Zn(DTACO)Br <sub>2</sub> ]	20	23	22	17	14	19	21
[Zn(DTACO)(NO <sub>3</sub> ) <sub>2</sub> ]	14	12	19	12	10	11	12

Diameter in mm around the disk: >15mm = Significant Activity; 7-14mm = Moderate Activity; <7mm = Weak Activity

Gram Negative: *Escherichia coli*, *Salmonella typhi*, *Enterobacter aerogenes*, *Proteus vulgaris*, *Pseudomonas aeruginosa*.

Gram Positive: *Staphylococcus aureus*.

Fungus: *Candida albicans*.

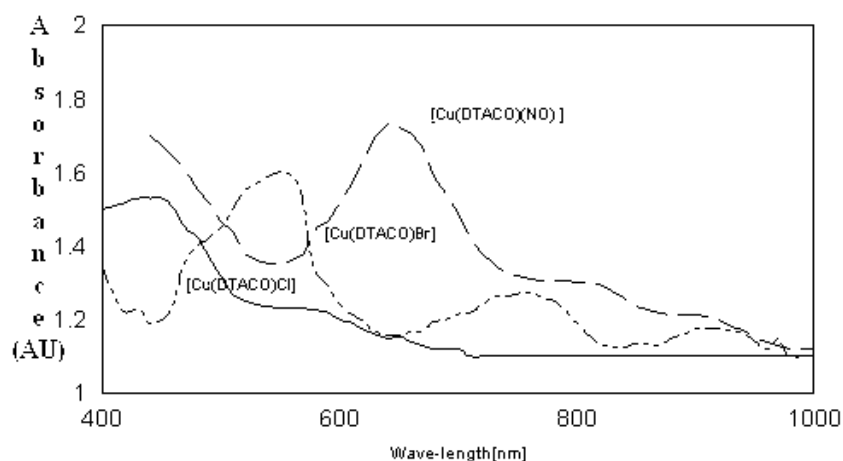


Figure 2. UV visible spectra of Cu(II) complexes of DTACO

Zn(II) to form tetrahedral complexes [6,16,17], same structure may be proposed for Zn(II) DTACO complexes with DTACO acting as bidentate ligand. Trzaskowski et al. observed by density functional calculations that deprotonated serine and cysteine,

which are close in structural features to DTACO, forms tetrahedral geometry around the zinc(II) ion with only four ligands around the metal ion [18]. These calculations are in agreement with the known experimental crystal structures of some

zinc-containing complexes. Dudev et al using Continuum Dielectric Calculations showed that zinc monochloride and dichloride *tetrahedral* complexes were calculated to be more stable than the respective *octahedral* complexes by -4.5 and 8.6 kcal/mol, respectively, at the B3LYP/6-31++G (2d,2p) level. Furthermore, stationary points for zinc octahedral complexes containing three or four Cl<sup>-</sup> could not be found since they isomerized into tetrahedral (4+2) complexes during optimization [19]. Roe et al. also showed that tetrahedral geometry for the zinc complexes are the most stable ones [17]. This geometry would also be consistent with the non-electrolytic behavior of the complexes [19].

### 3.4. Biological activities

The DTACO ligand and its metal complexes were screened for antibacterial activity against Gram Negative bacterial strains such as *Escherichia coli*, *Salmonella typhi*, *Enterobacter aerogenes*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, Gram Positive bacterial strain such as *Staphylococcus aureus* and Fungus such as *Candida albicans*.

The results obtained show that the metal complexes become more biologically active as compare to neat organic moiety. According to Meggers et.al complexes like [Cu(DTACO)Cl<sub>2</sub>] and [Zn(DTACO)Cl<sub>2</sub>] were found to be more active against both gram positive and gram negative bacteria as well as the fungus. [Cu(DTACO)Br<sub>2</sub>] is found to be less active against the bacterial and fungal strains. [Cu(DTACO)(NO<sub>3</sub>)<sub>2</sub>], [Zn(DTACO)Br<sub>2</sub>] and [Zn(DTACO)(NO<sub>3</sub>)<sub>2</sub>] are found to be moderately active. It means that metal centers increases the antimicrobial activity of certain organic molecules like DTACO [20, 21].

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