

## Synthesis and Spectroscopic Studies of the Complexes of Tumor Cell Differentiating Agent Hexamethylene Bisacetamide with Nickel Halides

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**Summary:** Complexes of the tumor cell differentiating agent hexamethylene bisacetamide (HMBA) with nickel(II) halides e.g.  $Ni_2(HMBA)_3Cl_4 \cdot 2H_2O$ ,  $Ni_2(HMBA)_3Br_4 \cdot H_2O$ ,  $Ni(HMBA)Cl_2 \cdot H_2O$  and  $Ni_3(HMBA)Cl_6 \cdot 3H_2O$  have been synthesized and characterized by elemental analysis. On the basis of their reflectance spectra and magnetic susceptibility data, the complexes with 2:3 stoichiometry are assigned as mixed octahedral-tetrahedral structures and can correctly be formulated as  $[Ni(HMBA)_3][NiX_4] \cdot nH_2O$  ( $X = Cl$ ;  $n=2$  and  $X = Br$ ;  $n=1$ ). On the other hand, the complex  $Ni(HMBA)Cl_2 \cdot H_2O$  has essentially a tetrahedral structure and the complex  $Ni_3(HMBA)Cl_6 \cdot 3H_2O$  a chloride-bridged polymeric octahedral structure.

### Introduction

Hexamethylene bisacetamide (HMBA) is known to induce *in vitro* morphological and functional differentiation of murine and human leukemia cells [1-5] as well as a variety of human and solid tumor cell lines [6-9] and has been the subject of clinical trials. HMBA was selected because in the series of bisacetamides, it has six methylene units separating the acetamide moieties (Fig. 1), and attained maximum differentiation potency [1,3]. In addition HMBA differs from previous differentiating agents such as dimethyl sulfoxide and N-methylformamide which have been clinically evaluated, in that carefully conducted clinical and pharmacokinetic studies have documented its ability to achieve concentrations of HMBA in patient plasma equal to the concentration *in vitro* [4].

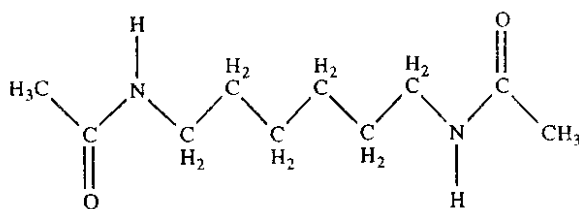


Fig. 1: Structure of the HMBA.

Although, marked progress has been made in studying the role played by HMBA in tumor cell

differentiation [1-9], the synthesis of the complexes of this compound with divalent metal halides has not been reported hitherto.

Complexes of the tumor cell differentiating agent HMBA with nickel(II) halides, synthesized in the present work, include  $Ni_2(HMBA)_3Cl_4 \cdot 2H_2O$ ,  $Ni_2(HMBA)_3Br_4 \cdot H_2O$ ,  $Ni(HMBA)Cl_2 \cdot H_2O$  and  $Ni_3(HMBA)Cl_6 \cdot 3H_2O$ . They have been characterized by elemental analysis and their structures have been established on the basis of their electronic spectra and magnetic susceptibilities.

### Results and Discussion

#### Electronic spectra

The electronic reflectance spectra of these complexes are measured over the range from  $30,000\text{ cm}^{-1}$  to  $4000\text{ cm}^{-1}$  and the characteristic bands are listed in Table-1. The reflectance spectra of nickel(II) complexes, with 2:3 stoichiometry, suggest the mixed octahedral-tetrahedral structures and can correctly be formulated as  $[Ni(HMBA)_3][NiX_4] \cdot nH_2O$  ( $X = Cl$ ;  $n=2$  and  $X = Br$ ;  $n=1$ ).

The intense, multiple absorptions in the  $16000\text{-}13000\text{ cm}^{-1}$  region, are then assigned to the  $V_3$  ( ${}^3T_1(F) \rightarrow {}^3T_1(P)$ ) transition of Ni(II) in  $T_d$  symmetry. The relatively weaker but still strong

Table-1: Reflectance spectra of complexes of HMBA with Nickel(II) Halides

Complex	Absorption Maxima (cm <sup>-1</sup> )
[Ni(HMBA) <sub>3</sub> ][NiCl <sub>4</sub> ].2H <sub>2</sub> O	23800 M, 16650 Sh, 16400 Sh, 15820 Sh, 14250 VS, 7450 SBr.
[Ni(HMBA) <sub>3</sub> ][NiBr <sub>4</sub> ].H <sub>2</sub> O	27400 VS, 18900 M, 15400 Sh, 14800 VS, 13300 M, 10750 Sh, 7100 S.
Ni(HMBA)Cl <sub>2</sub> .H <sub>2</sub> O	15650 S, 14330 VS, 11735 Sh, 7800 S.
Ni <sub>3</sub> (HMBA)Cl <sub>6</sub> .3H <sub>2</sub> O	26900 M, 22100 S, 12900 Sh, 11550M, 6900 MBr.

VS=Very Strong, S=Strong, M=Medium, Sh=Shoulder, Br = Broad.

band found between 7500-7000 cm<sup>-1</sup>, for both of these complexes, are assigned to the V<sub>2</sub>(<sup>3</sup>T<sub>1</sub>(F) — <sup>3</sup>A<sub>2</sub>(F)) transition of [NiX<sub>4</sub>]<sup>2-</sup> chromophores. There are some additional weak absorptions below 5000 cm<sup>-1</sup> which undoubtedly arise from the V<sub>1</sub>(<sup>3</sup>T<sub>1</sub>(F) — <sup>3</sup>T<sub>2</sub>(F)) transition, but the band maximum can not be measured with certainty due to the ligand vibrational bands in this region. The electronic band energies assigned to [NiCl<sub>4</sub>]<sup>2-</sup> and [NiBr<sub>4</sub>]<sup>2-</sup> anions, in these complexes, are very close to the values previously reported for tetrahalo nickelate (II) anions [10] and confirm the mixed Octahedral-tetrahedral structures for both of these complexes.

The bands observed in the region 24000-19000 cm<sup>-1</sup> are assigned to the V<sub>3</sub>(<sup>3</sup>T<sub>1g</sub>(P) — <sup>3</sup>A<sub>2g</sub>) transition of octahedral [Ni(HMBA)<sub>3</sub>]<sup>2+</sup> chromophore.

The electronic spectrum of the complex Ni(HMBA)Cl<sub>2</sub>.H<sub>2</sub>O suggests essentially a pseudo-tetrahedral stereochemistry (Fig. 2). The V<sub>3</sub> transition is assigned to strong, multiple bands in the 16000-14000 cm<sup>-1</sup> and the V<sub>2</sub> transition occurs at 7800 cm<sup>-1</sup>. Although, the exact position of the V<sub>1</sub> transition could not be measured with certainty, due to the ligand field vibrations in this region, but the unsplit nature of the V<sub>3</sub> band in this complex indicates an electronic symmetry not much lowered from T<sub>d</sub>. The occurrence of a tetrahedral nickel(II) complex containing water is unusual. It is not clear whether it is coordinated or hydrogen bonded.

With nickel(II) chloride, a yellow complex of stoichiometry Ni<sub>3</sub>(HMBA)Cl<sub>6</sub>.3H<sub>2</sub>O is prepared. The electronic spectrum of this complex suggests essentially an octahedral structure, with Δ ca: 6900 cm<sup>-1</sup>. A strong band at 22100 cm<sup>-1</sup> appears due to V<sub>3</sub>(<sup>3</sup>A<sub>2g</sub> — <sup>3</sup>T<sub>1g</sub>(P))transition of O<sub>h</sub> symmetry. The V<sub>2</sub>(<sup>3</sup>A<sub>2g</sub> — <sup>3</sup>T<sub>1g</sub>(F)) transition is assigned to the

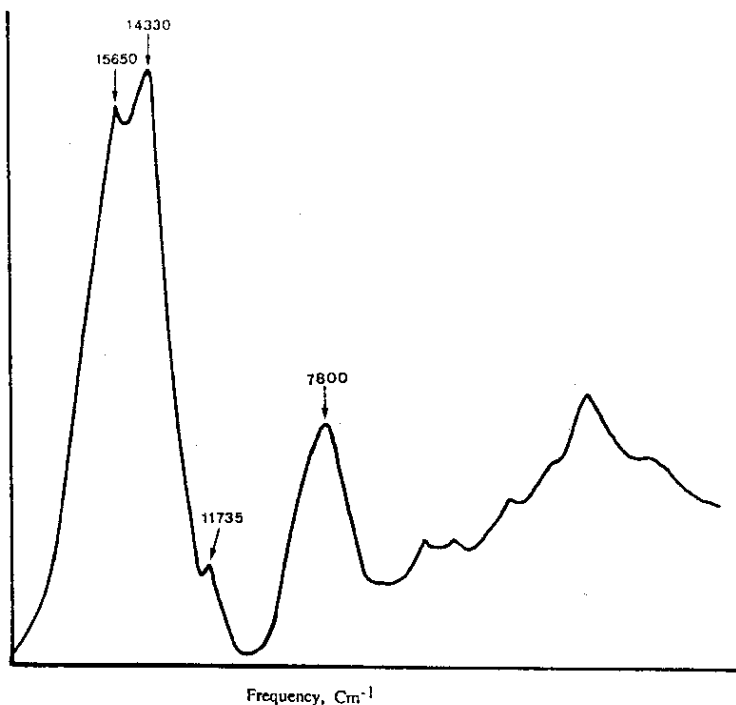


Fig. 2: Reflectance spectrum of Ni(HMBA) Cl<sub>2</sub>.H<sub>2</sub>O.

Table-2: Magnetic properties of complexes of HMBA with Nickel(II) Halides

Complex	Temp (°K)	$\chi_M$ (per metal ion) ( $m^3 \text{ mol}^{-1} \times 10^{11}$ )	$\mu_{\text{eff}}$ (per metal ion) (B.M.)
$[\text{Ni}(\text{HMBA})_3][\text{NiCl}_4] \cdot 2\text{H}_2\text{O}$	295	7450	3.73
$[\text{Ni}(\text{HMBA})_3][\text{NiBr}_4] \cdot \text{H}_2\text{O}$	296	6588	3.52
$\text{Ni}(\text{HMBA})\text{Cl}_2 \cdot \text{H}_2\text{O}$	297	6735	3.56
$\text{Ni}_3(\text{HMBA})\text{Cl}_6 \cdot 3\text{H}_2\text{O}$	297	5871	3.33

bands around  $11500 \text{ cm}^{-1}$ . A band observed at  $27000 \text{ cm}^{-1}$  in the spectrum of this complex most probably arises due to charge transfer. The weak ligand field, observed for this complex, is consistent with coordination through the carbonyl oxygens of the HMBA [11]. The spectrum of this complex is rather similar to that of  $\text{Ni}(\text{Py})\text{Cl}_2$  [12] ( $\Delta = 7000 \text{ cm}^{-1}$ ), which has a polymeric, chloride-bridged, octahedral structure [13]. This similarity in the spectra suggests that like  $\text{Ni}(\text{Py})(\text{Cl}_2)$ , the structure of  $\text{Ni}_3(\text{HMBA})\text{Cl}_6 \cdot 3\text{H}_2\text{O}$  is based on  $\text{NiCl}_2$  chains, with HMBA bonded to some of the metal ions and probably the water molecules coordinate at remaining sites.

#### Magnetic studies

The magnetic susceptibilities of all the four complexes of nickel(II) halides have been measured at room temperature. These values were then corrected for diamagnetism to provide the fully corrected molar susceptibilities,  $\chi_M$  which were then converted to  $\mu_{\text{eff}}$  and are listed in Table-2. The observed values of magnetic moments for the complexes  $[\text{Ni}(\text{HMBA})_3][\text{NiCl}_4] \cdot 2\text{H}_2\text{O}$  and  $[\text{Ni}(\text{HMBA})_3][\text{NiBr}_4] \cdot \text{H}_2\text{O}$  are in line with the proposed octahedral-tetrahedral structures for both of these complexes. Similar to the electronic spectrum, the magnetic moment of 3.72 B.M. for the complex  $\text{Ni}(\text{HMBA})\text{Cl}_2 \cdot \text{H}_2\text{O}$  is in agreement with the tetrahedral structure. Although, the magnetic moment of 3.33 B.M., observed for  $\text{Ni}_3(\text{HMBA})\text{Cl}_6 \cdot 3\text{H}_2\text{O}$ , seems slightly high for an octahedral environment, it is very close to the values previously observed for halide-bridged, polymeric, octahedral complexes [12].

#### Experimental

##### Preparation of complexes

All the chemicals were of the reagent grade and were used with out further purification.

##### Hexamethylene bisacetamide (HMBA)

This compound was prepared by previously reported method [14]. Found C, 59.53; H, 10.45; N, 14.23. Calculated for HMBA: - C, 60.00; H, 10.00; N, 14.00.

##### $[\text{Ni}(\text{HMBA})_3][\text{NiCl}_4] \cdot 2\text{H}_2\text{O}$

This complex was synthesized by dehydrating the nickel (II) chloride hexahydrate (0.001 mole) in ethanol:2,2-dimethoxy propane ( $10 \text{ cm}^3$ ) and adding a warm solution of HMBA (0.004 mole) in ethyl acetate ( $30 \text{ cm}^3$ ). The reaction mixture was then refluxed for four hours and the turquoise coloured precipitate thus formed was filtered off, washed with ethyl acetate and dried *in vacuo*. Found:- C, 40.15; H, 7.27; N, 9.21. Calculated for  $[\text{Ni}(\text{HMBA})_3][\text{NiCl}_4] \cdot 2\text{H}_2\text{O}$ :- C, 40.20; H, 7.15; N, 9.38.

##### $[\text{Ni}(\text{HMBA})_3][\text{NiBr}_4] \cdot \text{H}_2\text{O}$

It was synthesized by adding a warm solution of HMBA (0.003 mole) in ethylacetate ( $30 \text{ cm}^3$ ) in to the solution of nickel(II) bromide (0.001 mole) in ethanol:2,2-Dimethoxypropane ( $10 \text{ cm}^3$ ). The precipitate thus formed was filtered off, washed with ethyl acetate and dried *in vacuo*. Found:- C, 34.05; H, 7.07; N, 8.02. Calculated for  $[\text{Ni}(\text{HMBA})_3][\text{NiBr}_4] \cdot \text{H}_2\text{O}$ :- C, 34.11; H, 5.88; N, 7.96.

##### $\text{Ni}(\text{HMBA})\text{Cl}_2 \cdot \text{H}_2\text{O}$

A warm solution of nickel(II) chloride hexahydrate (0.001 mole) in ethanol was added into a warm solution of HMBA (0.002 mole) in ethylacetate. The reaction mixture was refluxed for three hours and turquoise coloured precipitate thus formed was filtered off, washed with ethylacetate and dried *in vacuo*. Found:- C, 35.19; H, 6.24; N, 8.05. Calculated for  $\text{Ni}(\text{HMBA})\text{Cl}_2 \cdot \text{H}_2\text{O}$ :- C, 34.51; H, 6.33; N, 8.05.

$Ni_3(HMBA)Cl_6 \cdot 3H_2O$ 

A warm solution of  $NiCl_2 \cdot 6H_2O$  (0.001 mole) in ethanol ( $10 \text{ cm}^3$ ) was added to a warm solution of HMBA (0.003 mole) in ethyl acetate ( $40 \text{ cm}^3$ ). The resulting solution was refluxed until the complete precipitation of yellow complex, which was then filtered off, washed with ethylacetate and dried *in vacuo*. Found:- C, 18.64; H, 3.69; N, 4.17. Calculated for  $Ni_3(HMBA)Cl_6 \cdot 3H_2O$ :- C, 18.66; H, 4.04; N, 4.17.

Analytical results were obtained by Imperial College Microanalytical Laboratory.

Diffuse reflectance spectra of the powder samples, over the range  $18500\text{-}4000 \text{ cm}^{-1}$ , were obtained on Beckman DK 2 spectrometer and for the range  $30000\text{-}12000 \text{ cm}^{-1}$  on a Pye Unicam SP8-100 spectrometer.

Magnetic susceptibilities of the powder samples were measured using the Evans Balance.

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