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# Metal Complexes of 2,6-Diacetylpyridine Bis(thiosemicarbazone): their Preparation, Characterization and Antitumour Activity

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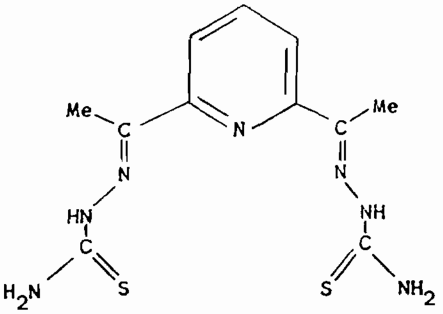
## Abstract

Complexes of Mn(II), Fe(II) Co(II), Ni(II), Cu(II), Zn(II) and Pt(II) with 2.6-diacetylpyridine bis(thiosemicarbazone) (daptsc-$H_2$) have been isolated and characterized by elemental analysis, conductance measurements, magnetic susceptibilities (from room temperature to liquid nitrogen temperature), diffuse reflectance and infrared studies. On the basis of these studies a seven-coordinate structure for Zn(daptsc-$H_2$)$(OAc)_2$, a six-coordinate structure for M(daptsc-$H_2$)$Cl_2$ (M = Mn(II), Co(II), Ni(II) or Cu(II)) and Fe(daptsc-$H_2$)$SO_4$, and a five-coordinate structure for Pt(daptsc) are suggested. $^{57}$Fe Mössbauer spectra at 300 and 78 K also suggest a distorted octahedral structure with $d_{xy}$ ground state for Fe(daptsc-$H_2$)$SO_4$ complex. All these metal(II) complexes have been screened for their antitumour activity in the P388 lymphocytic leukaemia test system in mice and showed enhanced antitumour activity relative to the free ligand.

## Introduction

Several types of metal complexes have been shown to have cytotoxic or antineoplastic activity [1–5]. Several α-(*N*)-heterocyclic carboxaldehyde thiosemicarbazones have demonstrated inhibitory activity against transplanted rodent neoplasms [6], spontaneous lymphomas of dogs [7], and DNA viruses of the Herpes family [8]. The activity of these compounds is apparently due to inhibition of the biosynthesis of DNA with the metabolic lesion occurring at the level of reduction of ribonucleotides to deoxyribonucleotides by the enzyme ribonucleoside diphosphate reductase [9, 10]. From studies on the mechanism by which members of this class inhibit the activity of ribonucleoside diphosphate reductase, it has been postulated that inhibition is due to the coordination of iron by these compounds either by a preformed iron complex binding to the enzyme or by the free ligand complexing with the iron-charged enzyme [11].

An interesting quinquidentate chelating thiosemicarbazone is 2,6-diacetylpyridine bis(thiosemicarbazone) (**1**) which will be abbreviated daptsc-$H_2$. Quinquedentate Schiff's base ligands have been little investigated compared with the vast amount of work reported dealing with bi-, tri-, and quadridentate ligands.



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Lindoy and Busch [12] reported the metal-ion induced rearrangement of 2,6-bis(2-methyl-2-benzenethiazolinyl)pyridine to afford five-coordinated zinc and cadmium complexes. The X-ray crystal structure analysis [13] showed that the zinc complex had a helical five-coordinate structure (**2**). The zinc and cadmium complexes readily react with methyl iodide to afford complexes containing the *S,S'*-dimethylated ligand and two coordinated iodide ions [14].

Busch *et al.* [15] reported that 2,6-diacetyl bis(2'-pyridylhydrazone)pyridine (**3**; NNNNNH) behaved as a quinquedentate ligand in the cobalt complex [Co(NNNNN)I]I. The macrocyclic ligand

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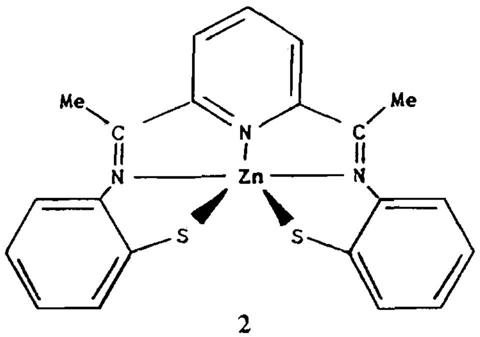

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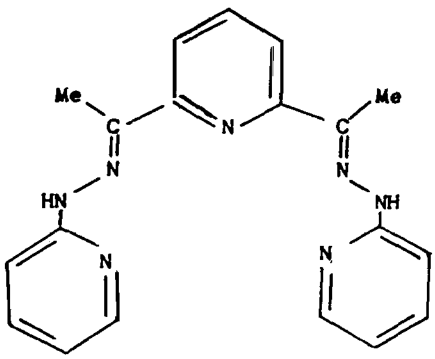

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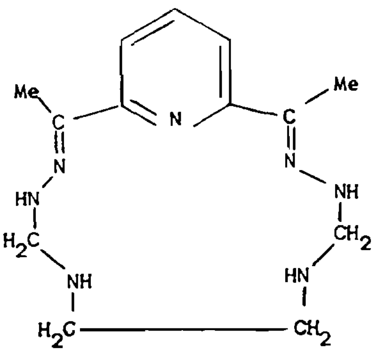
(4; mac-$N_5$) affords the iron complex [Fe(*mac*-$N_5$)-$(NCS)_2$]$ClO_4$ for which the X-ray crystal structural analysis showed that the ligand behaves as a quinquedentate and the iron atom is in a pentagonal bipyramidal arrangement [16].



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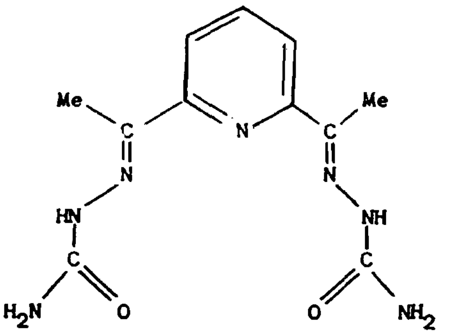
Wester and Palenik reported pentagonal bipyramidal transition metal chelates of 2,6-diacetylpyridine bis(semicarbazone) (5; dapsc) of the types M(dapsc)$Cl_2 \cdot 3H_2O$ (M = Fe, Co, Ni or Zn) and M(dapsc)$(NO_3)_2 \cdot 3H_2O$ (M = Ni or Cu) [17, 18]. Livingstone and Oluka reported [19] the transition metal chelates of the Schiff's base (6; R = Ph, 2-thienyl; ONNNO) of the types M(ONNNO) (M = Co, Ni, Cu, Zn, Cd or Pd) and $UO_2$(ONNNO).



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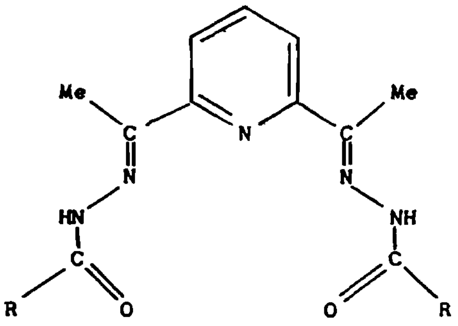

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Recently, Pelizzi *et al.* [20] observed a remarkable versatility in the chelation of (6) (R = Ph, 2-HOPh, 2-$NH_2$Ph, py) and its tendency to produce stereochemistry with high coordination numbers.

Because of the unusual stereochemistry associated with the above mentioned quinquedentates and interesting antitumour activity associated with various thiosemicarbazones, we report for the first time on the metal chelates of 2,6-diacetylpyridine bis(thiosemicarbazone) (1; daptsc-$H_2$) and their antitumour activity.

## Experimental

### *Materials*

Thiosemicarbazide (Merck) and 2,6-diacetylpyridine (Sigma Chemical Co.) were best-purity products and were used as received. Potassium tetrachloroplatinate(II) (Aldrich Chemical Co.) was used as such. Other metal(II) salts and solvents were of reagent grade chemicals.

### *2,6-Diacetylpyridine bis(thiosemicarbazone)*

A solution of thiosemicarbazide (0.02 mol) in 30 $cm^3$ of MeOH containing 2 $cm^3$ acetic acid was heated on a steam bath for a few min. This solution was added to a hot solution of 2,6-diacetylpyridine (0.01 mol) in MeOH (25 $cm^3$). The mixture was heated under reflux until clear and then allowed to cool at room temperature, whereupon the ligand separated out in the form of a greenish–yellow crystalline solid. The solid was filtered off, washed with 1:1 MeOH–water, dried and recrystallized from a MeOH–water mixture. Yield 90%; melting point (m.p.) 240–241 °C.

### *Metal Complexes*

All the complexes were isolated by the following general procedure. To a solution of metal(II) salt (1 mmol) in the minimum amount of MeOH or an aqueous solution of $K_2PtCl_4$ (0.415 g; 1 mmol) was added a suspension of 2,6-diacetylpyridine bis(thiosemicarbazone) (0.31 g; 1 mmol) in MeOH, and the mixture was heated under reflux with constant stirring for 2–4 h. The thiosemicarbazone gradually dissolved, and shining crystals of the complexes separated from the solution. The crystals were filtered off and washed with water (in the case of Pt(II) complex only), MeOH and $Et_2O$. The crystals were dried over $P_2O_5$ under vacuum. Yield 60–90%.

### *Template Reaction*

A mixture of 2,6-diacetylpyridine, thiosemicarbazide and a metal(II) salt (1:2:1 molar ratio) suspended in MeOH or MeOH–water (1:1 *v*/*v*), in the case Pt(II) salt only, was heated under reflux for 3–5 h. On cooling the coloured solutions at room temperature, crystalline solids of varying colours were obtained.

Elemental analysis for carbon, hydrogen and nitrogen was performed by the Microanalytical Laboratory of CDRI, Lucknow, India. Metal analyses were done by standard gravimetric procedures. The analytical data of the complexes obtained by template reaction agree well with the compounds obtained by the above method. The analytical data are reported in Table I.

All the complexes are insoluble in water, partially soluble in a large number of solvents of low coordinating ability like $CCl_4$, $CS_2$, $C_6H_6$, $C_6H_5NO_2$, $CHCl_3$, $Et_2O$, tetrahydrofuran and acetonitrile, and soluble in a number of solvents of moderate-to-good coordinating ability like dimethylformamide, dimethylsulphoxide, MeOH, EtOH and pyridine. Although the complexes do not possess sharp melting points, they decompose above 200 °C.

### *Physical Measurements*

Conductance measurements in methanol at *ca.* $10^{-3}$ M were made on a Toshniwal conductivity bridge type CL01/01. Magnetic measurements at room temperature were made on a standard Gouy's balance calibrated with $HgCo(NSC)_4$ [21]. Diamagnetic corrections were applied using Pascal's constants [22]

Diffuse reflectance spectra were recorded on Unicam SP700 spectrophotometer equipped with a reflectance accessory, using MgO as the reference. The infrared spectra were recorded on a Nicolet 5DX FTIR equipment in KBr pellets.

$^{57}Fe$ Mössbauer spectra were obtained on polycrystalline samples by using a constant acceleration Mössbauer spectrometer which was calibrated with natural α-iron foil. The source was $^{57}Co(Pd)$ and was at room temperature for all experiments. The low temperature measurements were made in a vacuum cryostat with a sample holder which protected the sample from the cryostat vacuum. The Mössbauer results were determined by inspection with an accuracy of ±0.01 mm/s.

## **Results and Discussion**

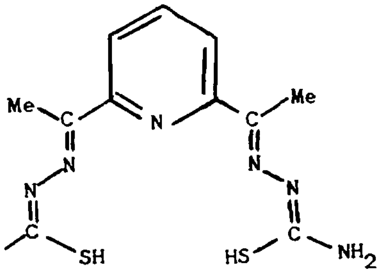
When the suspension of the free ligand daptsc-$H_2$ was stirred with methanolic or aqueous solution of metal(II) salt, it afforded the coloured crystalline complexes of the formula M(daptsc-$H_2$)$Cl_2$, Fe(daptsc-$H_2$)$SO_4$, Zn(daptsc-$H_2$)$(OAc)_2$ and Pt(daptsc). These metal(II) complexes are quite stable at room temperature and do not show any decomposition after a long period of standing. The molar conductances of the complexes in methanol at *ca.* $10^{-3}$

TABLE I. Analytical and Magnetic Data of Metal(II) Complexes of 2,6-Diacetylpyridine Bis(thiosemicarbazone)

| Complex | Color | Found (%) | | | | Calculated (%) | | | | $\mu_{eff}$ ($\mu_\beta$) at 302 K | $\Lambda_M$ (ohm$^{-1}$ cm$^2$ mol$^{-1}$) | $\theta$ (K) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | M | C | H | N | M | | | |
| Mn(daptsc-$H_2$)$Cl_2$ | Yellow | 30.37 | 3.50 | 22.60 | 12.60 | 30.34 | 3.45 | 22.53 | 12.62 | 5.99 | 72.07 | 0 |
| Fe(daptsc-$H_2$)$SO_4$ | Pale green | 28.72 | 3.26 | 21.34 | 12.14 | 28.64 | 3.26 | 21.30 | 12.10 | 5.42 | 28.07 | −4 |
| Co(daptsc-$H_2$)$Cl_2$ | Brownish-green | 30.10 | 3.40 | 22.28 | 13.50 | 30.07 | 3.42 | 22.33 | 13.42 | 5.13 | 105.24 | −6 |
| Ni(daptsc-$H_2$)$Cl_2$ | Brown | 30.04 | 3.41 | 22.38 | 13.47 | 30.08 | 3.41 | 22.34 | 13.38 | 3.09 | 62.45 | −2 |
| Cu(daptsc-$H_2$)$Cl_2$ | Green | 29.70 | 3.40 | 22.10 | 14.39 | 29.76 | 3.38 | 22.09 | 14.31 | 1.71 | 60.12 | −8 |
| Zn(daptsc-$H_2$)$(OAc)_2$ | Light Yellow | 26.86 | 3.04 | 19.98 | 13.20 | 26.83 | 3.03 | 19.92 | 13.27 | Diamag. | 4.29 | |
| Pt(daptsc) | Red | 26.34 | 2.56 | 19.60 | 38.90 | 26.29 | 2.59 | 19.52 | 38.77 | Diamag. | 19.69 | |

M (Table I) indicate that Mn(II), Co(II), Ni(II) and Cu(II) complexes are uni-univalent electrolytes while Fe(II), Zn(II) and Pt(II) complexes are non-electrolytes in solution [23].

The infrared spectrum of 2,6-diacetylpyridine bis(thiosemicarbazone)(daptsc-$H_2$) exhibits $\nu$(NH) absorption bands at 3390s and 3220s $cm^{-1}$ but no $\nu$(SH) at *ca.* 2570 $cm^{-1}$ is observed. Thus, in the solid state, daptsc-$H_2$ exists in the thione form (**1**). However, in solution and in the presence of some metal ions the compound may exist in equilibrium with the tautomeric form (**1a**). Tautomer **1a** by the loss of the thiol protons may act as a doubly negatively charged SNNNS quinquedentate.



**1a**

The assignments of some of the infrared spectral bands of free daptsc-$H_2$ and its metal(II) chelates are reported in Table II. In the NH stretching region, the high frequency component $\nu_{as}$(NH) remains practically unchanged on coordination, relative to that of the free ligand, but the low frequency component $\nu_s$(NH) is raised by about 60 $cm^{-1}$. This indicates that there are no direct bonds between the nitrogen atoms of the amino groups and the metal atom, which is partly confirmed by the high frequency shift of the scissors deformations of the NH group ($\Delta\delta(NH_2)$ $\simeq$35 $cm^{-1}$) and of the antisymmetric and symmetric stretches $\Delta\nu_{as}$(CN) and $\Delta\nu_s$(CN) of the $-\mathrm{N}-\underset{\underset{\mathrm{S}}{\|}}{\mathrm{C}}-\mathrm{N}-$ group ($\Delta\nu_{as}$(CN) $\simeq$40 $cm^{-1}$, $\Delta\nu_s$(CN) $\simeq$25 $cm^{-1}$). The coordination of the azomethine nitrogen atom to the metal(II) ion is indicated by the displacement of the band chiefly assigned to the N–N stretch [24]. The spectra of the complexes show a low frequency displacement of$\nu$(N–N) from 1080 $cm^{-1}$ for the ligand to about 1040 $cm^{-1}$ in the complexes. On the other hand, the $\nu$(C=N) frequency, 1600 $cm^{-1}$ in the spectrum of the ligand, is raised by an average of 45 $cm^{-1}$ in the spectra of the complexes.

In most complexes of thiosemicarbazones the second donor is the sulphur atom [25]. A sharp band observed at 800 $cm^{-1}$ is assigned mainly to the $\nu$(CS) stretching vibration. On coordination, $\nu$(CS) is displaced by approximately 100 $cm^{-1}$ in the Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes and by approximately 120 $cm^{-1}$ in Pt(II) complex. This situation is most probably consistent with the heterolysis of the thiol protons of the ligand molecule in Pt(II) complex [26]. The coordination of the nitrogen atom of the pyridine nucleus is confirmed by the shifting and splitting of the ring frequencies as is usually observed for other metal(II) pyridine complexes [27].

In the far-infrared region the Zn(II) complex exhibits bands at 285 and 244 $cm^{-1}$ which are assigned to $\nu$(M–S) and $\nu$(M–N) vibrations, respectively [25, 28]. The Mn(II), Fe(II), Co(II), Ni(II) and Cu(II) complexes show similar bands at *ca.* 300 and *ca.* 275 $cm^{-1}$, respectively [24]. In the Pt(II) complex the $\nu$(M–S) and $\nu$(M–N) vibrations are observed at 290 and 262 $cm^{-1}$, respectively [5]. In all these complexes the $\nu$(M–N) pyridine appeared at *ca.* 230 $cm^{-1}$ and $\nu$(M–Cl) in M(daptsc-$H_2$)$Cl_2$ at *ca.* 245 $cm^{-1}$ which are in good agreement with the reported values [29]. The $\nu$(Zn–OAc) vibrations are observed at 584s and 550m $cm^{-1}$. The appearance of $\nu_{as}$(COO) and $\nu_s$(COO) vibrations at 1560sb and 1420vs $cm^{-1}$, respectively, suggests the monodentate coordination of acetato groups in the Zn(II) complex [30]. The monodentate coordination of the sulphate group is indicated by the appearance of the $\nu$S–O band at 980 $cm^{-1}$ and $\nu$(Fe–$OSO_3$) at 250 $cm^{-1}$

TABLE II. Selected Infrared Vibrations of 2,6-Diacetylpyridine bis(thiosemicarbazone) and its Metal(II) Complexes

| daptsc-$H_2$ | Mn | Fe | Co | Ni | Cu | Zn | Pt | Assignment |
|---|---|---|---|---|---|---|---|---|
| 3390s | 3390s | 3385s | 3390s | 3380s | 3385s | 3380s | 3440s | $\nu_{as}$(NH) |
| 3220s | 3278s | 3280s | 3280s | 3275s | 3280s | 3270s | 3380s | $\nu_s$(NH) |
| 1620s | 1650s | 1645s | 1655s | 1655s | 1650s | 1650s | 1645s | $\delta$(NH) |
| 1600s | 1640m | 1640m | 1645s | 1640s | 1640m | 1645s | 1640m | $\nu$(C=N) |
| 1500s | 1480s | 1475m | 1475m | 1480s | 1480m | 1475m | 1480s | $\nu$(CN) + $\delta$(NH) |
| 1460m | 1460m | 1465s | 1460s | 1460m | 1465m | 1470w | 1470w | Band III(pyridine ring) |
| 1300m | 1340s | 1330m | 1330mb | 1330m | 1340mb | 1338m | 1340mb | $\nu$(CS) + $\nu$(CN) + $\delta(NH_2)$ |
| 1080s | 1040s | 1045s | 1040s | 1040s | 1048s | 1045s | 1040s | $\nu$(N–N) |
| 800s | 705s | 700m | 700m | 705m | 700s | 700m | 700s<br>690m | $\nu$(CS) |

[25, 31]. The other bands are obscured by ligand absorption bands.

The $\mu_{eff}$ values at room temperature with Weiss constant, $\theta$, are reported in Table I. The Zn(II) and Pt(II) complexes are diamagnetic. The magnitude and slight temperature dependence of the $\mu_{eff}$ values of Mn(II), Fe(II), Co(II) and Ni(II) complexes are in the range expected for tetragonally distorted octahedral complexes [32]. The $\mu_{eff}$ values of Cu(II) complex are very close to spin-only for one unpaired electron and are in the range normally observed for Cu(II) complexes having an orbitally nondegenerate ground state. In fact, no significant conclusion can be drawn from the magnetic data regarding the stereochemistry of Cu(daptsc-$H_2$)$Cl_2$ complex, since there is little difference in magnitude of various configurations in Cu(II) complexes [33, 34].

The UV spectrum of the free ligand daptsc-$H_2$ exhibits sharp bands at 44250, 41840, 40985, 38610, 35460, 32050 and 28570 $cm^{-1}$, which are assigned to $\pi \rightarrow \pi^*$ transitions. The high absorption by the ligand as compared to the metal(II) ions masks any splitting of the bands, and only the slight wavelength and intensity variations are significant in the complexes. The spectra of the metal(II) chelates are dominated by ligand absorption bands.

The diffuse reflectance spectrum of the Mn(II) complex in the visible region exhibits some broad absorption below 8000 $cm^{-1}$, but any band which might be attributed to the d–d transition of octahedral Mn(II) is masked by a strong charge-transfer or ligand absorption bands above 16000 $cm^{-1}$.

The spectrum of Fe(II) complex exhibits two broad bands at 9090 and 14290 $cm^{-1}$ (Fig. 1a) which are assigned to the components of ${}^5T_{2g} \rightarrow {}^5E_g$. The centroid of these bands 11510 $cm^{-1}$ corresponds to 10 Dq [35]. The spectrum also contains sharp bands at 16700 and 21250 $cm^{-1}$ which we assigned as charge-transfer absorption bands.

The spectrum of Co(II) complex shows three ligand field transitions at 8850, 11630 [$\nu_1$, ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$] and 18520 [$\nu_2$, ${}^4T_{1g} \rightarrow {}^4A_{2g}(F)$] $cm^{-1}$ in addition to the intense intraligand bands (Fig. 1b). The $\nu_3$, the ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transition is obscured by a very intense charge transfer band which appears at 23530 $cm^{-1}$ ($Co_{(eg)} \rightarrow ligand_{(\pi^*)}$). The Co(II) complex also exhibits a weak band at 7300 $cm^{-1}$, which is assigned to the spin-forbidden ${}^4T_{1g}(F) \rightarrow {}^2E_g(G)$ transition [36]. The significant splitting of the $\nu_1$ band into two components is probably due to distortion from regular octahedral symmetry.

The reflectance spectrum of Ni(II) complex displays three sets of low-intensity absorption bands at 10200, 11900 [$\nu_1$, ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$], 17000 [$\nu_2$, ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$] and 20000 $cm^{-1}$, analogous to other octahedral Ni(II) complexes (Fig. 1c). The presence of a very intense intraligand electronic absorption band extending into the visible region obscures the weak transition $\nu_3$ to the ${}^3T_{1g}(P)$ ligand field state.

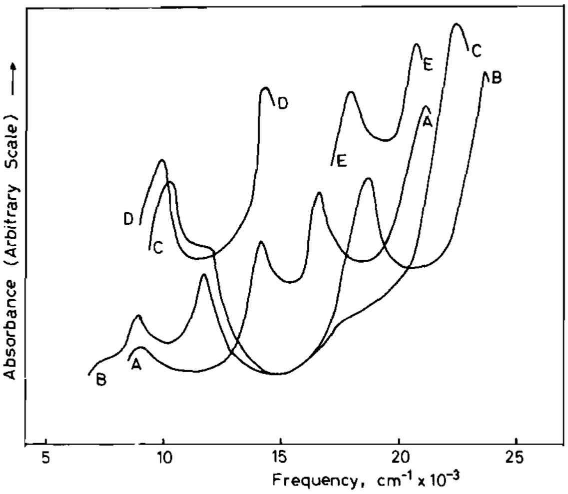


Fig. 1. Reflectance spectra of (a) Fe(daptsc-$H_2$)$SO_4$, (b) Co(daptsc-$H_2$)$Cl_2$, (c) Ni(daptsc-$H_2$)$Cl_2$, (d) Cu(daptsc-$H_2$)-$Cl_2$, (e) Pt(daptsc).

The reflectance spectrum of Cu(II) complex displays two symmetrical bands at 9700 and 14400 $cm^{-1}$ (Fig. 1d), which are assigned to the ligand field transitions commonly observed for Cu(II) complexes. The electronic spectra of some distorted octahedral Cu(II) complexes display two bands split by *ca.* 5000 $cm^{-1}$. Consequently, a distorted octahedral configuration is assigned to the complex [Cu-(daptsc-$H_2$)Cl] Cl.

The spectrum of [Pt(daptsc)] displays two spectral bands at 17860 sh and 20500 $cm^{-1}$ (Fig. 1e), which are assigned to the metal-to-ligand (Pt(II) $\rightarrow$ $ligand_{(\pi^*)}$) charge-transfer transition.

The Mössbauer spectra of Fe(II) complex, measured at room temperature and 78 K, are illustrated in Fig. 2, and the spectral parameters are reported in Table III. The chemical isomer shift, $\delta$, relative to a natural iron foil, is sensitive to both the oxidation state and the spin state of the iron, and is characteristic of Fe(II) high spin species in a tetragonally distorted octahedral environment [25, 37]. The chemical isomer shift ($\delta$) parameter decreases from 0.95 mm/s at 78 K to 0.83 mm/s at 300 K. Such a decrease in $\delta$ with increasing temperature can be attributed to a second order Doppler shift arising from lattice effects.

The quadrupole splitting parameter, $\Delta E_Q$, is sufficiently large and is characteristic of six-coordinate high-spin Fe(II), as demonstrated in a broad series of related complexes [25, 37] The large $\Delta E_Q$ values ruled out the presence of the $d_{xy}$, $d_{yz}$ ground state in the Fe(II) complex [37]. The ground state must, therefore, be $d_{x^2-y^2}$, $d_{xy}$ or $d_{z^2}$. The temperature dependence of the quadrupole splitting may be the

TABLE III. Mössbauer Spectral Parameters for Iron(II) Complex

| Complex | Temperature (K) | $IS^a$ (mm/s) | $\Delta Eq$ (mm/s) | $\Gamma_1{}^b$ (mm/s) | $\Gamma_2{}^b$ (mm/s) |
|---|---|---|---|---|---|
| Fe(daptsc-$H_2$)$SO_4$ | 300 | 0.83 | 3.16 | 0.29 | 0.28 |
| | 78 | 0.95 | 3.29 | 0.32 | 0.30 |

[a] Relative to natural iron foil. [b] Full width at half-maximum.

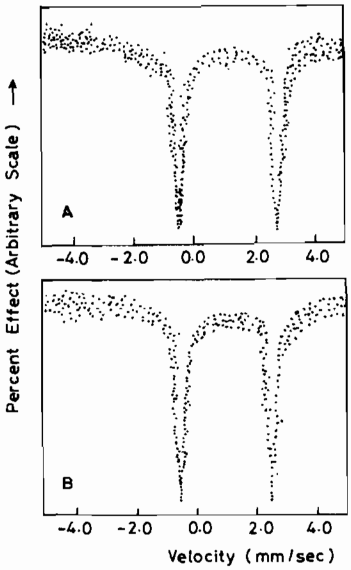


Fig. 2. Mössbauer spectra of [Fe(daptsc-$H_2$)$SO_4$] complex at 78 (K) (a) and 300 (K) (b).

result of a thermal equilibrium between an electronic orbital singlet ground state and a doublet excited state. This would be compatible with either of two structures, a tetragonally elongated octahedral structure with a predominantly $d_{xy}$ ground state and $d_{xy}$, $d_{yz}$ first excited state or a trigonally distorted octahedral structure with a $|d_{z^2} >$ ground state and $|t_{2g}\pm >$ first excited state. A $d_{xy}$ ground state is anticipated for the present tetragonally distorted Fe(II) complex, in analogy with the reported Mössbauer spectra of a number of thiosemicarbazone complexes of Fe(II) [25, 37].

### *Antitumour Activity*

The antitumour activity of the metal(II) complexes was determined at the National Cancer Institute (NIH) Bethesda, Md., by the standard screening procedure (*cf.* instruction 14) in the P388 lymphocytic leukaemia test system. The P388 lymphocytic leukaemia screen was carried out on $CD_2F_1(CDF_1)$ mice (male or female). On day 0, $1 \times 10^6$ ascites cells were injected intraperitoneally (ip). Test compounds were suspended in Saline with Tween-80 and administered ip on days 1 through 5. Six mice were used per test compound, and a T/C of greater than 125% was considered significant activity against P388 tumour growth.

All the metal(II) complexes were evaluated for antitumour activity against the leukaemia P388 cell line in mice and the results are reported in Table IV. The free ligand does not possess significant activity, having a *T/C* value of 93 at a dose of 25.00 mg/kg. Most of the complexes that were investigated do not possess significant activity and are toxic at the doses used. However, antitumour activity is enhanced by coordination; the Zn(II) complex had significant activity ($T/C \geqslant 140$).

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TABLE IV. Antitumour Activity of Metal(II) Complexes of 2,6-Diacetylpyridine Bis(thiosemicarbazone) against P388 Lymphocytic Leukaemia in Mouse

| Compound | Treatment schedule | Dose (mg/kg) | Weight difference (*T–C*) | *T/C* (%) |
|---|---|---|---|---|
| Mn(daptsc-H$_2$)Cl$_2$ | A[a] | 400.00 |  | Toxic |
|  |  | 200.00 | –0.1 | 94 |
|  |  | 100.00 | –4.2 | 102 |
| Fe(daptsc-H$_2$)SO$_4$ | A[a] | 200.00 |  | Toxic |
|  |  | 100.00 |  | Toxic |
|  |  | 50.00 | –0.8 | 100 |
| Co(daptsc-H$_2$)Cl$_2$ | A[a] | 400.00 |  | Toxic |
|  |  | 200.00 |  | Toxic |
|  |  | 100.00 | –1.63 | 100 |
|  |  | 50.00 | –0.3 | 101 |
|  |  | 25.00 | –0.7 | 107 |
| Ni(daptsc-H$_2$)Cl$_2$ | A[a] | 400.00 |  | Toxic |
|  |  | 200.00 |  | Toxic |
|  |  | 100.00 | –2.8 | 108 |
| Cu(daptsc-H$_2$)Cl$_2$ | A[a] | 400.00 |  | Toxic |
|  |  | 200.00 |  | Toxic |
|  |  | 100.00 | –1.9 | 103 |
| Zn(daptsc-H$_2$)(OAc)$_2$ | A[a] | 200.00 |  | Toxic |
|  |  | 100.00 | –4.8 | 126* |
|  |  | 50.00 | –2.7 | 140* |
| Pt(daptsc) | A[a] | 200.00 |  | Toxic |
|  |  | 100.00 |  | Toxic |
|  |  | 50.00 | –0.7 | 100 |
| daptsc-H$_2$ | A[a] | 400.00 | –5.2 | Toxic |
|  |  | 200.00 | –2.6 | Toxic |
|  |  | 100.00 | –10.0 | Toxic |
|  |  | 50.00 | –0.7 | 89 |
|  |  | 25.00 | –0.9 | 93 |
|  |  | 12.50 | –1.4 | 91 |

[a] Experimental animals were treated once daily with the indicated dose beginning on day 1 and ending on day 4.

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