

## Synthesis and FTIR Spectra of the Complexes of Tumor Cell Differentiating Agent Hexamethylene Bisacetamide with Metal (II) Halides

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**Summary:** The syntheses are reported of a number of complexes of tumor cell differentiating agent Hexamethylene bisacetamide (HMBA) with group II metal halides. These complexes have been characterized by elemental analyses. The FTIR spectra of all these complexes as well as those of previously reported Nickel (II), Manganese (II) and Cobalt (II) complexes [1-3] have been measured and the mode of coordination of ligand has been established. In all of these complexes, the HMBA molecules have been coordinated with the metal ions through their carbonyl oxygen atoms.

### Introduction

Among the class of agents which have the potential of inducing differentiation of tumor cells and which represent an exciting and novel approach to the chemotherapy of neoplasia, hexamethylene bisacetamide (HMBA) has proved to be the most potent inducer of differentiation of a number of transformed cells [4-6]. HMBA, a highly polar compound, induces murine erythroleukemia cells to express the erythroid phenotype including the cessation of proliferation. HMBA has recently been reported to inhibit the proliferation of human and rat vascular smooth-muscle cells [7]. HMBA has a number of characteristics which render it one of the most interesting and greatest potential clinical use [8-9] and it has entered clinical trials, for the treatment of human cancers [10].

Although, a tremendous amount of work has been done to understand the therapeutic roles played by HMBA, little efforts have been made to study the existence of complexes of HMBA with metal (II) halides. Previously, the synthesis of the complexes of Ni (II), Mn(II) and Co(II) halides [1-3] have been reported only but FTIR spectra of none of them was studied. The X-ray crystal structure of HMBA has previously been reported [11] and the amide groups were found in trans-configuration (Fig. 1).

Here we report the syntheses of a number of complexes formed by tumor cell differentiating agent, HMBA, with group (II) metal halides, which

include  $M(HMBA)_2 X_2$  ( $M=Mg$  and  $Ca$ ;  $X=Cl$  or  $Br$ ),  $Zn(HMBA)_2 Cl_2 \cdot H_2O$ ,  $M_2(HMBA) Cl_4$  ( $M=Cu$ ,  $Cd$  and  $Hg$ ) and  $Cd_3(HMBA) X_6$  ( $X = Cl$  or  $Br$ ). All these complexes have been characterized by elemental analysis and the mode of coordination of ligand, in these complexes and also in previously reported manganese, cobalt and nickel complexes has been established by FTIR spectra.

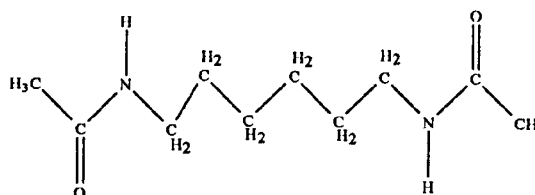


Fig. 1: Structure of the HMBA

### Results and Discussion

All the complexes of HMBA with group(II) metal halides, synthesized in the present work are reported in Table-1, together with their elemental analyses. The infra-red spectra of HMBA and its deuterated analogue have previously been reported and the assignments of the bands have been made on the basis of their shifts on deuteration [12] and present results are in good agreement with those reported previously.

The characteristic infra-red spectral bands for all the complexes of HMBA, together with those of

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Table-1: Analytical data of complexes of HMBA with metal (II) halides

Compound	Elemental analysis (%) <sup>a</sup>		
	C	H	N
[Mn(HMBA) <sub>3</sub> ][MnCl <sub>4</sub> ]	42.26(42.26)	7.02(7.04)	9.79(9.86)
[Mn(HMBA) <sub>3</sub> ][MnBr <sub>4</sub> ]	35.25(34.96)	5.88(5.83)	8.22(8.16)
[Co(HMBA) <sub>3</sub> ][CoCl <sub>4</sub> ]	41.69(41.87)	6.97(6.98)	9.66(9.77)
[Co(HMBA) <sub>3</sub> ][CoBr <sub>4</sub> ]	35.17(34.69)	5.96(5.78)	8.13(8.09)
[Ni(HMBA) <sub>3</sub> ][NiCl <sub>4</sub> ].2H <sub>2</sub> O	40.15(40.20)	7.27(7.15)	9.21(9.38)
[Ni(HMBA) <sub>3</sub> ][NiBr <sub>4</sub> ].H <sub>2</sub> O	34.05(34.11)	7.07(5.88)	8.02(7.96)
Ni(HMBA)Cl <sub>2</sub> .H <sub>2</sub> O	35.19(34.51)	6.24(6.33)	8.05(8.05)
Ni <sub>3</sub> (HMBA)Cl <sub>6</sub> .3H <sub>2</sub> O	18.64(18.66)	3.69(4.04)	4.17(4.35)
Mg(HMBA) <sub>2</sub> Cl <sub>2</sub>	48.79(48.45)	9.78(8.08)	11.19(11.31)
Mg(HMBA) <sub>2</sub> Br <sub>2</sub>	41.59(41.07)	8.07(6.85)	9.65(9.58)
Ca(HMBA) <sub>2</sub> Cl <sub>2</sub>	46.52(46.97)	7.73(7.83)	10.73(10.96)
Ca(HMBA) <sub>2</sub> Br <sub>2</sub>	40.11(40.00)	7.47(6.67)	9.31(9.33)
Cu <sub>2</sub> (HMBA)Cl <sub>4</sub>	25.34(25.58)	4.19(4.26)	5.74(5.97)
Zn(HMBA) <sub>2</sub> Cl <sub>2</sub> .H <sub>2</sub> O	43.08(43.29)	7.34(7.57)	10.12(10.10)
Cd <sub>3</sub> (HMBA)Cl <sub>6</sub>	16.30(16.00)	2.68(2.67)	3.74(3.73)
Cd <sub>3</sub> (HMBA)Br <sub>6</sub>	11.76(11.79)	1.91(1.97)	2.66(2.75)
Cd <sub>2</sub> (HMBA)Cl <sub>4</sub>	21.72(21.17)	3.58(3.53)	4.90(4.94)
Hg <sub>2</sub> (HMBA)Cl <sub>4</sub>	16.73(16.15)	2.59(2.69)	3.79(3.77)

<sup>a</sup>Calculated values in parentheses.

Table-2: Characteristic infra-red spectral bands of HMBA complexes.

Complex	C=O Str. (Amide I) band	Amide II band	CH Defor. C=O Char. band	Amide III band
HMBA	1648 Sh			
	1631 VS	1537 S	1475 S	1285 M
HMBA (Deuterated)	1625 VS	1422 S	1478 S	1137 M
			1462 S	
[Mn(HMBA) <sub>3</sub> ][MnCl <sub>4</sub> ]	1627 VS	1564 S	1437 S	1303 M
[Mn(HMBA) <sub>3</sub> ][MnBr <sub>4</sub> ]	1625 VS	1563 S	1438 S	1302 M
[Co(HMBA) <sub>3</sub> ][CoCl <sub>4</sub> ]	1620 VS	1564 S	1437 S	1303 M
[Co(HMBA) <sub>3</sub> ][CoBr <sub>4</sub> ]	1618 VS	1561 S	1438 S	1301 M
[Ni(HMBA) <sub>3</sub> ][NiCl <sub>4</sub> ].2H <sub>2</sub> O	1621 VS	1562 S	1430 S	1301 M
[Ni(HMBA) <sub>3</sub> ][NiBr <sub>4</sub> ].H <sub>2</sub> O	1620 VS	1556 S	1435 S	1301 M
Ni(HMBA)Cl <sub>2</sub> .H <sub>2</sub> O	1619 VS	1564 S	1438 S	1304 M
Ni <sub>3</sub> (HMBA)Cl <sub>6</sub> .3H <sub>2</sub> O	1627 VS	1565 S	1438 S	1308 M
Cu <sub>2</sub> (HMBA)Cl <sub>4</sub>	1596 VS	1569 S	1480 S	1303 M
			1442 S	
Mg(HMBA) <sub>2</sub> Cl <sub>2</sub>	1641 VS	1572 S	1433 S	1302 M
Mg(HMBA) <sub>2</sub> Br <sub>2</sub>	1630 VS	1564 S	1436 S	1309 M
Ca(HMBA) <sub>2</sub> Cl <sub>2</sub>	1633 VS	1568 S	1435 S	1297 M
Ca(HMBA) <sub>2</sub> Br <sub>2</sub>	1635 VS	1565 S	1435 S	1305 M
Zn(HMBA) <sub>2</sub> Cl <sub>2</sub> .H <sub>2</sub> O	1627 VS	1580 S	1475 S	1287 M
	1609 VS	1538 S	1432 S	
Cd <sub>3</sub> (HMBA)Cl <sub>6</sub>	1635 VS	1554 S	1486 S	1290 M
Cd <sub>3</sub> (HMBA)Br <sub>6</sub>	1635 VS	1548 S	1485 S	1289 M
Cd <sub>2</sub> (HMBA)Cl <sub>4</sub>	1635 VS	1565 S	1485 S	1297 M
Hg <sub>2</sub> (HMBA)Cl <sub>4</sub>	1632 VS	1568 Sh	1485 S	1288 M
		1538 S		

free ligand are listed in Table-2. The inspection of the infra-red data suggests that the HMBA molecules, in all of these complexes, have been coordinated with the metal ions through their carbonyl oxygen atoms. The criterion for the existence of such bonding in amide group containing complexes, is the shifting of carbonyl stretching frequencies (amide I bands) towards the lower side reflecting decreased bond order and the shifting of CN stretching bands (amide II and III bands) towards the higher frequencies. In all of these

complexes, the carbonyl stretching bands appeared at lower frequency than the free ligand and amide II and amide III bands, which have considerable contributions from CN stretching vibrations, appeared at higher frequencies, suggesting the coordination through carbonyl oxygens. This result is in line with the previously reported spectral data for Ni, Mn and Co complexes which suggested that in [M(HMBA)<sub>3</sub>]<sup>2+</sup> cations all three HMBA molecules coordinate with metal ions through both of their carbonyl oxygens giving octahedral MO<sub>6</sub><sup>2+</sup> chromophores with tetrahedral [MX<sub>4</sub>]<sup>2-</sup> anions [1-2] and the X-ray studies of CoCl<sub>2</sub> and MnBr<sub>2</sub> complexes with HMBA confirmed this coordination [3].

An important feature, in the infra-red spectra of Mg, Ca, Mn, Co, Ni and Zn complexes, is the shifting of a strong band of ligand at 1475 cm<sup>-1</sup>, towards the lower frequency side on complex formation. This decrease in frequency on complex formation is more than that observed for amide I band and suggests that this band of HMBA probably has considerable C=O character. This result eliminates the possibility of CN stretching character, as suggested previously for this band and supports the second idea that it could be due to an out-of-plane motion of the amide groups [12]. In the infra red spectra of Cd and Hg complexes this band appears at slightly higher frequencies than free ligand and suggests that in Cd and Hg complexes the ligand molecules appear in somewhat different conformation than that in other complexes.

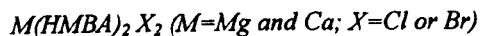
Another important feature is the appearance of some extra bands in the infra red spectrum of the complex Zn(HMBA)<sub>2</sub>Cl<sub>2</sub>.H<sub>2</sub>O. The positions of these extra bands correspond with those of free ligand. It seems likely that in this complex, either the HMBA molecules are acting as monodentate ligand, coordinating through one of the two carbonyl oxygens or only one of the two ligand molecules is chelating with the Zn and the second molecule of HMBA is only hydrogen bonded.

## Experimental

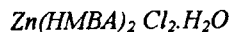
### Preparation of complexes

All the chemicals were of reagent grade and were used without further purification. The HMBA

and the complexes of Ni, Mn and Co(II) halides were prepared by using the methods reported previously [1-3].



All these complexes were prepared by dehydrating the corresponding metal halides (0.001 mole) in acetone: 2,2-dimethoxypropane and adding a warm solution of HMBA (0.003 mole) in acetone. The reaction mixture was then refluxed for 16 hours and the white precipitates thus formed were filtered off, washed with acetone and dried in vacuo.



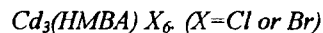
A warm solution of zinc chloride (0.001 mole) in ethylacetate (10 cm<sup>3</sup>) was mixed with warm solution of HMBA (0.002 mole) in ethylacetate (30 cm<sup>3</sup>). The reaction mixture was refluxed for half an hour and the oily liquid thus formed was converted into white powder on drying in vacuo over P<sub>2</sub>O<sub>5</sub>.



A warm solution of copper (II) chloride (0.001 mole) in ethanol (10 cm<sup>3</sup>) was added to a warm solution of HMBA (0.003 mole) in ethylacetate (40 cm<sup>3</sup>). The resulting solution was refluxed until the complete precipitation of complex, which was then filtered off, washed with ethylacetate and dried in vacuo.



This complex was prepared in a similar manner to that of analogous copper complex, except that the CdCl<sub>2</sub> · 2.5 H<sub>2</sub>O and HMBA ratio was 1:6 respectively.



The warm solutions of hydrated cadmium halides (0.001 mole) in ethanol (20 cm<sup>3</sup>) were mixed with the warm solution of HMBA (0.002 mole) in ethanol (30 cm<sup>3</sup>) and the reaction mixtures were allowed to evaporate at room temperature. Next day the white precipitates formed, which were then

filtered off, washed with ethanol and dried in vacuo at 100°C.



HgCl<sub>2</sub> (0.001 mole) and HMBA (0.003 mole) were dissolved in water (30 cm<sup>3</sup>) and refluxed for three hours. The reaction mixture was allowed to evaporate at room temperature. After several days white crystals were formed which were filtered off, washed with diethylether and dried in vacuo at 110°C.

Analysis for percentage composition of C, H and N were carried out by Imperial College Microanalytical Laboratory.

Infra red spectra (4000-400 cm<sup>-1</sup>) were obtained by using Perkin-Elmer 1720 FTIR spectrometer.

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