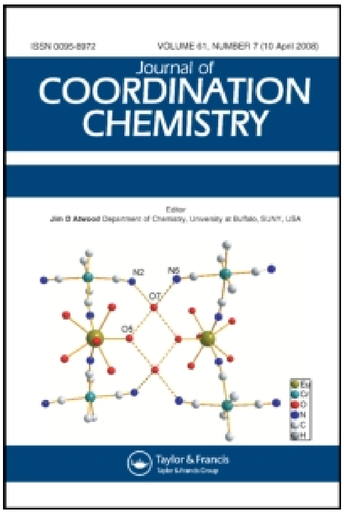

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SOME FIRST ROW TRANSITION METAL COMPLEXES OF ISONIAZID

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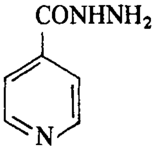
Complexes of the chlorides and bromides of manganese(II), iron(II), cobalt(II), nickel(II), copper(II) and zinc(II) with isoniazid (INH) have been prepared and studied by means of their magnetic susceptibilities, infrared and electronic spectra. All of the complexes have octahedral structures with the exception of the zinc complexes and the chloro- complexes of manganese and iron which are tetrahedral. The chloro- complex of copper is square planar.

INTRODUCTION

Isoniazid, isonicotinoylhydrazine (*I*) was introduced into medical practice in 1952 and is used in the treatment of tuberculosis.[1]



(*I*)

It has the advantage over other tuberculostatic drugs, such as streptomycin and *p*-aminosalicylic acid, of greater activity. An interesting discovery is that the tuberculostic activity of isoniazid is increased tenfold in the presence of copper ions.[2] Some other complexes of transition metal ions with isoniazid are known.[2-6] In this paper we report a study of the chloro- and bromo- complexes of isoniazid with the first row transition metal ions manganese(II), iron(II), cobalt(II), nickel(II), copper(II) and zinc(II). Information about the stereochemistry of the complexes has been obtained by studying the magnetic moment of each compound isolated from solution while the electronic and infrared spectra have been recorded for each complex.

EXPERIMENTAL

Four methods of preparation were used as follows.

(*A*) The manganese, cobalt, nickel and zinc complexes were prepared by the addition of an ethanolic solution of the metal halide in a 2:1 (ligand to metal) molar ratio for manganese and cobalt and a 1:1 molar ratio for nickel and zinc to an ethanolic solution of the ligand. The precipitated complexes were washed with ethanol and ether and dried over calcium chloride. (*B*) The copper complexes were prepared by the addition of an aqueous solution of isoniazid to the appropriate aqueous solution of the metal halide in a 1:1 molar ratio. The precipitated complexes were washed with water, ethanol and ether and dried over calcium chloride. (*C*) This method was similar to (*A*) except that the preparation was carried out under dry nitrogen. (*D*) The hydrated complexes were dehydrated quantitatively on a thermal balance.

The complexes prepared by these methods are listed in Table I. References are given to previous preparation. Where no reference is given, it is believed that this is a new compound.

A Stanton Redcroft TR-01 thermobalance with a DTA attachment was used to remove water of crystallisation from the compounds. Magnetic moments (Table I) were obtained by the Gouy method using the calibrant $Hg[Co(SCN)_4]$. Electronic spectra (Table II) were obtained using a Beckman ACTA M-IV spectrophotometer with DMSO as solvent. The infrared spectra (Table III) in KBr discs, (2000-600 cm^{-1}) and in a polyethylene matrix (600-200 cm^{-1}) were obtained using a Perkin-Elmer 598 spectrophotometer.

RESULTS AND DISCUSSION

The manganese(II) compounds have the stoichiometry $Mn(INH)Cl_2$ and $Mn(INH)_2Br_2$. The electronic spectra both in the solid state and in solution show no d-d transition bands in the visible region since they are spin- as well as Laporte-forbidden. The magnetic moment for each of the complexes corresponds to five unpaired electrons, suggesting either a tetrahedral or octahedral structure. The compound, $Mn(INH)Cl_2$ has a tetrahedral structure.[3] The presence of a band at 234 cm^{-1} in the compound, $Mn(INH)_2Br_2$ would suggest an octahedral structure.[9]

The iron compounds have the stoichiometry $Fe(INH)Cl_2$ and $Fe(INH)_2Br_2.H_2O$. The preparations of these species were carried out in a dry nitrogen atmosphere. The bromo-compound undergoes an endothermic reaction at 342 K with the loss of a water molecule. The magnetic moment for the chloro- compound is 5.56 B.M. The visible spectrum exhibits a broad band at 6328 cm^{-1} which suggests a tetrahedral structure.[7] The presence

TABLE I
Analyses and magnetic moments for the complexes.

Compound	Method of Preparation	Metal (found)	Halide (found)	Metal Calculated	Halide Calculated	μ_{eff} (B.M.)	Colour of Compound
$Mn(INH)Cl_2$ *	A	20.24	26.64	20.87	27.04	5.49	white
$MN(INH)_2Br_2$	A	11.12	32.42	11.22	32.86	6.20	white
$Fe(INH)Cl_2$ *	C	21.13	26.82	21.16	26.87	5.56	yellow
$Fe(INH)_2Br_2H_2O$	C	10.96	31.40	10.99	31.46	5.62	yellow
$Fe(INH)_2Br_2$	D	11.36	32.58	11.40	32.62		yellow
$Co(INH)_2Cl_2 3H_2O$	A	12.84	15.44	12.86	15.48	5.29	pink
$Co(INH)_2Cl_2$	D	14.56	17.52	14.58	17.54		pink
$Co(INH)_2Br_2 3H_2O$	A	10.74	29.18	10.77	29.21	5.01	pink
$Co(INH)_2Br_2$	D	11.92	32.40	11.95	32.41		pink
$Ni(INH)_2Cl_2 5H_2O$	A	11.84	14.30	11.89	14.35	3.59	blue
$Ni(INH)_2Cl_2$	D	14.51	17.52	14.54	17.56		blue
$Ni(INH)_2Br_2 3H_2O$	A	10.72	29.20	10.74	29.22	3.14	lilac
$Ni(INH)_2Br_2$	D	11.88	32.41	11.91	32.43		lilac
$Cu(INH)Cl.H_2O$	B	25.08	13.96	25.10	14.01	1.95	green
$Cu(INH)Br$	B	22.70	28.54	22.73	28.58	1.42	green
$Zn(INH)Cl_2 2H_2O$	A	21.10	22.90	21.12	22.91		white
$Zn(INH)Cl_2$	D	23.89	25.90	23.91	25.93		white
$Zn(INH)Br_2 3H_2O$	A	15.66	38.34	15.70	38.38		white
$Zn(INH)Br_2$	D	18.02	44.06	18.04	44.11		white

* Ref (3).

TABLE II
Electronic spectral details for selected complexes.

Complex	Peak Position[a] (cm^{-1})	Dq	B	β
Fe(INH)Cl$_2$[b]	ν_1 = 6238			
Fe(INH)$_2$Br$_2$H$_2$O[b]	ν_1 = 11110			
Co(INH)$_2$Cl$_2$3H$_2$O[c]	ν_2 = 6848 (3) ν_3 = 14771 (27)	370.9	699	0.72
Co(INH)$_2$Br$_2$3H$_2$O	ν_2 = 7812 (0.3) ν_3 = 18975 (3)	889.8	816	0.84
Ni(INH)$_2$Cl$_2$5H$_2$O	ν_1 = 8930 (5) ν_2 = 14710 (4) ν_3 = 24080 (15)	800	1006	0.96
Ni(INH)$_2$Br$_2$3H$_2$O	ν_1 = 10989 (2) ν_2 = 17241 (0.8) ν_3 = 25408 (1.7)	922	999	0.96
Cu(INH)ClH$_2$O	ν_1 = 13793 (3)			
Cu(INH)Br$_2$	ν_1 = 12937 (2.3)			

[a]Extinction coefficients (m^2 mol^{-1}) are given in parentheses. [b]Reflectance spectra. [c]This pink complex turned blue in DMSO. The reflectance spectra for the pink solid had bands at 8,850 and 19763 cm^{-1}. Dq = 998, B = 780.

of a band in the infrared spectrum at 271 cm^{-1} also supports a tetrahedral environment about iron.[8] The magnetic moment of the bromo- compound is 5.62 B.M. The visible spectrum has a broad band at 11110 cm^{-1} which suggests an octahedral coordination sphere.[9]

The cobalt compounds have the stoichiometry Co(INH)$_2$X$_2$.3H$_2$O. The compounds undergo endothermic reactions at 343 K and 367 K with the loss of the three water molecules. The magnetic data for the compounds suggest an octahedral arrangement of ligands around the cobalt atom. The magnetic moments are in the range 4.8-5.2 B.M.[10] The electronic spectra are typical of octahedrally coordinated cobalt.[10]

TABLE III
Important infrared bands for the complexes (cm^{-1})

Compound	νas(NH$_2$)	νs(NH$_2$)	νs(C-N)	ν_b(N-H)	Ring	Vibrations	ν(C=O)	ν(M-X)
INH	3275	3095	1535	1320	1599	1560	1660	
Mn(INH)Cl$_2$	3282	3160	1532	1338	1592	1532	1655	290
Mn(INH)$_2$Br$_2$	3280	3168	1540	1327	1600	1546	1645	234
Fe(INH)Cl$_2$	3420	3120	1542	1328	1598	1560	1655	271
Fe(INH)$_2$Br$_2$	3376	3106	1546	1329	1598	1560	1650	230
Co(INH)$_2$Cl$_2$	3250	3120	1545	1330	1595	1545	1645	250
Co(INH)$_2$Br$_2$	3240	3120	1550	1335	1595	1550	1645	261
Ni(INH)$_2$Cl$_2$	3260	3150	1548	1330	1600	1555	1640	238
Ni(INH)$_2$Br$_2$	3280	3140	1542	1332	1598	1556	1645	260
Cu(INH)Cl.H$_2$O	3402	3120			1598	1560	1655	262
Cu(INH)Br	3420	3100			1600	1560	1705	240
Zn(INH)Cl$_2$	3500	3230	1550	1330	1600	1560	1650	272
Zn(INH)Br$_2$	3500	3220	1550	1330	1600	1560	1652	206

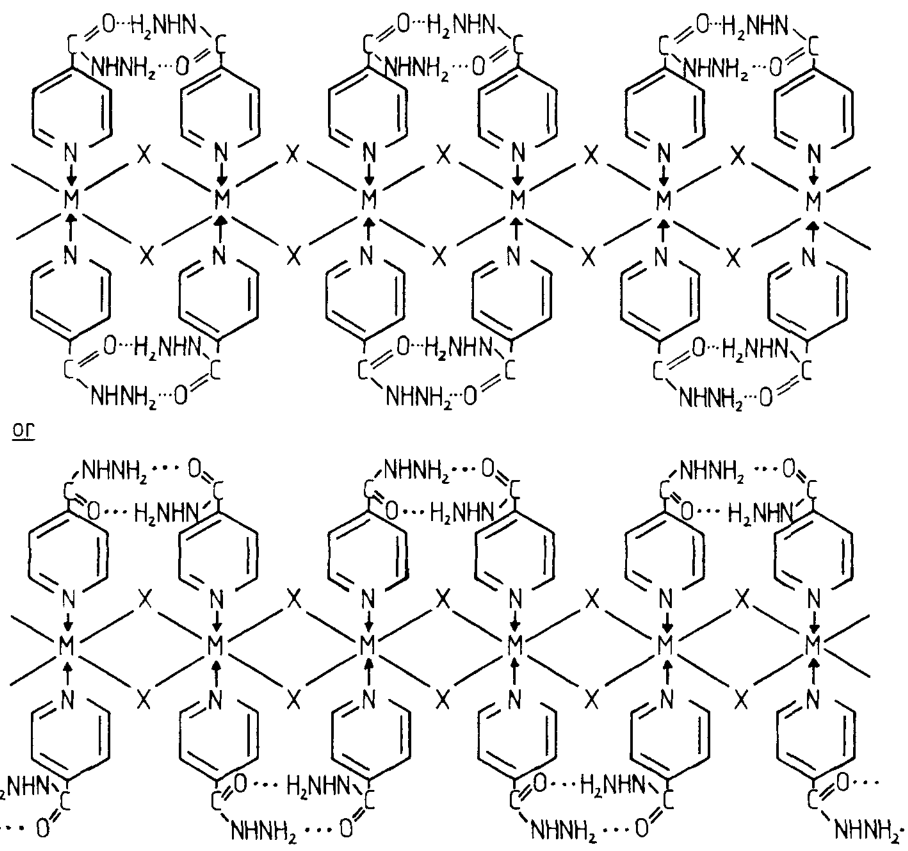
The nickel(II) complexes have the stoichiometry $Ni(INH)_2Cl_2.5H_2O$ and $Ni(INH)_2Br_2.3H_2O$ respectively. Both compounds undergo an endothermic reaction at 362 K and 368 K with loss of five and three water molecules respectively. The magnetic data for the compounds suggest an octahedral arrangement of ligands around the nickel atom since the magnetic moments are in the range 2.8-3.2 B.M.[10] The electronic spectra are typical of nickel(II) in an octahedral environment.

The copper compounds have the stoichiometry $Cn(INH)Cl.H_2O$ and Cu(INH)Br. The chloro- compound undergoes an endothermic reaction at 430 K with loss of the water molecule. The fact that the water is removed at this high temperature suggests that it is coordinated to the copper atom.[10] The compounds are paramagnetic indicating that the copper exists in the +2 oxidation state. It is suggested that a proton is removed from the amide group of the isoniazid upon complex formation.[5] The visible spectra of $Cu(INH)Cl.H_2O$ and Cu(INH)Br show broad absorption maxima at 13793 and 12937 cm^{-1} respectively.

The zinc compounds have the stoichiometry $Zn(INH)Cl_2.2H_2O$ and $Zn(INH)Br_2.3H_2O$. Both compounds undergo endothermic reactions at 308 K and 302 K with loss of two and three molecules of water respectively. The infrared spectra show a band for the chloro- compound at 272 cm^{-1} and for the bromo- compound at 206 cm^{-1} indicating that the zinc atom is in a tetrahedral environment in each complex.[8]

The stoichiometries of the compounds, Table I, show that all of them are hydrated with the exception of $Mn(INH)Cl_2$, $Mn(INH)_2Br_2$, $Fe(INH)Cl_2$ and Cu(INH)Br. The infrared spectra of the hydrated compounds have a broad band from 3680 cm^{-1} to lower frequency; this band is absent in the anhydrous compounds, it is considered to be due to O-H stretching vibrations of the water molecules. The water molecules, except in the case of the compound $Cu(INH)Cl{\cdot}H_2O$, are removed below 393 K indicating that the water is present in these compounds as water of crystallisation.[10] In the case of $Cu(INH)Cl{\cdot}H_2O$ the water molecule is not removed until 430 K. This, together with the presence of a weak band at 312 cm^{-1} in the infrared spectrum suggests that the water molecule is coordinated to the copper ion in this compound.[10]

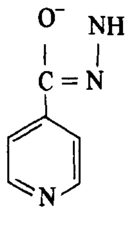
The compounds isolated from solution were all powders and without X-ray analysis no definite structures can be deduced. However, spectroscopic and magnetic data along with the composition of the compounds enable us to predict probable structures. The infrared spectrum of isoniazid is almost identical to that of the compounds in the region 2000-650 cm^{-1} with the exception of the compound $Cu(INH)Cl.H_2O$ where the ν(C=O) band shifts to higher frequency. However, differences in the spectra are observed at 3100-3600 cm^{-1} for the ν(N-H) bands; the number of bands increases in the compounds in contrast to the two intense bands in the spectrum of the free ligand. This indicates that the nitrogen atom of the amino group is not bonded to a metal.[9] The infrared spectrum of a dilute solution of isoniazid in tetrachloromethane gives bands at 3624 and 3293 cm^{-1} which are assigned to free NH_2, ν(N-H). Comparison of the spectrum of isoniazid, in potassium bromide disc shows that the frequencies of these bands are lowered to 3275 and 3095 cm^{-1}. This is considered to be due to the transition from monomer to the dimer form of the molecule by intermolecular dimerization.[9] Thus the infrared spectra would suggest that adjacent isoniazid molecules are linked by hydrogen bonds in the compounds. It is thus suggested that each isoniazid molecule is bonded to a transition metal ion by the ring nitrogen. The poor solubility of the compounds in most polar and non-polar solvents leads to the conclusion that the compounds have polymeric structures.[11] Thus the compounds $M(INH)_2X_2$ are considered to have a chain of metal atoms bonded to halogen atoms with isoniazid molecules above and below the plane of the M-X chain, with adjacent isoniazid molecules linked by hydrogen bonds as shown in (II).



(II)

hydrated has the water molecule coordinated to the copper. The electronic spectrum of the compound Cu(INH)Cl.H_2O indicates that the copper atom is in a square-planar group and the nitrogen atom of the amine group to the metal ion.

The copper complexes show some interesting peculiarities. In the first place they do not fit the $M(INH)_2X_2$ or $M(INH)X_2$ scheme of the other transition metal complexes with their formulae of Cu(INH)Cl.H_2O and Cu(INH)Br. The compounds are paramagnetic; thus in order to form these complexes the isoniazid must first form an amine, (III),



(III)

which is the chelating species. In both complexes a proton dissociates from the amide nitrogen and the ν_s(C-N) and ν_b(N-H) bands do not appear in the infrared spectra. Furthermore, neither of the complexes contains water of crystallisation; the one which *is*

The compounds M(INH)X_2 have tetrahedral structures with the isoniazid molecule functioning as a bidentate ligand, bonding through the oxygen atom of the carboxyl environment with the water molecule coordinated to the copper and the isoniazid acting as a bidentate ligand. The copper atom in the compound Cu(INH)Br has a similar type of environment. The low value for the magnetic moment would suggest some copper-copper interaction in the compound and the poor solubility of the compound in both polar and non-polar solvents is indicative of a polymeric structure. It is thus suggested that this compound exists as a chainlike polymer in which an isoniazid molecule is coordinated to a copper atom by forming a chelate ring and another isoniazid molecule is coordinated to the same copper by donation of the electron pair on the ring nitrogen atom. This gives a simple repeating structure of indeterminate length. The chains immediately above and below have atoms which occupy the fifth and sixth positions of a distorted octahedron.

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