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Metal(II) Chelates of 4-Methyl-5-Amino-1-Formylisoquinoline Thiosemicarbazone: Their Preparation, Characterization and Antitumour Activity

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Abstract

The metal(II) complexes [M(4-Me-5-NH_2-1-iqtsc-H)Cl_2] (M = Co(II), Ni(II) or Cu(II) and 4-Me-5-NH_2-1-iqtsc-H = 4-methyl-5-amino-1-formylisoquinoline thiosemicarbazone), [Zn(4-Me-5-NH_2-1-iqtsc-H)-$(OAc)_2$]·H_2O and [Pt(4-Me-5-NH_2-1-iqtsc)Cl)] were isolated and characterized by elemental analysis, conductance measurement, magnetic moments (300–78 K) and spectral studies. On the basis of these studies distorted trigonal-bipyramidal structures for the Co(II), Ni(II), Cu(II) and Zn(II) complexes and a square-planar structure for the Pt(II) complex are proposed. All these complexes were screened for their antitumour activity in the P388 lymphocytic leukaemia test system in mice. With the exception of the Pt(II) and Zn(II) complexes, the complexes showed no significant activity; the Zn(II) and Pt(II) complexes showed T/C (%) values of 150 and 144 at a much lesser extent [2].

Introduction

From 1969, a search for active antitumour substances among complex compounds of metals has been undertaken in many countries. Although the overwhelming majority of the complexes studied up to the present day have been platinum compounds, possessing both a relatively simple structure (*e.g.*, cisplatin *cis*-Pt$(NH_3)_2Cl_2$) and containing complex bioinorganic ligands [1], complex compounds of essential metals, in particular the first-row transition metals cobalt, nickel, copper and zinc have also been investigated for activity though to a much lesser extent [2].

Thiosemicarbazones, in particular bis(thiosemicarbazones) and α-N-heterocyclic carboxaldehyde thiosemicarbazones, constitute an interesting class of experimental cancer chemotherapeutic agents in that they are strong metal chelating agents [3–8]. The thiosemicarbazones are potent inhibitors of the growth of a variety of transplanted rodent tumours [9], spontaneous lymphomas of dogs [10], and DNA viruses of the Herpes group [11]. They are also strong inhibitors of the mammalian form of the enzyme ribonucleoside diphosphate reductase [12, 13] which catalyzes a critical and possibly rate-limiting step in DNA synthesis and cell division. Furthermore, it has been postulated that inhibition is due to the coordination of iron by these compounds through their N*–N*–S* tridentate ligand system either by a preformed iron complex binding to the enzyme or by the free ligand complexing with the iron-charged enzyme [14]. Studies have shown *in vivo* and *in vitro* cytotoxic activity for iron(II) and copper(II) complexes of 1-formylisoquinoline thiosemicarbazone and certain 5-substituted 2-formylpyridine thiosemicarbazones [4, 15] as well as *in vivo* activity for a number of metal complexes of the ligands having the N*–N*–S* tridentate ligand system [2]. In our previous paper we reported Co(II), Ni(II), Cu(II), Zn(II) and Pt(II) complexes of 1-formylisoquinoline thiosemicarbazone and observed that, except for the Pt(II) complex, all complexes showed antitumour activity against the P388 lymphocytic leukaemia test system in mice; the Ni(II) complex gave a T/C (%) value of 161 at optimum dosage [16]. To investigate more potent antitumour metal compounds, we have extended our studies to other α-(N)-heterocyclic carboxaldehyde thiosemicarbazones. In this paper we report the characterization and antitumour properties of Co(II), Ni(II), Cu(II), Zn(II) and Pt(II) complexes of 4-methyl-5-amino-1-formyliso-

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TABLE I. Analytical and Magnetic Data of Metal(II) Complexes of 4-Methyl-5-Amino-1-Formylisoquinoline Thiosemicarbazone.

Compound	Colour	Found			Calculated			μ_{eff}, μ_B at RT	θ °K
		%C	%H	%N	%C	%H	%N		
1. [Co(4-Me-5-NH_2-1-iqtsc-H)Cl_2]	Brown	37.08	3.34	17.92	37.02	3.34	17.99	4.42	−4
2. [Ni(4-Me-5-NH_2-1-iqtsc-H)Cl_2]	Red	37.01	3.35	18.10	37.04	3.34	18.00	3.26	−2
3. [Cu(4-Me-5-NH_2-1-iqtsc-H)Cl_2]	Green	36.64	3.32	17.80	36.59	3.30	17.78	1.85	−6
4. [Zn(4-Me-5-NH_2-1-iqtsc-H)$(OAc)_2$]·H_2O	Orange	41.74	4.50	15.17	41.70	4.56	15.20	Diamagnetic	
5. [Pt(4-Me-5-NH_2-1-iqtsc)Cl]	Dark red	29.45	2.46	14.30	29.47	2.45	14.32	Diamagnetic	

quinoline thiosemicarbazone (4-Me-5-NH_2-1-iqtsc-H), an excellent antitumour agent [17, 18].

Experimental

4-Methyl-5-amino-1-formylisoquinoline thiosemicarbazone was obtained as a gift from the National Cancer Institute and has been previously characterized [17]. Potassium tetrachloroplatinate(II) (Aldrich Chemical Co.) was used as received. Other metal(II) salts and solvents were of reagent grade chemicals.

Synthesis

All the complexes were isolated using the following procedure. To a suspension of 4-methyl-5-amino-1-formylisoquinoline thiosemicarbazone (0.260 g, 1 mmol) in methanol (25 ml) was added a solution of metal(II) salt (1 mmol) in methanol (15 ml) or an aqueous solution of K_2PtCl_4 (0.415 g, 1 mmol) and the mixture was stirred at room temperature for 50–60 min. The thiosemicarbazone gradually dissolved and the shining crystals of the complexes separated from the solution. These were filtered, washed with methanol, water (in the case of the Pt(II) complex only) and finally with ether. The crystals were then dried over P_2O_5 under vacuum. Yield 60–80%.

Elemental analysis for carbon, hydrogen and nitrogen was performed in the Microanalytical Laboratory of C.D.R.I., Lucknow (U.P.), India. The analytical data are reported in Table I.

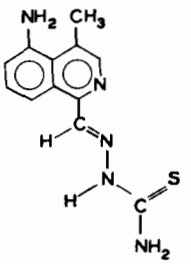
Physical Measurements

Conductance measurements in MeOH at 10^{-3} M were carried out on a Toshniwal conductivity bridge type CL 01/01. The magnetic moments were measured from room temperature down to liquid N_2 temperature on a standard Gouy's balance calibrated with $HgCo(NCS)_4$ [19]. Diamagnetic corrections were made using Pascal's constant [20].

Diffuse reflectance spectra were recorded on a Cary 14 spectrophotometer equipped with a reflectance accessory, using MgO as the reference. The infrared spectra (4000–200 cm^{-1}) were taken on a Perkin-Elmer 337 spectrophotometer in CsI pellets.

Results and Discussion

The infrared spectrum of free 4-methyl-5-amino-1-formylisoquinoline thiosemicarbazone (4-Me-5-NH_2-1-iqtsc-H) exhibits ν(N–H) absorption bands at 3325 s and 3240 s cm^{-1} but no ν(S–H) at *ca.* 2570 cm^{-1} is observed. Thus, in the solid state the compound exists in the thione form (**I**). However, in solution and in the presence of some metal ions the compound probably exists in equilibrium with the tautomeric form (**Ia**). Tautomer (**Ia**) by the loss of the thiol proton may act as a singly charged tridentate ligand coordinating through the mercapto sulphur, the central nitrogen and the isoquinoline nitrogen atoms. When the suspension of 4-Me-5-NH_2-1-iqtsc-H in MeOH is stirred at room temperature with methanolic or aqueous solutions of the metal(II) salt, it gradually dissolves to yield coloured crystalline complexes of the formula [M(4-Me-5-NH_2-1-iqtsc-H)Cl_2] (M = Co(II), Ni(II) or Cu(II)), [Zn(4-Me-5-NH_2-1-iqtsc-H)$(OAc)_2$]·H_2O and [Pt(4-Me-5-NH_2-1-iqtsc)Cl]. All the complexes are quite stable at room temperature and do not show any sign of decomposition after a long period of standing. All the complexes are insoluble in water, partially soluble in a large number of low coordinating solvents like CCl_4, CS_2, C_6H_6, $C_6H_5NO_2$, $CHCl_3$,



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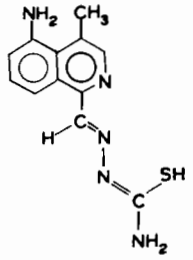

Ia

TABLE II. Selected Infrared Vibrations of 4-Me-5-NH_2-1-iqtsc-H and Metal(II) Complexes (cm^{-1}).

4-Me-5-NH_2-1-iqtsc-H	Co	Ni	Cu	Zn	Pt	Assignment
3325s	3330s	3325s	3320s	3330s	3325s	ν_{as}(NH)
3240s	3290s	3290s	3288s	3285s	3290s	ν_s(NH)
1630s	1645s	1648s	1650s	1650s	1645s	$\delta(NH_2)$
1590s	1610s	1620s	1620s	1610s	1610s	Band I ring
1540s	1575s	1580s	1580s	1575m	1580m	ν(C=N)
1460m	1465s	1460s	1460s	1465s	1465s	ν(CS) + ν(CN) + $\delta(NH_2)$ Band III ring
1410s	1410s	1415s	1415s	1410s	1410s	Band IV ring
1365m	1400s	1400s	1405s	1400s	1400s	ν(CS) + ν(CN) + $\delta(NH_2)$
1060m	1040m	1035s	1040s	1035s	1035m	ν(N–N)
805s	735s	740s	735s	735s	705s	ν(CS)

tetrahydrofuran, diethylether and acetonitrile and soluble in a number of solvents of moderate-to-good coordinating ability like dimethylformamide, dimethylsulphoxide, methanol, ethanol and pyridine. The molar conductance of the complexes in methanol at *ca.* 10^{-3} M determined at 27 °C lies in the range 10.0–14.5 ohm^{-1} cm^2 mol^{-1} indicating their non-electrolytic behaviour [21]. Not all of the complexes possess sharp melting points but they decompose above 250 °C.

The assignment of some of the bands observed in the spectra of free 4-Me-5-NH_2-1-iqtsc-H and its metal(II) complexes is reported in Table II. In the NH stretching region, the high-wavenumber component ν_{as}(NH) does not change its position on coordination relative to that of the free ligand, while the low-wave number component ν_s(NH) is raised by about 50 cm^{-1}. This suggests that there is no bond formation between the nitrogen atom of the amino group and the metal(II) ion as partly confirmed by the shifting to a lower-wave number of the scissors deformation of the NH_2 group ($\Delta\delta(NH_2)$ *ca.* 20 cm^{-1}) and the antisymmetric and symmetric stretches ν_{as}(CN) and ν_s(CN) of the –N–C(=S)–N– group ($\Delta\nu_{as}$(CN) *ca.* 40 cm^{-1} and $\Delta\nu_s$ *ca.* 20 cm^{-1}). The coordination of the azomethine nitrogen atom to the central metal(II) ion is deduced by the low-wave number shifting of the band assigned [22] chiefly to the ν(N–N) stretches. The spectra of the complexes studied show a low-wave number shifting of ν(N–N) from 1060 cm^{-1} for the ligand to approximately 1040 cm^{-1} in the spectra of the compounds. On the other hand, the ν(C=N) wave number, 1540 cm^{-1} in the free ligand, is shifted towards the higher wave number side by an average of 40 cm^{-1} in the spectra of the complexes. These displacements in the wave numbers of the >C=N–N–C(=S)– group are typically associated with the coordination of the ligand through the azomethine nitrogen atom to the metal(II) ion.

In most complexes of thiosemicarbazones, the second donor in the thiosemicarbazone moiety is the sulphur atom [23]. If coordination occurs through the thioamide sulphur, the ν(C=S) stretches will shift to low-wave numbers and the coupled δ(NH) and ν(CN) should shift in opposite directions. A perusal of the spectral data shows that the bonding of 4-Me-5-NH_2-1-iqtsc-H indeed occurs through thioamide sulphur. The coordination of the isoquinoline nitrogen atom to the metal(II) ion is indicated by the displacement and splitting of the spectral bands as is usually observed in metal(II)–pyridine complexes [24].

In the far-infrared spectral region the Co(II), Ni(II), Cu(II) and Zn(II) complexes showed bands at 285s and 252m cm^{-1} which are assigned to the ν(M–S) and ν(M–N) stretching vibrations, respectively [25]. In the Pt(II) complex the ν(Pt–S) and ν(Pt–N) stretching vibrations are observed [26] at 280s and 270s cm^{-1}, respectively. In all these complexes the ν(M–N) isoquinoline appears at 228m cm^{-1} and the ν(M–Cl) (M = Co(II), Ni(II) and Cu(II)) stretching vibration is observed at 240s cm^{-1}. Although the assignments of these bands are tentative because of the possibility of accidental coincidences and intensity variations, the position of the bands is consistent with five-(Co(II), Ni(II), Cu(II) and Zn(II)) and four-(Pt(II)) coordinate geometries. The appearance of ν_{as}(COO) and ν_s(COO) bands at 1560s,b and 1410s cm^{-1} confirms the presence of monodentate coordination of acetato groups in the Zn(II) complex [27].

The magnetic moments for Co(II), Ni(II) and Cu(II) complexes have been measured from room

TABLE III. Antitumour Activity of Metal(II) Complexes of 4-Methyl-5-Amino-1-Formylisoquinoline Thiosemicarbazone against the P388 Lymphocytic Leukaemia test System in the Mouse.

Compound	Treatment schedule	Dose (mg/kg)	Wt. difference (T–C) (%)	T/C (%)
[Co(4-Me-5-NH_2-1-iqtsc-H)Cl_2]	A[a]	200	−2.2	97
[Ni(4-Me-5-NH_2-1-iqtsc-H)Cl_2]	A	400	−1.0	109
[Cu(4-Me-5-NH_2-1-iqtsc-H)Cl_2]	A	400		TOXIC
		200	−3.5	109
		100	−3.5	96
[Zn(4-Me-5-NH_2-1-iqtsc-H)$(OAc)_2$]	B[b]	200	−5.4	TOXIC
		100	−3.2	150*
		50	−1.5	136*
[Pt(4-Me-5-NH_2-1-iqtsc)Cl]	B	240		TOXIC
		120	−3.2	TOXIC
		60	−2.5	140*
		30	−1.0	129*
		15	−0.5	123

[a]Experimental animals were treated once daily with the indicated dose, beginning on day 1 and ending on day 5. [b]Experimental animals were treated 5 times daily with the indicated dose, beginning on day 1 and ending on day 5.

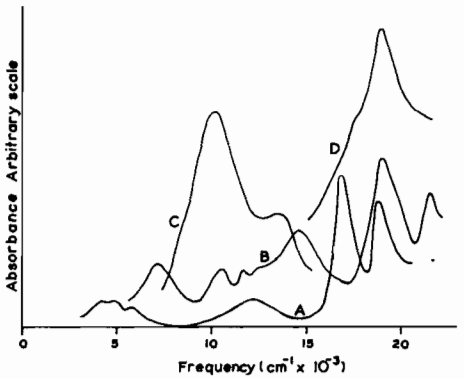

Fig. 1. Diffuse reflectance spectra: (A) [Co(4-Me-5-NH_2-1-iqtsc-H)Cl_2]: (B) [Ni(4-Me-5-NH_2-1-iqtsc-H)Cl_2]: (C) [Cu(4-Me-5-NH_2-1-iqtsc-H)Cl_2]; (D) [Pt(4-Me-5-NH_2-1-iqtsc)Cl].

temperature down to liquid N_2 temperature and the μ_{eff} values at room temperature with Weiss constant, θ, are reported in Table I. The magnitude and slight temperature dependence of the μ_{eff} values are in accordance [25, 28–31] with distorted five-coordinate high-spin structures, the Curie-Weiss law is obeyed with a relatively small value of θ, the Weiss constant. The Zn(II) and Pt(II) complexes are diamagnetic.

The UV spectrum of free ligand 4-Me-5-NH_2-1-iqtsc-H exhibits intense bands at 27030, 28000, 30760, 32040, 35710 and 40000 cm^{-1} which are assigned to $\pi \rightarrow \pi^*$ transitions. The position of these bands suggests the anti-(E)-form(I) of free ligand in the solid state [32]. The UV spectra of all the metal(II) complexes show bands of varying intensity almost at the same positions as in the anti-form of the ligand, suggesting that the ligand has anti-configuration in all these complexes in the solid state.

The diffuse reflectance spectrum of the Co(II) complex in the visible region (Fig. 1 A) is similar to the spectra of [Co(Me_6tren)X]X[Me_6tren= tris(2-dimethylaminoethyl)amine] complexes [33, 34] which are five coordinate with C_{3v} symmetry. Thus the spectral bands observed at 4273, 4880, 5814, 12345, 16890 and 18870 cm^{-1} are assigned to $^4A_2 \rightarrow {}^4A_1(F)$, $^4A_2 \rightarrow {}^4A_2(F)$, $^4A_2 \rightarrow {}^4E(F)$, $^4A_2 \rightarrow {}^4E(F)$, $^4A_2 \rightarrow {}^4A_2(P)$ and $^4A_2 \rightarrow {}^4E(P)$ transitions respectively.

The reflectance spectrum of [Ni(4-Me-5-NH_2-1-iqtsc-H)Cl_2] shows a marked similarity in position and intensities of the spectral bands to the spectra of high-spin five-coordinate nickel(II) complexes, particularly with the spectrum of [Ni(Me_6tren)]Br]Br for which a trigonal-bipyramidal structure with C_{3v} symmetry has been suggested [35]. Thus the spectral bands observed at 7194, 10526, 12500sh, 14598, 19230 and 21740 cm^{-1} are assigned to $^3E(F) \rightarrow {}^3E(F)$, $^3E(F) \rightarrow {}^3A_2(F)$, $^3E(F) \rightarrow {}^3A_1(F)$, $^3E(F) \rightarrow {}^3A_2(F)$, $^3E(F) \rightarrow {}^3E(P)$ and $^3E(F) \rightarrow {}^3A_2(P)$ transitions, respectively [16]. In addition to the above transitions a shoulder appears at 11764 cm^{-1} which is assigned as a spin-forbidden transition, $^3F \rightarrow {}^1D$.

The reflectance spectrum of [Cu(4-Me-5-NH_2-1-iqtsc-H)Cl_2] exhibits the features which are similar to those of [Cu(Me_6tren)Br]Br for which a trigonal-bipyramidal structure with C_{3v} symmetry is suggested [33, 35]. Thus the spectral bands observed at 10204 and 13514sh cm^{-1} in the Cu(II) complex are assigned [36] to the $^2A_1 \rightarrow {}^2E$ and $^2A_1 \rightarrow {}^2E$ transitions, respectively.

The reflectance spectrum of [Pt(4-Me-5-NH_2-1-iqtsc)Cl] exhibits two spectral bands at 17850sh and 19047 cm^{-1} which are assigned to the metal-to-ligand (Pt → Lπ^*) charge-transfer transition [37].

Antitumour Activity

The antitumour activity of metal(II) complexes was evaluated at the National Cancer Institute (NIH), Bethesda, MD, by the standard screening procedure (*cf.* Instruction 14) in the P388 lymphocytic leukaemia test system. The tumour inoculum of 10^6 ascites cells was implanted intraperitoneally (ip) on day 0 in CD_2F_1 (CDF_1) mice (female). The drugs were suspended in saline with Tween 80 and administered daily ip in accordance with the treatment schedule indicated in Table III. Six mice were used per test compound and the compound is considered active when T/C (test/control) survival times give a percentage > 125.

With the exception of the Zn(II) and Pt(II) complexes, the complexes showed no significant activity against the P388 lymphocytic leukaemia test system in mice. It is a surprising finding because the free ligand is associated with excellent antitumour activity *in vivo* against the Sarcoma 180 ascites tumour [17, 18]. The Zn(II) and Pt(II) complexes gave T/C values of 150 and 140 at optimum dosage, respectively.

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