ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
http://www.e-journals.net
2011, **8(1),** 361-367

New Ternary Transition Metal Complexes of 2-{[(2-aminophenyl)imino] methyl}Phenol and Metformin: Synthesis, Characterization and Antimicrobial Activity

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Received 21 June 2010; Accepted 15 August 2010

Abstract: Complexes of Co(II), Ni(II) and Cu(II) were synthesized from Schiff base 2-{[(2-aminophenyl)imino]methyl}phenol and metformin. The authenticity of the transition metal complexes were characterized by elemental analyses, conductance and magnetic susceptibility measurements, as well as spectroscopic (IR, electronic) and thermal studies. IR spectral studies revealed the existence of the ligands in the amine form in the solid state. The magnetic and electronic spectral studies suggest an octahedral geometry for all the complexes. The metformin acts as a bidentate ligand and Schiff base of *o*-phynelendiamine and salicylaldehyde acts as a tridentate ligand. Antimicrobial screening of the Schiff base, metformin and transition metal complexes were determined against the bacteria *Escherichia coli* and *Bacillus megaterium.*

Keywords: Complexes, Ligand, Schiff base, Transition metal, Antimicrobial

Introduction

Metformin hydrochloride (*N,N*-dimethyl-imido-dicarbonimidic diamide hydrochloride) is a strongly basic bisusbstituted guanidine derivative with short side chains. It is an orally administered biguanide that has been widely used in the treatment and management of non-insulin dependent diabetes mellitus (NIDDM). Metformin lowers both basal and postprandial elevated blood glucose in patients with NIDDM, when hyperglycemia cannot be satisfactorily managed on diet alone[1-4]. Schiff bases offer a versatile and flexible series of ligands capable to bind with various metal ions to give complexes with suitable properties for theoretical and/or practical applications. The chemistry of metal complexes containing salen-type Schiff-base ligands derived from condensation of aldehydes and amines is of enduring significance, since they have common features with metalloporphyrins with respect to their electronic structures and catalytic activities that mimic enzymatic hydrocarbon oxidation[5]. Catalytic activity of such metal complexes has been highlighted in the past few decades[6]. The presence of transition metals in human blood plasma indicates their importance in the mechanism for accumulation, storage and transport of transition metals in living organisms[7-9].

Experimental

The compounds *o*-phenylenediamine, salicylaldehyde, metformin and transition metal salts were obtained from S. d. fine chemicals Ltd. India and *Escherichia coli;* MTCC 1687, *Bacillus megaterium;* MTCC 428 were collected from MTCC Bangalore, India.

Preparation of Schiff base and transition metal complexes

The Schiff base under investigation was prepared by mixing an ethanolic solution (50 cm^3) of (1.22 g) 0.01 mole of salicylaldehyde with (1.08 g) 0.01 mole of *o*-phenylenediamine in the same volume of ethanol. Few drops of 10% NaOH were added to adjust pH 7 and the obtained mixture then refluxed with stirring for two hours. The obtained precipitate was collected by filtration through Buchhner funnel, recrystallized from ethanol and dried at room temperature. The yield was 65% and its melting point obtained was195 ºC.

The complexes under investigation were prepared by mixing 50 cm^3 ethanolic solution of 0.01 M Schiff base, 0.01 M metal salt and 0.01 M metformin. The obtained mixture was refluxed with continues stirring for four hours. The resulted mixture was filtered; the product was collected and then washed several times with hot ethanol until the filtrate became clear. The complexes were dried in desiccator over anhydrous $CaCl_2$ under vacuum. The yield ranged from 60-75% and the melting points of all complexes was above 350 ºC.

Analysis and physical measurements

Elements like C, H, O and N were analyzed with a Perkin-Elmer 2400 series II elemental analyzer. Magnetic susceptibilities were measured at room temperature on a Gouy[10] balance using $Hg[Co(CNS)]_4$ as calibrate. The IR spectra were recorded on a Perkin-Elmer Lamda-983 spectrometer with samples prepared as KBr pellets and UV Visible reflectance spectra were obtained on a Beckman DK-2A spectrophotometer using MgO as reference. Thermal measurements were carried out using Perkin-Elmer TGA-7DSC-PYRIS-1-DTA-7 thermal analyzer maintained at a 10 $^{o}C\ min^{-1}$ heating rate.

Antimicrobial assay

The experiments were designed so as to test the effect of the presence of the ligand and their metal chelates in liquid culture media. $2x10^{-3}$ M of ligands and their metal chelates Co(II), Ni(II) and Cu(II) were supplemented in nutrient broth. The flasks were inoculated with 5% (v/v) actively growing inoculums and incubated for 24 hours on rotary shaker adjusted at 120 rpm and 37 ^{0}C**.** After the incubation growth was measured spectrophotometrically at 660 nm. The % growth inhibition was calculated with reference to growth in the respective medium without any inhibitory compounds.

Results and Discussion

The analytical data of the complexes is presented in Table 1 indicates 1:1:1 stoichiometry. The general equation for the formation of the complexes is shown as below:

$$M^{2+} + HA + HL \longrightarrow MAL + 2H^{+}$$

Where M^{2+} = Co(II) or Ni(II) or Cu(II),

A = Schiff base and L = Metformin.

All synthesized complexes are colored and possess high decomposition points. All are amorphous and stable in air. The complexes are partially soluble in methanol and insoluble in water and other organic solvents.

Conductance measurements

The conductivity of complexes was measured in 1:1 mixture of methanol and water at room temperature. All the complexes showed the molar conductance values for 10^{-3} M concentration in range 8 to 14 $ohm^{-1}cm^2\ mol^{-1}$. It is suggesting that all complexes have non electrolyte nature[11]. The molar conductance values of the complexes are listed in Table 1.

Table 1. Analytical data and some physical properties of the metal complexes

Complex	Molecular Formula	Colour	Formula Weight	Yield %, (g)	Analysis of elements (%) found (calcd) M	C	H	O	N	Cl	Molar cond. $ohm^{-1}\ cm^2\ mol^{-1}$	D.P. °C
[Ni·A·L·H_2O].Cl	$NiC_{17}H_{24}N_7O_2Cl$	Cherry red	452.26	68 (7.34)	12.98 (12.89)	45.11 (44.65)	5.31 (5.42)	7.07 (7.39)	20.67 (19.90)	7.85 (7.40)	78.9	>400
[Co·A·L·H_2O] $4H_2O$·Cl	$Co\,C_{17}H_{32}N_7O_6Cl$	Brown	524.43	68 (8.42)	11.25 (11.19)	38.90 (38.98)	6.10 (5.88)	18.30 (17.99)	18.67 (18.85)	6.77 (6.49)	73.7	>350
[Cu·A·L·H_2O] $4H_2O$·Cl	$Cu\,C_{17}H_{32}N_7O_6Cl$	Dark green	529.05	65 (8.48)	12.03 (12.10)	38.56 (37.90)	6.05 (6.69)	18.15 (18.77)	18.52 (17.26)	6.71 (6.46)	55.8	>350

A = Schiff Base, D.P. = Decomposition point, L = Metformin

Infrared spectra

There is strong coupling among the IR bands of ternary complexes and hence, quantitative interpretation of the bands in the IR spectra is not possible without normal coordinate analysis. Important IR frequencies of the complexes are listed in Table 2 along with their suggested assignments.

Table 2. Infrared spectral data of the metal complexes (cm^{-1})

Complex	υ-NH Metformin	υ-C=NH Metformin	υ-N-CH3 Metformin	υ-C=N- Schiff base	υ –OH Schiff base/complexes	υ-C=C- Schiff base	υ-NH Schiff base	υ M-N	υ M-N=C	υ M-0	υ M-OH2
Metformin	1580 Sh.(s)	3367 Sh.(s)	1381 Sh.(m)	-	-	-	-	-	-	-	-
Schiff Base	-	-	-	1660 Sh.(s)	3090 Sh.(m)	1612 sh.(s)910 sh.(m)	1361 Sh.(m)	-	-	-	-
[Ni·A·L·H_2O].Cl	1558 Sh.(s)	3053 Sh.(m)	1371 Sh.(m)	1641 Sh.(s)	3370 (m)	1610 sh.(s)812 sh.(m)	1260 Sh.(m)	580 sh.(m)	812 sh.(m)	472 Sh.(m)	848 Sh.(m)
[Co·A·L·H_2O] $4H_2O$·Cl	1529 Sh.(s)	3059 Sh.(m)	1357 Sh.(m)	1639 Sh.(s)	3450 (m)	1612 sh.(s)758 sh.(m)	1329 sh..(m)	567 sh.(m)	783 sh.(m)	470 Sh.(m)	820 Sh.(m)
[Cu·A·L·H_2O] $4H_2O$·Cl	1522 Sh.(s)	3020 Sh.(m)	1377 Sh.(m)	1644 Sh.(s)	3490 Sh.(m)	1595 sh.(s)846 sh.(m)	1289 Sh.(m)	580 Sh.(m)	802 sh.(m)	480 Sh.(m)	856 Sh.(m)

A = Schiff Base, L = Metformin, (s) = Strong, (m) = Medium, Sh. = sharp

The IR spectra of all of the complexes differed from those of the ligands. A strong band ascribed to the presence of υ_{OH} of schiff base appears at 3090 cm^{-1} in spectrum. This band disappeared in spectra of all metal complexes which accounts for coordination of -OH. Similarly a frequency appears at 3200 cm^{-1} to 3500 cm^{-1} in complexes, which gives indication for presence of water molecules. The spectra of Schiff base shows a $\upsilon_{C=N-}$ stretching band at 1660 cm^{-1}, which is displaced on complexation to 1641 cm^{-1} with Ni(II), 1522 cm^{-1} with Cu(II) and 1529 cm^{-1} with Co(II). There was a shift of 8-38 cm^{-1} for various heterochelates formed indicating the involvement of this frequency in coordination[12]**.** Two more bands which were strong and of medium intensity were found in range of 624-590 and 783-800 cm^{-1} can be assigned as M-N and M-N=C stretchings respectively[13]. A sharp and strong band obtained at 480 cm^{-1} in heterochelates can be attributed to M-O stretching[14].

Thermo gravimetric analysis

Thermogravimetric analysis of the metal complexes was studied using a Perkin-Elmer TGA-7DSC-PYRIS-1 DTA-7 thermal analysis system. The complexes lost weight gradually during every phase of the experiment, then the samples underwent an accelerated weight loss and finally in the temperature range of about 500-600 °C rate of weight loss became much more moderate. During the initial phase the gradual weight loss may be due to water of hydration which may be either crystal or coordinated water (Table 3 and 4).

Table 3. Cumulative % weight loss data of metal complexes at various temperatures (°C) from thermogram

Complex	% Weight loss at temperature, °C											
	50	100	150	200	250	300	350	400	450	500	550	600
Metformin	0.1	0.1	0.1	1.2	12.1	42.0	71.2	80.0	82.0	86.5	88.0	90.0
Schiff Base	0.1	0.1	1.5	1.8	8.0	31.5	56.5	70.0	74.2	77.5	79.9	80.0
[Ni·A·L·H_2O].Cl	0.1	0.1	2.0	1.5	1.8	2.0	4.0	11.4	47.5	71.0	73.0	77.1
[Co·A·L·H_2O] 4H_2O·Cl	1.0	2.0	2.5	13.5	17.0	22.0	25.0	34.0	35.3	37.2	40.0	44.2
[Cu·A·L·H_2O] 4H_2O·Cl	0.1	1.1	1.5	2.5	3.5	6.5	17.0	21.0	24.0	27.0	30.0	33.3

A = Schiff Base L = Metformin

Table 4. Cumulative weight loss data of metal complexes at 50 °C to 250 °C

Complex	Found									
	50 °C		100 °C		150 °C		200 °C		250 °C	
	g	%	g	%	g	%	g	%	g	%
[Ni·A·L·H_2O].Cl	0.48	0.1	0.48	0.1	0.97	0.2	7.34	1.5	8.80	1.8
[Co·A·L·H_2O] 4H_2O·Cl	5.61	1.0	11.22	2.0	14.03	2.5	75.76	13.5	95.41	17.0
[Cu·A·L·H_2O] 4H_2O·Cl	0.56	0.1	6.22	1.0	8.48	1.5	14.14	2.5	19.80	4.5

A= Schiff Base, L = Metformin

The rate of decomposition of metal complexes was lower than that of the ligands suggesting that there may be weak intermolecular hydrogen bonding. The percentage of loss observed in all complexes above 300 °C was higher, indicating the decomposition of complexes and formation of oxides.

Electronic spectra and magnetic measurements

The information regarding geometry of these complexes is also obtained from their electronic data and magnetic moments which are presented in Tables 5 and 6.

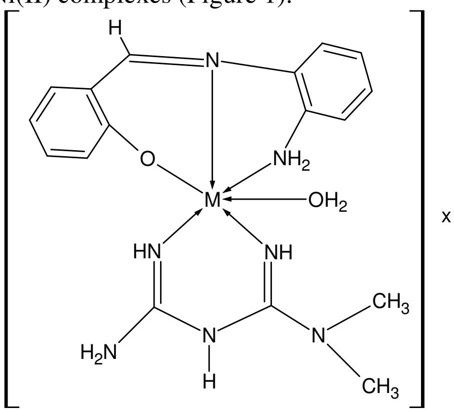
Table 5. Electronic spectra and magnetic moment data for the complexes

Complex	Absorption region, cm^{-1}	Band assignment	Magnetic moment μ_{eff} (B.M.)	Geometry
$[Co\cdot A\cdot L\cdot H_2O]$ $4H_2O\cdot Cl$	4255 cm^{-1} 6450 cm^{-1} 14230 cm^{-1}	$^4T_{1g} \rightarrow {}^4T_{2g}$ $^4T_{1g} \rightarrow {}^2E_g$ $^4T_{1g} \rightarrow {}^4A_{2g}$	3.87	Octahedral
$[Ni\cdot A\cdot L\cdot H_2O].Cl$	4273 cm^{-1} 11627 cm^{-1} 15384 cm^{-1}	$^3A_{2g} \rightarrow {}^3T_{2g}$ $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ $^3A_{2g} \rightarrow {}^3T_1(P)$	2.83	Octahedral
$[Cu\cdot A\cdot L\cdot H_2O]$ $4H_2O\cdot Cl$	14492cm^{-1}------5208cm^{-1} Broad band	$e_g \rightarrow t_{2g}$ $x^2\text{-}y^2 \rightarrow z^2$ $x^2\text{-}y^2 \rightarrow xy$	1.87	Octahedral

Table 6. Parameters of the electronic spectra of metal complexes

Complex	d-d transition, cm^{-1}			Dq cm^{-1}	B cm^{-1}	β= B/B°	β °, %
	υ_2	υ_3	υ_4				
$[Co\cdot A\cdot L\cdot H_2O]$ $4H_2O\cdot Cl$	6450	14230	-	4255	735	0.80	20
$[Ni\cdot A\cdot L\cdot H_2O].Cl$	11627	15384	-	4273	509	0.49	51
$[Cu\cdot A\cdot L\cdot H_2O]$ $4H_2O\cdot Cl$	-	-	-	-	-	-	-

Magnetic moment 3.87, 2.83, 1.87 B.M. value of Co(II), Ni(II), Cu(II) suggests an octahedral geometry respectively. The electronic spectrum of Co(II), Ni(II) and Cu(II) complexes exhibits electronic transitions at [4255 $cm^{-1}(\upsilon_1)$, 6450 cm^{-1} (υ_2) and 14230 cm^{-1} (υ_3)], [4273 $cm^{-1}(\upsilon_1)$, 11627 cm^{-1} (υ_2) and 15384 cm^{-1} (υ_3)] and [14492 - 5208 cm^{-1} broad band] respectively. The calculated values of B are (735, 509), β are (0.80, 0.49) and β° are (20%, 51%) for Co(II) and Ni(II) complexes respectively. These values indicate covalent character in Co(II) and Ni(II) complexes (Figure 1).



M = Co or Ni or Cu and X = 4H₂O.Cl or Cl or 4H₂O.Cl respectively

Figure 1. Octahedral geometry for Co(II), Ni(II), Cu(II) complexes

Antimicrobial activity

The highest activity was reported with Cu(II) complexes with 11.57 mm and 12.29 mm growth inhibition for *E. coli and B. megaterium* respectively. The least activity has been reported for the Co(II) complexes (Table 7).

Table 7. Effect of ligand and metal complexes on the growth of bacteria

Compound	Bacteria	
	Escherichia coli Inhibition in, mm	*Bacillus megaterium* Inhibition in, mm
Schiff Base	7.14	8.01
Metformin	10.41	10.07
$[Co{\cdot}A{\cdot}L{\cdot}H_2O]\ 4H_2O{\cdot}Cl$	11.29	8.29
$[Ni{\cdot}A{\cdot}L{\cdot}H_2O].Cl$	11.31	10.71
$[Cu{\cdot}A{\cdot}L{\cdot}H_2O]\ 4H_2O{\cdot}Cl$	11.57	12.29

All synthesized metal complexes have shown more inhibitory activity against bacteria as compared to parental ligands. Similar correlation and increase in antibacterial activity of ligands on complexation with reference to parent ligands has been well cited[15-17]. Such increased activity of the metal chelates can be explained on the basis of overtone's concept and chelation theory. According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid soluble materials due to which liposolubility is an important factor that controls antimicrobial activity. On chelation, the polarity of metal ion is reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of π-electrons over the whole chelates ring and enhances the lipophilicities of the complex. The increased lipophilicities of complexes permit easy penetration into lipid membranes of organisms and facilitates as blockage of metal binding sites in enzymes[18].

Conclusion

On the basis of elemental analyses, IR, thermogravimetric analyses, UV Visible reflectance spectra, molar conductance and magnetic properties, it is possible to assign octahedral geometry to the all metal complexes as shown in Figure 1. The calculated values of β are favorable for assigned structure of accounted for covalent character of complexes. We are optimistic that future studies on biological properties of these complexes of Schiff base, metformin and there derivatives may lead to the development of a new class of specific and effective pharmaceutical agents.

Cu(II) complexes have shown promising antibacterial activity against *E. coli and B. megaterium*. Least activity is shown for Co(II) complexes because Co(II) act as cofactor in many systems. The antimicrobial activity was explored on the basis of overtone concept of cell permeability.

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