

## Synthesis and spectral characterization of copper(II) complexes of dithiosemicarbazone

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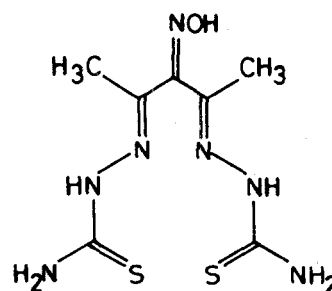
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The complexes of Cu(II) with isonitrosoacetylacetone dithiosemicarbazone of the type  $[Cu(INacacBT)X_2]$  (where  $X = Cl^-, Br^-, NO_3^-, OAc^-$ ) have been synthesized and characterized on the basis of analytical, magnetic, infrared, electronic and electron spin resonance spectral data. The non-electrolytic complexes exist in six coordinate distorted octahedral symmetry with the ligands, chelated through the azomethine nitrogen and thiocarbonyl sulphur atoms.

The ligand thiosemicarbazone forms coloured complexes with metal ions in solution<sup>1</sup>. The medicinal properties exhibited by these ligands have been thought to be due to their ability to chelate trace metals. Liebermeister<sup>2</sup> showed that copper ions enhance the anti-tubercular activity of *p*-acetamidobenzaldehyde thiosemicarbazone. Similarly, the active intermediate in the anti-tumor activity of 3-ethoxy-2-oxobutyraldehyde bis(thiosemicarbazone) was shown to be due to its Cu(II) chelate<sup>3,4</sup>. An excellent review on the structure-activity relationships amongst thiosemicarbazone compounds has recently appeared<sup>5</sup>. Owing to the importance of the above ligands in chelation and therapy, we thought it worthwhile to study the structure of copper(II) complexes of isonitrosoacetylacetone dithiosemicarbazone (INacacBT) (Structure I). The complexes were isolated and characterized by elemental analysis, conductivity, magnetic susceptibility and spectral (infrared, electronic and electron spin resonance) measurements. The preliminary screening of the Cu(II) complexes for antibacterial, antifungal and anti-tubercular activity has been reported.

### Materials and Methods

The solvents used for the synthesis of ligand and its complexes were distilled before use. Acetylacetone and thiosemicarbazide (both from BDH) were employed for the synthesis of ligand. Isonitrosoacetylacetone was prepared from acetylacetone and sodium nitrite in the presence of dilute sulphuric acid by the



INacacBT

(I)

known method<sup>6</sup> (m.p. 73°C, yield 86%). The dithiosemicarbazone was synthesized by condensing the isonitrosoacetylacetone (12.9 g, 1 mmol) and the thiosemicarbazide (18.2 g, 0.2 mmol)<sup>7</sup>. The reddish brown coloured crystals of the ligand were purified by recrystallization from alcohol (m.p. 173°C, yield 60%).

The copper(II) complexes of isonitrosoacetylacetone dithiosemicarbazone (INacacBT) were synthesized by adding a hot ethanolic solution of  $CuCl_2 \cdot 2H_2O$  (1 mmol) to a hot ethanolic solution of the ligand (1 mmol) and refluxed for 30 min. The brown coloured complex which separated was filtered, washed with water, alcohol and ether. It was dried over anhydrous  $CaCl_2$  *in vacuo*, yield 85-87%.

The Cu(II) complexes were analyzed for metal, nitrogen, carbon, hydrogen and sulphur by standard methods<sup>8</sup>. The conductivity measurements were carried out on Elico conductivity bridge CM-82 in  $10^{-3}$  M DMF solution. The infrared spectra of the ligands ( $4000-400$   $cm^{-1}$ ) and complexes were recorded on

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Perkin Elmer Model 983 instrument using KBr pellet method. The far infrared spectra of the ligands and a few representative complexes were scanned on fourier far IR instrument for solid samples suspended on polyethylene plates in nujol mull. The magnetic susceptibility measurements at room temperature were carried out by Gouy method using  $[\text{HgCo}(\text{SCN})_4]$  as the calibrant. The UV-VIS-near IR spectra (300-1250 nm) of the complexes in DMF were taken on Carl-Zeiss VSU-2P spectrophotometer. The electron spin resonance powder spectra of Cu(II) complexes were recorded at 298°K on Varian E-4, x-band ESR spectrometer using cylindrical quartz sample tube, operating at 9.32 GHz. Diphenyl picryl hydrazyl (DPPH) free radical was used as 'g' marker.

The antibacterial activity of the ligands and their metal complexes was assayed against *E. coli* (gram -ve), *Staphylococcus aureus* and *Bacillus subtilis* (gram + ve) microorganisms. The preparation of subcultures, drug solution and the method of testing were as per the standard methods<sup>9</sup>. A 5% aqueous phenol solution was employed as the reference for computing the inhibition values. The antifungal activity of the ligands and their copper complexes was evaluated against the pathogenic fungi *Aspergillus niger*, *Candida albicans* and *Aspergillus flavus*. The fungal growth inhibitory action of these compounds was measured by turbidity method using Klett-Sommerson colorimeter. An aqueous salicylic acid (5%) was used as the standard and DMF as solvent control. *In vitro* antitubercular screening was made against H<sub>37</sub>Rv strain of *Mycobacterium tuberculosis* by the method of Doub and Youmans<sup>10</sup>. For the preparation of inoculum, a loopful of 14 days old growth of *M. tuberculosis* in Lowenstein-Jensen medium was transferred to Youmans medium (10 ml) and incubated at 37°C for 21 days. The strength of the culture at the end of the incubation period was adjusted to approximately  $1 \times 10^6$  viable organisms/ml by diluting it with Yo-

umans medium and comparing it with Browns opacity tube No.4. This standardized culture was then used as inoculum. Control tubes with isoniazid and *para*-amino salicylic acid as standard drugs were used.

### Results and Discussion

The amorphous  $[\text{Cu}(\text{INacacBT})\text{X}_2]$  complexes are insoluble in common organic solvents, but partially soluble in DMF and DMSO. Due to the limited solubility in organic solvents, molecular weights by cryoscopic method could not be determined. The molar conductance values of the brown Cu(II) complexes lie in the range  $22\text{-}53 \Omega^{-1}\text{cm}^2\text{mol}^{-1}$  ( $10^{-3}$  M in DMF) indicating their non-electrolytic behaviour. The physical and analytical data of the complexes are presented in Table 1.

The infrared spectrum of INacacBT in KBr shows a medium sharp absorption band at  $3370 \text{ cm}^{-1}$  which may be attributed to the intramolecular hydrogen bonded OH stretching frequency of the =NOH group<sup>11</sup>. This frequency remains almost unaltered in the complexes suggesting its non-involvement in coordination. The bands at  $3260 \text{ cm}^{-1}$  and  $3170 \text{ cm}^{-1}$  are assigned to  $\nu\text{NH}$  stretching frequency of amino and imino groups. These bands appear at the same positions even on complexation indicating that terminal  $\text{NH}_2$  groups are not-coordinated to the metal. The shift to higher wavenumbers of  $\nu\text{C}=\text{N}$  stretching vibrations ( $\sim 1610 \text{ cm}^{-1}$ ) of the order of  $15\text{-}65 \text{ cm}^{-1}$  and in  $\nu\text{N-N}$  vibrations ( $\sim 860 \text{ cm}^{-1}$ ) to the extent of  $4\text{-}25 \text{ cm}^{-1}$  support nitrogen coordination of  $\text{C}=\text{N}$  group<sup>12,13</sup>. The non-participation of oximino nitrogen in coordination is concluded from the unaltered position of  $\nu\text{NO}$  ( $1000 \text{ cm}^{-1}$ ) frequency. A shift to lower wavenumbers pertaining to  $\nu\text{CS} + \nu\text{CN}$  ( $762 \text{ cm}^{-1}$ ) and the thiocarbonyl  $\nu\text{CS}$  ( $720 \text{ cm}^{-1}$ ) vibrations of  $12\text{-}55 \text{ cm}^{-1}$  support the coordination of thioketo sulphur atom. Hence the infrared studies reveal the

Table 1—Analytical data of copper(II) complexes

Complex (m.pt. °C)	Found (calc.), %						$\lambda\text{M}$ in DMF $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$	$\mu_{\text{eff}}$ BM
	Cu	N	S	C	H	Cl		
$[\text{Cu}(\text{INacacBT})\text{Cl}_2]$ 244(d)	15.40 (15.41)	23.75 (23.92)	15.48 (15.65)	20.38 (20.52)	3.14 (3.20)	17.19 (17.30)	17.1	1.8
$[\text{Cu}(\text{INacacBT})\text{Br}_2]$ 320(d)	12.63 (12.74)	19.49 (19.66)	12.68 (12.86)	16.71 (16.86)	2.57 (2.63)	—	53.7	2.0
$[\text{Cu}(\text{INacacBT})\text{SO}_4]$ 320(d)	14.49 (14.61)	22.38 (22.54)	22.02 (22.11)	19.31 (19.33)	2.89 (3.01)	—	43.9	2.0
$[\text{Cu}(\text{INacacBT}) (\text{NO}_3)_2]$ 320(d)	13.60 (13.73)	27.09 (27.23)	13.71 (13.85)	18.01 (18.16)	2.74 (2.83)	—	27.9	2.0
$[\text{Cu}(\text{INacacBT}) (\text{OAc})_2]$ 290(d)	13.82 (13.91)	21.33 (21.46)	13.89 (14.03)	28.75 (28.91)	4.11 (4.19)	—	22.3	1.8

tetradentate nature of the ligand with bonding taking place through two sulphur atoms of two  $>C=S$  groups and two nitrogen atoms of two  $>C=N$  groups. This is also supported by the strong  $\nu_{M-S}$  ( $375\text{ cm}^{-1}$ ) and  $\nu_{M-N}$  ( $488\text{ cm}^{-1}$ ) bands appearing in the far infrared spectra of the complexes. The  $\nu_{asy}OCO$  and  $\nu_{sym}OCO$  bands appear at  $1560$  and  $1378\text{ cm}^{-1}$  respectively. The difference of  $182\text{ cm}^{-1}$  between these two bands in the  $[Cu(INacacBT)(OAc)_2]$  complex suggests unidentate coordination of the acetate ion in this complex<sup>14</sup>. The  $[Cu(INacacBT)(NO_3)_2]$  complex exhibits bands due to nitrate ion at  $1465\text{ sh}$  ( $\nu_1$ ),  $1050\text{ ms}$  ( $\nu_2$ ),  $746\text{ mbr}$  ( $\nu_3$ ),  $1328\text{ s}$  ( $\nu_4$ ),  $710\text{ vs}$  ( $\nu_5$ ) and  $840\text{ brs}$  ( $\nu_6$ ) respectively. The separation between  $\nu_1$  (symmetric stretching) and  $\nu_4$  (doubly degenerate in plane bending) amounts to  $137\text{ cm}^{-1}$  which is in the range for a monodentate nitrate coordination<sup>15,16</sup>. The sulphate anion may coordinate in one of the three ways, unidentate ( $C_{3v}$  symmetry) bidentate ( $C_{2v}$  symmetry) or as bridging ( $C_{2v}$  symmetry). The fundamental bands due to  $SO_4^{2-}$  in  $[Cu(INacacBT)SO_4]$  complex appear at  $972\text{ cm}^{-1}$  ( $\nu_1$  singlet)  $1150$ ,  $1110$  and  $1090\text{ cm}^{-1}$  ( $\nu_3$  triplet) and  $665$ ,  $620\text{ cm}^{-1}$  ( $\nu_4$  doublet). The  $\nu_2$  band was not observed. As the complex is a non-electrolyte, the ionic nature of the sulphate is ruled out. Hence the sulphate has  $C_{2v}$  symmetry and acts as bidentate. Similar observations have been reported in the literature<sup>17,18</sup>.

The corrected values of magnetic moments of Cu(II) complexes vary in the range  $1.82$ - $2.04$  B.M. which are higher than the spin-only value of  $1.73$  B.M. for one unpaired electron. This reveals that these complexes are monomeric in nature and the absence of metal-metal interaction along the axial positions. However, the slightly higher  $\mu_{eff}$  values indicate quenching of orbital moment to some extent.

The assignment of transitions in the electronic spectra of copper(II) - INacacBT complexes is based on the molecular model proposed by Ballhausen and Gray<sup>19</sup>. The Cu(II) complexes are subjected to considerable Jahn-Teller distortion (since the ground state is  $E_g$ ) which renders their absorption spectra quite complex and in practice no regular octahedral configuration for Cu(II) has been observed.

The principal absorption bands are expected are due to the transition  ${}^2A_{1g} \leftarrow {}^2B_{1g}$ ,  ${}^2B_{2g} \leftarrow {}^2B_{1g}$  and  ${}^2E_g \leftarrow {}^2B_{1g}$  in the order of increasing energies. The energy level sequence will depend on the amount of distortion due to ligand field and Jahn-Teller effect<sup>20,21</sup>. In Cu(II) complexes, the latter two transitions merge and only two bands appear in the region  $14285$ - $15037\text{ cm}^{-1}$  and  $20000$ - $21730\text{ cm}^{-1}$  in DMF;  $14705$ - $15151\text{ cm}^{-1}$  and  $17391$ - $20661\text{ cm}^{-1}$  in nujol mull. In addition to these bands, a band at  $27000\text{ cm}^{-1}$  is attributed to the  $d-\pi^*$

charge-transfer transition<sup>20</sup>. These three components may be assigned as transitions from the  $d_{xy}$ ,  $d_{z^2}$  and  $d_{xz}$ ,  $d_{yz}$  pair to the  $\sigma$ -antibonding and half-filled  $d_{x^2-y^2}$  level<sup>22</sup>. Unfortunately, it is not possible to determine the values of the interelectronic repulsion parameters, since all the  $d-d$  transitions take place within components of the same free ion term  ${}^2D$  (ref. 23). On the basis of analytical and infrared spectral data, a six-coordinate distorted octahedral symmetry can be proposed for the Cu(II) complexes.

The ESR spectra recorded on polycrystalline samples are depicted in Fig. 1. The complexes possess a characteristic spectrum having one asymmetric band with two  $g$  values. The  $g_{||}$  and  $g_{\perp}$  values were computed from the spectrum using DPPH free radical as 'g' marker. The ESR spectra are interpretable in terms of an effective spin of  $1/2$ . The 'g' values and Spin-Hamiltonian parameters are summarized in Table 2. Kivelson and Neiman<sup>24</sup> have reported that  $g_{||}$  value is  $< 2.3$  for covalent character of the metal-ligand bond and  $\geq 2.3$  for ionic character. Applying this criterion, the covalent character of the metal-ligand bond in the complexes under study can be predicted. The trend  $g_{||} > g_{\perp} > g_e$  ( $2.0023$ ) observed for these complexes shows that the unpaired electron is localized in  $d_{x^2-y^2}$  orbital<sup>25</sup> of the copper(II) ion and the spectral features are characteristic of axial symmetry. Further, the shape of the ESR lines indicate that the geometry around the Cu(II) ions is not trigonal bipyramidal in these complexes since the low field side of ESR spectra is less intense than the high field side<sup>26</sup>. The present complexes may have either a square pyramidal, square planar or an elongated octahedral geometry as is evident from the spectral nature. However, the values (Table 2) indicate a six coordinate geometry, thus ruling out the former two possibilities. In addition, there is an exchange coupling between the two copper cent-

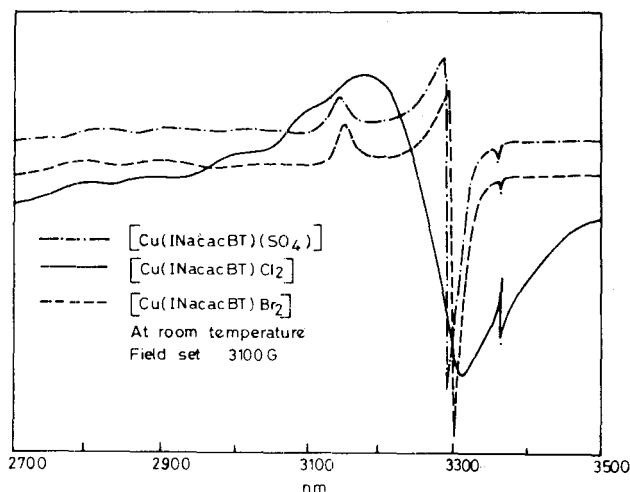


Fig. 1—ESR spectra of Cu(II)-INacacBT complexes

Table 2—ESR spectral parameters of Cu(II)-INacacBT complexes

Complex	$g_{\perp}$	$g_{\parallel}$	$g_{av}$	$\alpha^2$	$\lambda'$ ( $\text{cm}^{-1}$ )	$A_{\parallel} \times 10^4$ $\text{cm}^{-1}$	$G = \frac{g_{\parallel} - 2}{g_{\perp} - 2}$
[Cu(INacacBT)Cl <sub>2</sub> ]	2.06	2.21	2.11	0.66	403.6	139.4	3.3
[Cu(INacacBT)Br <sub>2</sub> ]	2.04	2.14	2.07	0.58	259.0	139.5	3.6
[Cu(INacacBT)SO <sub>4</sub> ]	2.04	2.14	2.07	0.57	267.0	139.6	3.5
[Cu(INacacBT) (NO <sub>3</sub> ) <sub>2</sub> ]	2.06	2.22	2.12	0.67	417.3	134.8	3.4
[Cu(INacacBT) (OAc) <sub>2</sub> ]	2.05	2.19	2.10	0.86	366.7	220.0	3.8

$$A_{\parallel} (\text{cm}^{-1}) = [g \times 4.6688 \times A(G)] \times 10^{-5}; g \text{ is } g_{\parallel} \text{ value}$$

Table 3—Biological activity of isonitrosoacetylacetone dithiosemicarbazone and its copper(II) complexes

Complex No.	Antibacterial			Antifungal			Antitubercular <i>M. tuberculosis</i> (mic in $\mu\text{g/ml}$ )
	<i>E. Coli</i> (% inhibition)	<i>S. aureus</i> (% inhibition)	<i>B. subtilis</i> (% inhibition)	<i>A. niger</i> (% inhibition)	<i>C. albicans</i> (% inhibition)	<i>A. flavus</i> (% inhibition)	
INacacBT	15.7 (19.3)	23.7 (23.8)	18.9 (22.4)	45.8 (49.0)	26.4 (31.1)	24.1 (29.6)	100
1	28.0 (28.1)	27.1 (35.6)	18.9 (25.8)	35.3 (69.4)	Inactive	62.6 (78.0)	50
2	19.3 (21.1)	28.8 (33.9)	27.5 (34.1)	21.1 (88.2)	20.7 (56.6)	36.2 (47.2)	75
3	33.3 (35.0)	32.2 (28.9)	34.5 (37.9)	76.5 (83.3)	52.8 (66.0)	71.4 (73.6)	25
4	24.5 (22.8)	27.1 (28.8)	31.0 (32.7)	69.4 (76.5)	57.5 (58.8)	37.3 (54.9)	50
5	22.8 (23.1)	22.0 (25.4)	20.7 (31.0)	14.1 (32.9)	36.9 (39.6)	59.3 (67.0)	75

Values in paranthesis are at 1000  $\mu\text{g/ml}$

res in the solid state as the axial parameter  $G$  is less than four<sup>27,28</sup>. The factor  $\alpha^2$  which is taken as a measure of covalency is evaluated by the expression,

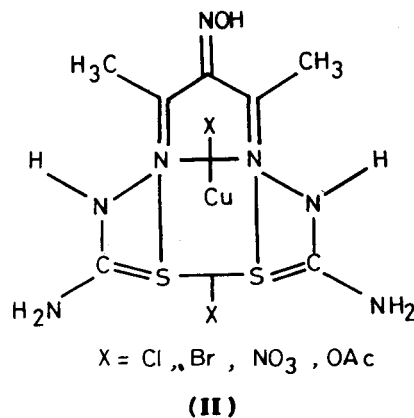
$$\alpha^2 = -(A_{\parallel}/0.036) + (g_{\parallel} - 2.0023) + 3/7 (g_{\perp} - 2.0023) + 0.04$$

where  $A_{\parallel}$  is the parallel coupling constant expressed in  $\text{cm}^{-1}$ . The  $\alpha^2$  values for the present copper complexes lie in the range 0.57-0.86 supporting the covalent nature of these complexes. The covalent nature can also be ascertained from the spin-orbit coupling constant  $\lambda$ . For octahedral  $d^9$  ions E ground terms can occur. The spin-orbit interaction with higher  $T_2$  term of the same spin multiplicity gives the following  $g_{av}$  value,

$$g_{av} = 2.00 \left( 1 - \frac{2\lambda}{10Dq} \right) \dots (1)$$

$g_{av}$  value is obtained from the relation,  $g_{av} = 1/3 (g_{\parallel} + 2g_{\perp})$  and  $10Dq$  from the electronic spectrum (Table 2). From equation (1) the  $\lambda'$  values were calculated. The lower  $\lambda'$  values for the Cu(II)-INacacBT complexes compared to that of the free ion ( $-830 \text{ cm}^{-1}$ ) also suggest a considerable orbital overlap.

The microbial activity of INacacBT and its copper complexes was screened against *E. coli*, *S. aureus* and *B. subtilis* at 1000 and 500  $\mu\text{g/ml}$  concentrations. It is



evident from the preliminary data (Table 3) that both the ligands and their Cu(II) complexes are inhibitory at the screening concentration with the latter being slightly more active than the parent ligands. The activity of the complexes against *A. niger*, *C. albicans* and *A. flavus* were evaluated and compared with that of the standard (salicylic acid, 5%). From the results obtained the copper complexes, in general, showed higher activity than the thiosemicarbazone ligand. The results obtained from the *in vitro* anti-tubercular studies are presented in Table 3. Once again the copper(II) complexes were found to be more active than the ligand. The effect of anion on the % inhibition does not vary in a fixed order. In addition to the role of the metal ion and the nature of the ligand, detailed *in*

*vivo* studies is necessary for obtaining fruitful information on the structure-activity relationship<sup>5,30</sup> in these compounds.

Based on the physicochemical investigations, structure(II) has been proposed for the copper(II) complexes of isonitrosoacetylacetonedithiosemicarbazone.

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