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Complexes of some Trace Metal Ions with 5-Fluorouracil

UDAI P. SINGH, RANJANA GHOSE and ANIMESH K. GHOSE*

Chemical Laboratories, Faculty of Science, Banaras Hindu University, Varanasi-221005, India

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Abstract

The preparation of 5-fluorouracil complexes with Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) are reported. The new complexes have been characterised by elemental analysis, solid-state infrared, electronic spectra and magnetic measurements. These measurements suggest that the ligand is bonded to the metal ions through the carbonyl group, behaving as a monodentate ligand. On the basis of the ν(OH) bending frequencies and the insolubility of the complexes in common organic solvents, polymeric structures have been proposed for the complexes, with bridging through OH groups. Mn(II), Zn(II) and Cd(II) form four-coordinated complexes, while six coordination numbers have been suggested for Co(II), Ni(II) and Cu(II).

Introduction

Only a few substituted pyrimidines have been reported to be active as chemotherapeutic agents. These agents have the ability to bind to metals or to bind to tissues via metals. Some of the pyrimidines have been found to be chemically useful. The most useful is 5-fluorouracil (5-FURL) which was introduced in 1957 [1]. It has been extensively investigated as a potential anti-cancer drug in man and animals. This drug has proved to be quite effective in solid human tumours and also when used in conjunction with X-rays [2]. It can also be used as an antibacterial agent [3] and for the treatment of gastric cancer [4]. Through a study of the etiology and treatment of cancer a recent possible mechanism has been suggested in which the transition metal ions play an important role directly or through metal binding agents. Hence, a study of the metal complexes of 5-FURL would prove to be interesting from the point of view of biochemical reactions. Thus the present paper investigates the interaction of some trace metal ions with 5-FURL and studies the binding sites of the drug.

Experimental

Throughout the experiment, reagent grade chemicals were used. The metal nitrates used were of Merck grade. 5-FURL (Aldrich) was dissolved in the minimum amount of ethyl alcohol and an alcoholic solution of the metal nitrate was mixed to the hot solution of the ligand. NaOH solution was added to the above mixture to precipitate the new complexes in the pH range 4–6. The precipitate was then filtered, washed several times with dried ethyl alcohol and finally with ether. It was oven-dried at about 50 °C.

The metal ions were estimated by EDTA titrations [5] after dissolving the complexes in dil. HNO_3. Nitrogen was analysed by a Coleman model 29 nitrogen analyzer. Solid state infrared spectra were obtained on Nujol mulls between 4000–200 cm^{-1} with a Perkin-Elmer 783 spectrophotometer. Solid state (Nujol mull) electronic spectra were recorded with a Hitachi 320 spectrophotometer. The magnetic susceptibility measurements were made at 305 K by using a Faraday magnetic susceptibility balance.

Results and Discussion

All the new complexes synthesized are coloured (Table I) except those of zinc and cadmium. They are generally insoluble in common organic solvents (*viz.* ethyl alcohol, methyl alcohol, acetone, ether, carbon tetrachloride, chloroform, benzene, acetonitrile, carbon disulphide, pyridine, tetrahydrofuran, dimethylformamide, dimethylsulphoxide, etc.). The insolubility of the complexes in various organic solvents made studies like NMR, molar conductivity, etc. impossible in solution. The complexes do not melt below 300 °C. All the metal ions under test, i.e. Mn(II), Co(II), Cu(II), Zn(II) and Cd(II), form 1:1 metal:ligand complexes except Ni(II) which forms a 1:2 complex.

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*Author to whom correspondence should be addressed.

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TABLE I. Analytical Data (%) and Colour of the Complexes

Complex	Colour	M		N		H	
		Calculated	Found	Calculated	Found	Calculated	Found
$Mn(OH)_2(5\text{-FURL})\cdot H_2O$	black	23.18	23.12	11.81	11.70	2.95	2.90
$Co(OH)_2(5\text{-FURL})\cdot 3H_2O$	violet	21.28	21.20	10.11	10.02	3.97	3.91
$Ni(OH)_2(5\text{-FURL})_2\cdot 2H_2O$	green	16.63	16.62	14.40	14.30	3.08	3.04
$Cu(OH)_2(5\text{-FURL})\cdot 3H_2O$	light blue	22.56	22.47	9.94	9.89	3.90	3.85
$Zn(OH)_2(5\text{-FURL})\cdot H_2O$	white	26.42	26.35	11.31	11.20	2.82	2.79
$Cd(OH)_2(5\text{-FURL})\cdot H_2O$	white	38.17	38.09	9.51	9.46	2.37	2.33

TABLE II. Infrared Spectral Data of Uracil (URL) and 5-Fluorouracil (5-FURL) (cm^{-1})

Band assignment	URL	5-FURL
ν(N–H) in-phase	3160m	3160m
ν(N–H) out-of-phase	3160m	3160m
ν(C–H) in-phase	3100s	3120s
ν(C–H) out-of-phase	3080s	3100s
ν(C(2)=O)	1712s	1710s
ν(C(4)=O), ν(C=C) in-phase	1675s	1695s
δ(N–H(1))	1510m	1512m
ν(C–F)		1470s
ν ring	1453s	1462s
δ(N–H(3))	1417s	1430m
δ(C–H) in-phase	1390m	1417w
ν(C–F)		1376s
ν ring	1238s	1245s
δ(C–H) out-of-phase	1217w	1220m
ν ring	1099w	1180m
ν ring	1003m	1020w
ν, δ ring	993m	995m
ν, δ ring	781w	809w
δ ring	587m	642s
δ(C=O) in-phase	566m	603s
δ ring	550s	552s
C–F deformation		470
C–F deformation		330
C–F deformation		252
C–F deformation		218

Infrared Spectra

Table II shows the characteristic IR spectrum of 5-FURL. The IR spectrum of uracil (URL) is available in the literature [6]. The assignments of the spectrum of 5-FURL have been made by comparing its spectrum with URL. The C–F frequencies have been assigned on the basis of the literature data [7]. The C–F bands absorb intensely between 1400–1000 cm^{-1}. In the IR spectrum of 5-FURL, strong ν(C–F) bands appear at 1470 cm^{-1} and 1376 cm^{-1}. These bands are absent in the spectrum of URL. C–F deformation bands [8] appear at 470 cm^{-1}, 330 cm^{-1}, 252 cm^{-1} and 218 cm^{-1}. Fluorines linked alpha or beta to carbonyl groups raise the ν(C=O) frequency considerably because of the strong $-I$ effect. The same has also been observed in the present case. The ν(C(4)=O) + ν(C=C) in-phase band occurs at 1675 cm^{-1} in URL, but in 5-FURL the band shifts to a higher frequency region (about 1695 cm^{-1}) due to the inductive effect of fluorine. However, the ν(C(2)=O) band which appears at 1712 cm^{-1} in URL remains almost unchanged in 5-FURL (1710 cm^{-1}). The IR spectra of the metal complexes of 5-FURL (Table III) do not show any shift in the frequencies of either the ν(C–F) or ν(C(2)=O) bands, indicating that neither F nor C(2)=O is taking part in coordination with the metal ions.

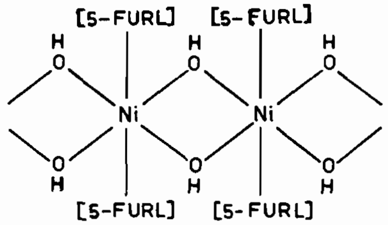
Table III also shows a considerable shift in the frequency of the ν(C(4)=O) band towards the lower frequency side of about 30 to 40 cm^{-1} on complex formation with the ligand, with respect to 5-FURL. This indicates that 5-FURL forms a complex with the metal ion only through its 4-keto group.

The ν(OH) bending frequencies of the complexes appear at about 950 cm^{-1}, showing a bridge structure formation through OH groups [9]. Since the complexes are insoluble in common organic solvents, it can be inferred that formation of a polymeric structure of the complexes through OH bridging groups takes place.

The ν(M–O) frequencies appear at the lower frequency region of the complexes, showing that Mn(II), Zn(II) and Cd(II) have the coordination number four in the complexes, whereas Co(II), Ni(II) and Cu(II) form hexacoordinate complexes [10]; ν(OH) frequencies assigned in the range 3500–3250 cm^{-1} [11] and ν(M–O)(aqua) band assignments, as shown in Table III, suggest the coordination of aqua ligand to the complexes. The tentative structures (**I** and **II**) of the complexes are as follows:

TABLE III. Some Characteristic IR Bands of the Ligand and its Metal Complexes

Complexes and ligand	ν(O–H)	ν(N–H) in-phase	ν(N–H) out-of-phase	ν(C–H) in-phase	ν(C–H) out-of-phase	ν(C(2)=O)	ν(C(4)=O), ν(C=C) in-phase	δ(N–H(1))	ν(C–F)	δ(N–H(3))	ν(C–F)	ν(M–O) (aqua)	ν(M–O)
5-FURL		3160m	3160m	3120s	3100s	1710s	1695s	1512m	1470s	1430m	1376s		
$Mn(OH)_2(5\text{-}FURL)\cdot H_2O$						1710s	1646s	1503m	1470s	1436m	1378s	378m	276m
$Co(OH)_2(5\text{-}FURL)\cdot 3H_2O$	3270, 3390	3160s	3160s	3140s	3030s	1710s	1651s	1504m	1470s	1437w	1378s	435w	240m
$Ni(OH)_2(5\text{-}FURL)_2\cdot 2H_2O$	3340b	3180s	3180s	3110s	3070s	1710s	1660s	1505m	1470s	1428w	1378s	405m	240m
$Cu(OH)_2(5\text{-}FURL)\cdot 3H_2O$	3340, 3390			3160s	3085s	1710s	1652s	1504m	1470s	1424w	1378s	469m,b	240m
$Zn(OH)_2(5\text{-}FURL)\cdot H_2O$						1710s	1652s	1505m	1470s	1436w	1378s	375m	276m
$Cd(OH)_2(5\text{-}FURL)\cdot H_2O$						1710s	1650s	1510m	1470s	1430w	1378s	355m	278s



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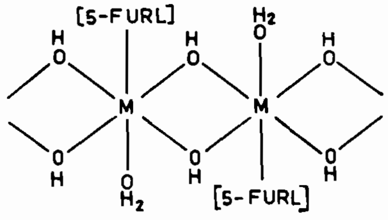

II

Electronic Spectra and Magnetic Susceptibilities

The solid state (Nujol mull) spectrum of 5-FURL shows $\pi \rightarrow \pi^*$ transition bands at 220 nm, 242 nm and an $n \rightarrow \pi^*$ transition band at 285 nm [12] (Table IV). Changes in the UV bands have been observed upon metal complex formation. The $\pi \rightarrow \pi^*$ transition bands which appear at 220 nm and 242 nm in 5-FURL undergo a sizeable shift to the lower range upon complexation. All the metal complexes show two $\pi \rightarrow \pi^*$ transition bands of the ligand between 215 to 217 nm and 234 to 237 nm, respectively. The bands become sharp in the spectrum of the Co(II) complex while they appear to be broad for other metal complexes. The $n \rightarrow \pi^*$ transition band appearing at 285 nm in 5-FURL disappear in the spectra of Zn(II) and Ni(II) complexes. The spectra of other metal complexes do not show any shift of the $n \rightarrow \pi^*$ transition band.

The d–d transition bands of the Mn(II) complex appear at 266 nm (^4F term), 364 and 347 nm (^4P and ^4D terms) and 494 and 465 nm (^4G term), indicating a tetrahedral structure [13] for the Mn(II) complex which has a magnetic susceptibility of 5.91 B.M. The magnetic moment value of the Co(II) complex is 5.14 B.M. The Co(II) complex shows bands at 520 nm ($^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$) and 820 nm ($^4T_{1g}(F) \rightarrow {}^4A_{2g}$). The second band is the weaker [13]. The band due to the $^4T_{1g}(F) \rightarrow {}^4T_{2g}$ transition has not been observed in the present case as it is likely to appear above 1000 nm. On the basis of the above assignments, an octahedral structure for the Co(II)–5-FURL complex may be proposed. The new Ni(II) complex has a magnetic moment value of 3.03 B.M., suggesting it to be of octahedral geometry [14]. Its electronic spectrum shows bands at 390 nm and 675 nm, corresponding to $^3A_{2g} \rightarrow {}^3T_{1g}(P)$ and $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ transitions, respectively. The band due to the transition

TABLE IV. Solid State (Nujol Mull) Electronic Spectra and Magnetic Susceptibilities (305 K) of the New Complexes

Complexes	λ_{max} (nm)[a]	μ_{eff} (BM)
$Mn(OH)_2(5\text{-FURL})\cdot H_2O$	215b, 237b, 285b, 266, 347, 364, 465, 494	5.91
$Co(OH)_2(5\text{-FURL})\cdot 3H_2O$	215s, 237s, 285s, 520, 820	5.14
$Ni(OH)_2(5\text{-FURL})_2\cdot 2H_2O$	215b, 235b, 390, 675	3.03
$Cu(OH)_2(5\text{-FURL})\cdot 3H_2O$	216b, 235b, 285s, 670, 720	1.97
$Zn(OH)_2(5\text{-FURL})\cdot H_2O$	217b, 234b	diamagnetic
$Cd(OH)_2(5\text{-FURL})\cdot H_2O$	217b, 234b, 285s,b	diamagnetic

[a] Nujol mull spectrum of 5-FURL, nm: 220s, 242s, 285s,b; s = sharp, b = broad.

$^3A_{2g} \rightarrow {}^3T_{2g}$ could not be observed as it is likely to appear beyond 900 nm. This suggests an octahedral geometry for the complex. The magnetic moment value of the Cu(II) complex is 1.97 B.M. Its electronic spectrum bands appear at 670 nm and 720 nm and are consistent with six-coordination complexes. Thus, a distorted octahedral structure may be proposed in this case.

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