P: ISSN NO.: 2321-290X RNI : UPBIL/2013/55327 VOL-6 * ISSUE-6 * (Part-1) February- 2019
E: ISSN NO.: 2349-980X **Shrinkhla Ek Shodhparak Vaicharik Patrika**

Systhesis, Structural and Antitumor Studies of Metal Complexes of Guanine with Cytosine and Its Derivatives

Mangey Ram
Lecturer,
Dept. of Chemistry
M.S. College,
Saharanpur, U.P., India

Magan Singh
Lecturer,
Dept. of Chemistry
M.S. College,
Saharanpur, U.P., India

Ravideep Singh
Lecturer,
Dept. of Chemistry
M.S. College,
Saharanpur, U.P., India

Abstract

Present study is based on the interaction of DNA with Ca(II), Mn(II) and cu(II) ions in a solution of low ionic strength by differential UV spectroscopy and CD spectroscopy. We studied the formation of metal complexes of cytosine and its derivatives in the presence of its complementary urine base (guanine) with metal ions viz., Co(II), Ni(II), Cu(II) Zn(II) and Cd(II) subsequently the structure of the new mixed complexes have been suggested. The antitumor activity of these mixed complexes has also been tested both in vivo and in vitro.

Keywords: Cytosine, Guanine, Antitumor, Inhibitors, Mispair, Dalton's Lymphona.

Introduction

Due to the interesting biological properties of cytosine, its halo derivatives, guanine and other interesting organic compounds. Mixed ligand complexes of cytosine are known to play an important role in biological systems. Szalda and coworkers reported the preparation and structure of the complex (N-salicylidene-N'-methylethylenediamine) (cytosine) copper(II) nitrate. Khan and coworkers[316] have synthesized K[Ru(edta)(Cyt)]. $2H_2O$ and ruthenium (III) perchlorate complexes with purines, pyrimidine s and nucleosides. Cervantes and co workers synthesized and characterized the nickel(II) complexes of purine and pyrimidine bases.Various workers used theoretical methods to calculate metal-ligand bond energies of different nucleobases present in DNA and RNA.

Results and Discussion

The composition of the complexes and analytical data are listed in Table. The new complexes were obtained according to the general reaction in aqueous alkali solution

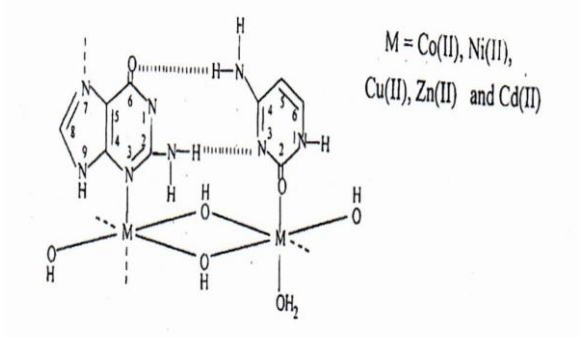
$$2M(NO_3)_2 + L + G + 4NaOH \quad [M_2(OH)_4(L)(G)(H_2O)]\ 2H_2O + 4NaNO_3$$

Here author represents as cytosine and 5-azacytosine and G represented as guanine. The molar ratio of the mixed ligand complexes was M:L:G (2:1:1), All of the complexes are coloured except those of Zn(II) and Cd(II) as reported in Table .1. They are insoluble in almost all common organic solvents as well as in water. Due to their insolubility in different solvents, studies electronic spectroscopy). It may be inferred from the insolubility of the mixed-ligand complexes in most of the solvents that they are polymeric in nature.It is therefore concluded from the results obtained in present studies that all the synthesized metal complexes with cytosine-guanine, 5-azacytosine guanine and 5-fluorocytosine-guanine base pair have octahedral geometry. Regarding the antitumor activity studies. Metal complexes of 5-Azacytosine-guanine mispair are effective antitumor agents against Dalton's Lymphona (ascites) both in vitro and in vivo.

Electronic Spectra and Magnetic Moments

The magnetic moment value is 4.85 B.M. for [Co_2(C) (G)(OH)4(H2O)]. 2H2O and 4.90 B.M. for [CO_2(5AC)(G)(OH)4(H2O)] 2H2O. Their electronic spectra exhibit bands at 520 nm (4_{T1}g(P) 4T1g(F)(V3)), 825 nm (4A2g(F) 4T1g(F)(V2)) for [Co_2(C)(G) (OH)4(H2O) and 528 nm (4_{T1g}(P) 4_{T1g}(F)(V_3)), 832 nm (4_{A2g}(F) 4_{T1g}(F)(V_2)) for [Co_2(5AC)(G)(OH)4(H2O) 2H2O.The 4T2g(F)4 T1g(F)(V1) transition could not observe in above complexes as it is likely to appear above 1000 nm. The above magnetic moment values and electronic spectra spectra suggested an octahedral geometry for all these above complexes.The

electronic spectral band at 384 nm (3T1g(P) 3_{A2g}(F)(V3)), 584 nm (3_{T2g}(F)3 A_{2g}(F)(V_2)) for [Ni_2(C)(G)(OH)4(H_2O)] 2H2O ad 386 nm (3_{T1g}(P) $3A_{2g}$(F)(V_3)), 684 nm (3_{T2g}(F) $3A_g$(F)(V_2)) for [Ni_2(5AC)(G)(OH)4(H2O)] 2H_2O complexes. The $3T_{2g}$(f) $3A_{2g}$(F)(V1), transitions however, could not be obtained as they are likely to appear beyond 1000 nm. These data thus favour an octahedral geometry for this entire mixed compound which have the magnetic value 3.10 B.M. and 3.63 B.M. respectively. The magnetic moment values for Cu(II) complexes with C-G and 5AC-(i) are 1.80 B.M. and 1.74 B.M. respectively. Showing the presence of one unpaired electron. The occurrence of d-d transition bands at 690 nm for [Cu_2(C)(G)(OH)4(H_2O)] 2H2O and 712 nm for [Cu_2(5AC)(G)(OH)4(H2O)] 2H_2O favoured distorted octahedral geometry for these complexes On the basis of above studies the structure of the complexes may be suggested as shown here where



show the start of another unit of polymer. The complexes are polymeric in nature involving adenine as well as-OH group as bridging legends. During polymerization one metal atom is bound via-N3 atom of one adenine legend and-N7 atom of other adenine legend. On the basis of the above studies, the structure of the complexes may be supported as shown in the above figure. As shown in figure the complexes are polymeric in nature involving adenine as well as-OH group as bridging legends. During polymerization one metal atom is bound via-N_3 atom of one adenine legend and –N_7 atom of other adenine legend.

Antitumor Activity Study against Dalton's Lymphoma

All the synthesized metal complexes were tested for their antitumor activity against Dalton's Lymphoma (ascites) at the doses reported in chapter 2. It was observed that the metal complexes of 5-azacytosine-guanine mispair had better antitumor acitivity in comparison to cytosine-guanine and 5-azacytosine-guanine complexes. Hence the antitumor activity for 5-azacytosine-guanine mispair complexes are reported.

As shown in Table 5.4, out of the five metal complexes with 5-fluorocytosine- guanine mispair, four complexes i.e. [Ni2(5AC)(G)(Oh)4(H2O)] 2H2O, [CU2(5AC) (G)(OH)4(H2O)] 2H2O, [Zn2(5AC) (G) (OH)4 (H2O)] 2H2O, [Cd2(5AC) (G)(OH)4(H2O)] 2H2O has significant antitumor activity with T/C value $\geq$ 115. [Co2(5AC)(G)(OH)4(H2O)]2H2O was not therapeutically effective at the tested dose as its T/C value is 107. Similar results were obtained from in vitro experiment as reported in Table 5.4 DL cells ere inhibited in vitro in medium alone or contgaining the indicated dose of the complexes and the cell proliferation was estimated by MTT assy. The in vitro results cooperated the in vivo finding where all the four complexes namely [Ni2(5AC)(G)(OH)4(H2O)]2H2o, [Cu2(5AC)(G) (OH)4(H2O)]2H2O, [ZN2(5AC)(G)(OH)4(H2O)].2H2O and [Cd2(5AC) (G) (OH)4(H2o)].2H2o showed the higher % inhibiton of DL cells proliferations as compared to that with [Co2(5AC)(G) (OH)4(H2O).2H2o or cell inhibited in medium alone. In order to find out the antitumor effect of these complexes was specific to tumor cells alone their effect was also checked on growth of two normal proliferating cell types.

It is therefore concluded from the results obtained in present studies that all te synthesized metal complexe with cytosine-guanine, 5-azacytosine guanine and 5-fluorocytosine-guanine base pair have octahedral geometry. Regarding the antitumor activity studies. Metal complexes of 5-Azacytosine-guanine mispair are effective antitumor agents against Dalton's Lymphona (ascites) both in vitro and in vivo.

TABLE 5.1 ANALYTICAL DATA AND COLOUR OF THE COMPLEXES

S N	COMPLEXES	FORMULA WEIGHT	COLOUR	YIELD	% OF ELEMENTS FOUND (CALCULATED)			
					METAL	CARBON	HYDROGEN	NITROGEN
1	$[Co_2(C)(G)(OH)_4(H_2O)].2H_2O$ $(Co_2C_9H_{20}N_8O_9)$	502.17	VIOLET	82	23.15 (23.48)	21.76 (21.54)	3.98 (4.02)	22.02 (22.32)
2	$[Ni_2(C)(G)(OH)_4(H_2O)].2H_2O$ $(Ni_2C_9H_{20}N_8O_9)$	501.72	GREEN	86	23.22 (23.40)	21.20 (21.56)	4.14 (4.02)	22.14 (22.34)
3	$[Cu_2(C)(G)(OH)_4(H_2O)].2H_2O$ $(Cu_2C_9H_{20}N_8O_9)$	511.42	GREEN	88	24.45 (24.85)	21.02 (21.15)	3.80 (3.95)	21.82 (21.92)
4	$[Zn_2(C)(G)(OH)_4(H_2O)].2H_2O$ $(Zn_2C_9H_{20}N_8O_9)$	515.10	WHITE	90	25.00 (25.40)	20.70 (21.00)	4.00 (3.92)	21.62 (21.75)
5	$[Cd_2(C)(G)(OH)_4(H_2O)].2H_2O$ $(Cd_2C_9H_{20}N_8O_9)$	609.10	WHITE	92	36.88 (36.90)	17.55 (17.75)	3.20 (3.32)	18.20 (18.40)
6	$[Co_2(5AC)(G)(OH)_4(H_2O)].2H_2O$ $(Co_2C_8H_{19}N_9O_9)$	503.18	PINK	82	23.16 (23.40)	19.00 (19.10)	3.84 (3.80)	25.20 (25.10)
7	$[Ni_2(5AC)(G)(OH)_4(H_2O)].2H_2O$ $(Ni_2C_8H_{19}N_9O_9)$	502.70	GREEN	85	23.30 (23.36)	19.00 (19.12)	3.76 (3.80)	25.15 (25.10)
8	$[Cu_2(5AC)(G)(OH)_4(H_2O)].2H_2O$ $(Cu_2C_8H_{19}N_9O_9)$	512.40	GREEN	88	24.60 (24.80)	18.50 (18.75)	3.64 (3.74)	24.76 (24.60)
9	$[Zn_2(5AC)(G)(OH)_4(H_2O)].2H_2O$ $(Zn_2C_8H_{19}N_9O_9)$	516.10	WHITE	85	25.20 (25.35)	18.45 (18.60)	3.60 (3.70)	24.52 (24.42)
10	$[Cd_2(5AC)(G)(OH)_4(H_2O)].2H_2O$ $(Cd_2C_8H_{19}N_9O_9)$	610.10	WHITE	86	36.60 (36.85)	15.85 (15.75)	3.20 (3.15)	20.80 (20.66)

Materials and MethodsDoubly Distilled Water (Conductivity Water)

Doubly distilled water was prepared by redistilling distilled water in corning glass round bottom flask containing few crystals of potassium permanganate and potassium hydroxide to expel carbon dioxide and was cooled in stoppered corning flasks. Doubly distilled water was stored in flask mad of corning glass.

Sodium Hydroxide, NaOH

Sodium hydroxide of Merck was used.

Oxalic Acid $C_2H_2O_4 . 2H_2O$

The solution of oxalic acid (Merck) was prepared directly by dissolving appropriate weighed amount of its sample in doubly distilled water. It is easily soluble in water.

Potassium Nitrate, KNO_3

The solution of potassium nitrate (Merck) was prepared directly by dissolving appropriate weighed amount of its sample in doubly distilled water.

Nitric Acid HNO_3.

(2.0 mol dm^{-3}) stock and standard solution of nitric acid (Merck) was prepared by dissolving appropriate volume of its sample (analytical reagent grade) slightly higher than that required. In doubly distilled water.

Metal Nitrates

Cobalt nitrate $Co(NO3)_2$. $6H_2O$ Nickel Nitrate Ni $(NO_3)_2$ $6H_2O$ Copper Nitrate, Cu $(NO_3)_2$ $3H_2O$ Zinc Nitrate Zn $(NO_3)_2$ $4H_2O$ Cadmium Nitrate Cd $(NO_3)_2$ Calcium Nitrate, Ca $(NO_3)_2$ $4H_2O$ Strontium nitrate Sr $(NO_3)_2$ Barium Nitrate Ba $(NO_3)_2$ (All Merck make) The solution of metal nitrate were prepared by dissolving appropriate weighed amount of their sample (analytical reagent grade)

Guanine (Ligand)

The stock and standard solution of guanine ($1.0x10^{-2}$ mol dm-3) was prepared by dissolving appropriate amount of its sample (SRL make) in known concentration of sodium hydroxide solution. The final concentration of sodium hydroxide was$5.0x10^{-2}$ mol dm-3 in guanine solution.

Others Ligands

Cytosine Cytidine (SRL make) 5-Azacytosine (Fluka make) 5-Fluorocytosine (Fluka make),5-Bromocytosine (Fluka make),5-Bromouracil (Fluka make) The stock and standard solution of ligands ($1.0x10^{-2}$ mol dm^{-3}) were prepared by dissolving appropriate amount of their sample in minimum volume of doubly distilled water

Magnetic Susceptibility Measurements

Room temperature magnetic susceptibility was done on Cahn Faraday magnetic susceptibility balance suing cobalt mercury tetra thiocyanate as a calibrant and the experimental magnetic susceptibilities were corrected for diamagnetism using the procedure described by Figgis and Lweis.

CHN Analyzer

Carbon, hydrogen and nitrogen were analysed with a Vario EL III elemental analyser.

Determination of Stepwise Formation Constants

As the majority of organic completing legends used in analytical chemistry are moderately strong bases and become protonated in the Ph RANGE mostly applied in practice (i.e. acidic Ph range), methods based on Ph measurement are often applicable for the determination of stability constants.

Aim of the Study

We Studied the formation of metal complexes of cytosine and its derivatives in the presence of its complementary purinine base (guanine) with metal ions viz., Co(II), Ni(II), Cu(II), Zn(II) and cd(II) subsequently the structure of the new mixed complexes have been suggested. The antitumor activity of these missed complexes has also been tested both in vivo and in vitro.

Conclusion

The study of base pair instruction with metal ions is very scanty It inspired us to studies of the base pair interaction in several binary as well as ternary complexing systems in solution on the base of above study the five metal complexes with five fluorocytosine g, Co, Ni, Cu, Zn, Cd % of T/C, the value of T/C Co=107, Ni= 127, Cu= 152, Zn= 150, Cd= 137 on the above result the poor result of Co=107 complex, Ni=

127, Cd=137 medium and Zn=150 Cu= 152 good result, complexes against Diltion Lemphoma both in vitro in vivo.

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