Metal(II) Complexes of 1-Formylisoquinoline Thiosemicarbazone: Their Preparation, Characterization and Antitumour Activity

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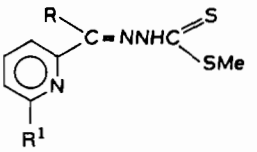
Abstract

Complexes of Co(II), Ni(II), Cu(II), Zn(II) and Pt(II) with 1-formylisoquinoline thiosemicarbazone (1-iqtsc-H) were prepared and characterized by elemental analyses, conductance measurement and spectral studies. On the basis of these studies a distorted octahedral structure for $[Co(1\text{-iqtsc})_2]\cdot 2H_2O$, a distorted trigonal-bipyramidal structure for $[Ni(1\text{-iqtsc-H})Cl_2]$, $[Cu(1\text{-iqtsc-H})Cl_2]$ and $[Zn(1\text{-iqtsc-H})(OAc)_2]\cdot H_2O$ and a square-planar structure for [Pt(1-iqtsc)Cl] are suggested. All these metal(II) complexes were screened for their antitumour activity in the P388 lymphocytic leukaemia test system in mice. Except for Pt(II), the complexes were found to possess significant activity; the Ni(II) complex showed a T/C value of 161 at the optimum dosage.

Introduction

Thiosemicarbazones of 1-formylisoquinoline and 2-formylpyridine and a multitude of their derivatives have been shown to possess antineoplastic activity against a variety of transplanted tumours [1]. These agents primarily block DNA synthesis in mammalian cells by inhibiting the enzyme ribonucleoside diphosphate reductase (RDR). From studies on the mechanism by which the agents of this class inhibit the activity of RDR, it has been hypothesized that the inhibition is due to the coordination of iron by these agents 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 [2].

Petering *et al.* [3] have isolated iron(II) and copper(II) complexes of several α-(N)-heterocyclic carboxaldehyde thiosemicarbazones and have shown that the iron complexes are three to sixfold more active as inhibitors of RDR than the free ligands. They also noted an intensification of antitumour activity upon complexation. Das and Livingstone [4] reported the antitumour activity of a number of transition metal complexes with Schiff bases derived from S-methyldithiocarbazate **I**. Of the



I

derivatives of **I**, the chloro–Ni(II) complex (R = Me, R^1 = H) showed marked activity against the P388 leukaemia test system in mice, giving a T/C of 153% at a dose of 6.2 mg/kg. The nitrato–Zn(II) complex (R = H, R^1 = Me) was less active, giving a T/C of 137% at a dose of 100 mg/kg. Recently Klayman *et al.* [5] prepared Cu(II), Ni(II), Fe(III) and Mn(II) complexes with several selected 2-acetylpyridine thiosemicarbazones and selenocarbazones to investigate their antimalarial and antitumour properties. They observed that the antimalarial activity in mice infected with *Plasmodium berghei* is reduced, while antitumour activity against the leukaemia P388 cell line in mice is enhanced by coordination with the above mentioned metals relative to free ligands.

Because of these interesting results, we decided to prepare transition-metal(II) complexes with 1-formylisoquinoline thiosemicarbazone (1-iqtsc-H) and to evaluate their antitumour activity.

Experimental

1-Formylisoquinoline thiosemicarbazone was obtained as a gift from the National Cancer Institute

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

Compound	Colour	Found			Calculated			μ_{eff} μ_B at RT	θ K
		%C	%H	%N	%C	%H	%N		
1. $[Co(1\text{-iqtsc})_2]\cdot 2H_2O$	reddish brown	47.70	4.00	20.07	47.74	3.97	20.25	4.48	−4
2. $[Ni(1\text{-iqtsc-H})Cl_2]$	red	36.73	2.76	15.60	36.69	2.78	15.56	3.27	−2
3. $[Cu(1\text{-iqtsc-H})Cl_2]$	green	35.98	2.72	15.28	36.21	2.74	15.36	1.84	−8
4. $[Zn(1\text{-iqtsc-H})(OAc)_2]\cdot H_2O$	light yellow	41.70	4.19	13.04	41.72	4.17	12.98	Diamagnetic	
5. [Pt(1-iqtsc)Cl]	dark red	39.88	2.00	12.19	49.82	1.95	12.18	Diamagnetic	

and has been previously characterized [6]. Potassium tetrachloroplatinate(II) (Aldrich Chemical Co.) was used as such. Other metal(II) salts and solvents were reagent grade chemicals.

Synthesis

All the complexes were obtained by the following general method. To a solution of metal(II) salt (1 mmol) in the minimum amount of methanol or an aqueous solution of K_2PtCl_4 (0.415 g, 1 mmol) was added a suspension of 1-formylisoquinoline thiosemicarbazone (0.460 g, 2 mmol or 0.230 g, 1 mmol) in methanol and the mixture was stirred at room temperature for 40–60 min. The thiosemicarbazone gradually dissolved, and the shining crystals of the complexes separated from the solution. The crystals were filtered off, and then washed with water (in the case of Pt(II) complex only), methanol and finally ether. The crystals were dried over P_2O_5 under vacuum. Yield 60–85%.

Chemical analyses for carbon, hydrogen and nitrogen were carried out by the Microanalytical Laboratory of C.D.R.I., Lucknow, India. The analytical data are presented in Table I.

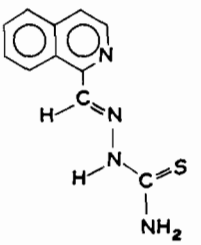
Physical Measurements

Conductance measurements in methanol at *ca.* 10^{-3} M were made on a Toshniwal conductivity bridge type CL 01/01. Magnetic measurements from room temperature down to liquid N_2 temperature were made on a standard Gouy's balance calibrated with $HgCo(NCS)_4$ [7]. Diamagnetic corrections were applied using Pascal's constants [8].

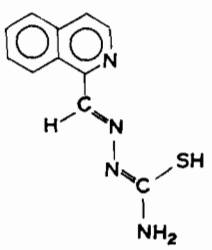
Diffuse reflectance spectra were recorded on a Cary-14 spectrophotometer equipped with a reflectance accessory, using MgO as the reference. The infrared spectra (4000–200 cm^{-1}) were recorded on a Perkin-Elmer 337 spectrophotometer in CsI pellets.

Results and Discussion

The infrared spectrum of 1-formylisoquinoline thiosemicarbazone (1-iqtsc-H) shows ν(NH) absorption bands at 3390(s) and 3260(s) cm^{-1} but no ν(SH) at *ca.* 2570 cm^{-1} is observed. Hence, in the solid state 1-iqtsc-H exists in the thione form **II**. However, in solution and in the presence of some metal ions 1-iqtsc-H probably forms an equilibrium mixture of the thione **II** and thiol **IIa** tautomers. Loss of the thiol proton from the form **IIa** affords a singly charged tridentate ligand coordinating through the mercapto sulphur, the central nitrogen and the isoquinoline nitrogen atoms. When 1-iqtsc-H in methanol is stirred at room temperature with methanolic or aqueous solutions of metal(II) salt,



II



IIa

it yields the complexes corresponding to the formula $[Co(1\text{-iqtsc})_2]\cdot 2H_2O$, $[M(1\text{-iqtsc-H})Cl_2]$ (M = Ni(II) or Cu(II)), $[Zn(1\text{-iqtsc-H})(OAc)_2]\cdot H_2O$ and [Pt(1-iqtsc)Cl]. These complexes are coloured crystalline compounds and quite stable at room temperature and do not show any decomposition after a long period of standing. 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, $C_6H_5NO_2$, $CHCl_3$, 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 lies in the 10.0–15.5 ohm^{-1} cm^2 mol^{-1} range indicating their non-electrolytic behaviour in solution [9]. Although the complexes do not possess sharp melting points, they decompose above 250 °C.

The assignments of some of the infrared spectral bands of free 1-iqtsc-H and its metal(II) complexes

TABLE II. Infrared Spectra of Metal(II) Complexes with 1-Formylisoquinoline Thiosemicarbazone (cm^{-1}).

1-iqtsc-H	Co	Ni	Cu	Zn	Pt	Assignment
3390s	3410s	3390s	3415s	3385m	3380s	ν_{as}(NH)
3260s	3295s	3300m	3300s	3305m	3300s	ν_s(NH)
1660s	1690s	1690m	1695s	1690s	1695s	$\delta(NH_2)$
1590s	1620s	1620s	1620m	1615s	1595m	Band I ring
1540s	1555s	1560s	1555m	1554s	1556s	ν(C=N)
1490m	1470s	1490m	1500m	1485m	1450s	ν(CS) + ν(CN) + $\delta(NH_2)$ Band III ring
1445m	1440m	1460sh	1448m	1450s	1455w	Band IV ring
1360s	1370b,m	1365sh	1365sh	1368m	1380m	ν(CS) + ν(CN) + $\delta(NH_2)$
1050s	1035sh	1028m	1025m	1030m	1030sh	ν(N–N)
800s	745s,b	746s,b	750s	748m	700s,b	ν(CS)

are reported in Table II. In the NH stretching frequency region, the high frequency spectral band ν_{as}(NH) remains practically unchanged on coordination with metal(II) ion relative to the free ligand, but the low frequency band of ν_s(NH) shifts to the high frequency side by about 40 cm^{-1}. This suggests that the nitrogen atom of the amino group does not take part in bond formation with the metal(II) ion as is partially confirmed by the shifting of the scissors deformation of the NH_2 group to the high frequency side by about 30 cm^{-1} and the high frequency shift of asymmetric and symmetric stretches of ν_{as}(CN) and ν_s(CN) of the –N–C(=S)–N– group by 25 and 20 cm^{-1}, respectively. The coordination of the azomethine nitrogen atom to the metal(II) ion is confirmed by the shifting of the ν(N–N) stretching band towards the low frequency side from 1050 cm^{-1} in the ligand [10] to approximately 1030 cm^{-1} and by the shifting of the 1540 cm^{-1} band, assigned mainly to ν(C=N) in the ligand, to higher frequency by approximately 15 cm^{-1} in the complexes.

In most complexes, the second donor in the thiosemicarbazone moiety is the sulphur atom [11]. The sharp band observed at 800 cm^{-1} in 1-iqtsc-H and assigned mainly to the ν(CS) stretching vibration shifts to a lower frequency on coordination by approximately 100 cm^{-1} in the Co(II) and Pt(II) complexes and by approximately 50 cm^{-1} in the Ni(II), Cu(II) and Zn(II) complexes. This situation is most probably consistent with the different geometries of these complexes (*vide infra*). The coordination of the nitrogen atom of the isoquinoline nucleus is confirmed by the shifting and splitting of the ring frequencies as is usually observed for other metal(II) pyridine complexes.

In the far-infrared spectral region the Co(II) complexes showed bands at 296(s) and 278(m) cm^{-1} which are assigned [11] to the ν(Co–S) and ν(Co–N) stretching vibrations, respectively. In the Ni(II), Cu(II) and Zn(II) complexes the ν(M–S) and ν(M–N) vibrations are observed at 290(s) and 260(s) cm^{-1} approximately and in the Pt(II) complex at 280(s) and 270(m) cm^{-1}, respectively [13]. In all these complexes the ν(M–N) isoquinoline appeared at 240m cm^{-1} [14] and ν(Ni–Cl) at 250(s) cm^{-1} [13]. Although these assignments are tentative because of the possibility of accidental coincidences and intensity variations, the position of the bands is consistent with six-(Co(II)), five-(Ni(II), Cu(II) and Zn(II)) and four-(Pt(II)) coordinate geometries [11, 13]. The monodentate coordination of acetato groups in the Zn(II) complex is confirmed [15] by the appearance of ν_{as}(COO) and ν_s(COO) bands at 1560(sb) and 1410(s) cm^{-1}, respectively.

The magnetic moments of the Co(II), Ni(II) and Cu(II) complexes were measured as a function of temperature from room temperature down to liquid N_2 temperature and the μ_{eff} values at room temperature with the Weiss constant, θ, are reported in Table I. The Zn(II) and Pt(II) complexes are diamagnetic. The μ_{eff} values of the Co(II) complex are consistent with those generally found for distorted octahedral monomeric cobalt(II) complexes [16], whereas the μ_{eff} values of the Ni(II) complex are in the range expected for distorted five-coordinate nickel(II) complexes [17]. The μ_{eff} values of the Cu(II) complex indicate that this complex is paramagnetic with one unpaired electron. The magnetic moments are of little use in determining the stereochemistry of the [Cu(1-iqtsc-H)Cl_2] complex, since there is little difference in magnitude between magnetic moments of the various configurations in copper(II) complexes [18, 19].

The UV spectra of free ligand 1-iqtsc-H exhibits intense bands at 27027, 28010, 30760, 32050, 35715 and 39840 cm^{-1} which are assigned to $\pi \rightarrow \pi^*$ transitions. The position of the bands suggests

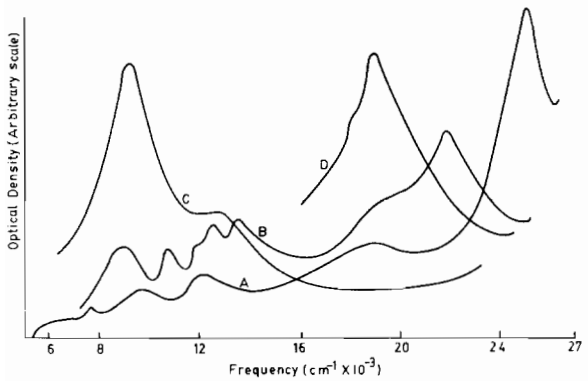


Fig. 1. Diffuse reflectance spectra: (A) $[Co(1\text{-iqtsc})_2]\cdot 2H_2O$; (B) $[Ni(1\text{-iqtsc-H})Cl_2]$; (C) $[Cu(1\text{-iqtsc-H})Cl_2]$; (D) [Pt(1-iqtsc)Cl].

the anti-(E)-form **II** of 1-iqtsc-H in the solid state [6]. The spectra of all metal(II) complexes in the UV region show bands of varying intensity almost at the same region as in the anti-form of the ligand, suggesting that in all the complexes the ligand has an anti-configuration in the solid state.

The diffuse reflectance spectrum of $[Co(1\text{-iqtsc})_2]\cdot 2H_2O$ exhibits three ligand field transitions in addition to the intense intraligand bands (Fig. 1(A)). The ligand field bands at 9800 and 12000 cm^{-1} are assigned to the components of ν_1, the $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ transition and the band at 19000 cm^{-1} is assigned to ν_2, the $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ transition. The ν_3, $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transition is obscured by a very intense charge transfer band which appears at 25000 cm^{-1} ($Co_{(eq)} \rightarrow Ligand_{(\pi^*)}$). In addition to the water overtone at 6530 cm^{-1}, a weak band is visible at 7580 cm^{-1} which is assigned to the spin-forbidden $^4T_{1g}(F) \rightarrow {}^2E_g(G)$ transition [20]. The significant splitting of the ν_1 band may be due to pronounced reduction in the ligand field symmetry caused by the greater steric requirements of two ligand molecules.

The reflectance spectrum of the $[Ni(1\text{-iqtsc-H})Cl_2]$ complex does not show any similarity with the spectra of regular or distorted octahedral nickel(II) complexes, although it bears a marked similarity in position and intensity of the spectral bands to the spectra exhibited by some high-spin five-coordinate nickel(II) complexes (Fig. 1(B)). In particular, the reflectance spectrum of the present complex resembles the spectrum of the $[Ni(Me_6tren)Br]$ [Me_6tren = tris(2-dimethylaminoethyl)amine] complex for which a distorted trigonal bipyramidal struc-

TABLE III. Antitumour Activity of Transition Metal Complexes of 1-Formylisoquinoline Thiosemicarbazone against the P388 Lymphocytic Leukaemia test System in Mice.

Compound	Treatment schedule	Dose mg/kg.	Wt. difference (T − C), %	T/C %
$[Co(1\text{-iqtsc})_2]\cdot 2H_2O$	A[a]	200.00		TOXIC
		100.00	−5.9	TOXIC
		50.00	−2.8	125*
		25.00	−0.5	103
		12.50	−0.8	106
$[Ni(1\text{-iqtsc-H})Cl_2]$	A	158.70	−3.4	161*
		79.35	−0.6	112
		39.68	−0.2	102
$[Cu(1\text{-iqtsc-H})Cl_2]$	A	150.15		TOXIC
		75.08		TOXIC
		37.04	−4.3	TOXIC
		18.50	−4.2	115
		9.25	−1.8	100
		4.63	−0.8	103
$[Zn(1\text{-iqtsc-H})(OAc)_2]\cdot 2H_2O$	A	240.00		TOXIC
		120.00		TOXIC
		60.00		TOXIC
		30.00	−1.6	126*
		15.00	−0.9	113
		7.50	−0.1	117
[Pt(1-iqtsc)Cl]	A	240.00	−0.8	95
		120.00	−0.1	104
		60.00	−0.7	91

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

ture (C_{3v} symmetry) has been suggested [21]. Thus the spectral bands observed at 8850, 10750, 12500, 13350, 19230sh 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 [22]. In addition to these transitions a band appears as a shoulder at 11900 cm^{-1} which is assigned as a spin-forbidden transition ($^3F \rightarrow {}^1D$).

The reflectance spectrum of the [Cu(1-iqtsc-H)-Cl_2] complex is similar to that of [Cu(Me_6tren)Br]-Br for which a trigonal-bipyramidal symmetry (C_{3v}) is suggested [21, 23] (Fig. 1(C)). Thus, the spectral bands observed at 9260 and 12500(sh) cm^{-1} in the [Cu(1-iqtsc-H)$(Cl)_2$] complex are assigned to $^2A_1 \rightarrow {}^2E$ and $^2A_1 \rightarrow {}^2E$ transitions, respectively [22].

The reflectance spectrum of the [Pt(1-iqtsc)-(Cl)] complex exhibits a shoulder at 17850 cm^{-1} and a maximum at 18860 cm^{-1} (Fig. 1(D)). These bands are assigned as metal-to-ligand ($Pt \rightarrow L_{\pi^*}$) charge transfer transitions [24].

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 leukaemic test system. The P388 lymphocytic leukaemia screen was carried out on $CD_2F_1(CDF_1)$ mice (male or female). On day one 0.1×10^6 ascites cells were injected intraperitoneally (ip). 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 a T/C of greater than 125% was considered significant activity against P388 tumour growth.

The thiosemicarbazone metal(II) complexes were evaluated for antitumour activity against the P388 lymphocytic leukaemia test system in mice and the screening data are listed in Table III. Except for Pt(II), the complexes showed significant antitumour activity. The highest level of activity was shown by the Ni(II) complex (T/C, 161%) at the optimum dosage.

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References

1 K. C. Agrawal and A. C. Sartorelli, *Prog. Med. Chem., 15,* 321 (1978).
2 A. C. Sartorelli, K. C. Agrawal, A. S. Tsiftsoglou and E. C. Moore, *Adv. Enzyme Regul., 15,* 117 (1977).
3 L. A. Saryan, E. Ankel, C. Krishnamurti and D. H. Petering, *J. Med. Chem., 22,* 1218 (1979).
4 M. Das and S. E. Livingstone, *Br. J. Cancer, 37,* 466 (1978).
5 J. P. Scovill, D. L. Klayman and C. F. Franchino, *J. Med. Chem., 25,* 1261 (1982).
6 I. Antonini, F. Claudi, P. Franchetti, M. Grifantini and S. Martelli, *J. Med. Chem., 20,* 447 (1977).
7 B. N. Figgis and R. S. Nyholm, *J. Chem. Soc.,* 4190 (1958).
8 F. E. Mabbs and D. J. Machin, 'Magnetism and Transition Metal Complexes', Chapman and Hall, London, 1961.
9 W. J. Geary, *Coord. Chem. Rev., 7,* 81 (1971).
10 G. R. Burns, *Inorg. Chem., 7,* 277 (1968).
11 M. J. M. Campbell, *Coord. Chem. Rev., 15,* 279 (1975).
12 B. F. Little and G. J. Long, *Inorg. Chem., 17,* 3401 (1978) and references therein.
13 B. Beecroft, M. J. M. Campbell and R. Grzeskowiak, *Inorg. Nucl. Chem. Lett., 8,* 1097 (1972); *J. Inorg. Nucl. Chem., 36,* 55 (1974).
14 D. M. Adams, 'Metal–Ligand and Related Vibrations', Edward Arnold, London, 1967, p. 269, 316.
15 A. B. P. Lever and D. Ogden, *J. Chem. Soc. A:,* 2041 (1967) and references therein.
16 D. A. Baldwin, A. B. P. Lever and R. V. Parish, *Inorg. Chem., 8,* 107 (1969).
17 M. Ciampolini and J. Gelsomini, *Inorg. Chem., 6,* 1821 (1967).
18 A. Earnshaw, 'Introduction to Magnetochemistry', Academic Press, New York, 1968.
19 B. J. Hathaway, in J. N. Bradley, R. D. Gillard and R. F. Hudson (eds.), 'Essays in Chemistry, Vol. 2', Academic Press, New York, 1971, p. 61.
20 C. K. Jørgensen, 'Absorption Spectra and Chemical Bonding in Complexes', Pergamon Press, Oxford, 1964, p. 134.
21 M. Di Vaira and P. L. Orioli, *Acta Crystallogr., Sect. B:, 24,* 595 (1968).
22 M. Ciampolini, *Struct. Bonding (Berlin), 6,* 52 (1969).
23 M. Ciampolini and N. Nardi, *Inorg. Chem., 5,* 41 (1966).
24 M. Akbar Ali, S. E. Livingstone and D. J. Phillips, *Inorg. Chim. Acta, 5,* 493 (1971).