HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 3: (4), 2013, 481-491**

SYNTHESIS, SPECTRAL, THERMAL AND ANTIBACTERIAL INVESTIGATION OF NI(II) MIXED LIGAND COMPLEXES WITH CLIOQUINOL AND COUMARIN DERIVATIVE

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Abstract: The antibiotic agent clioquinol is well known for its drug design and coordinating ability towards metal ions. Ni(II) complexes of clioquinol with various monobasic bidentate ligands have been prepared. All the complexes have been synthesized, characterized and screened for their *in vitro* antibacterial activity against a range of Gram-positive and Gram-negative bacteria. Structural and spectroscopic properties have been studied on the basis of elemental analysis, infrared spectra, NMR spectra, electronic spectra, magnetic measurements, FAB mass spectrum and thermo gravimetric analysis. The kinetic parameters such as order of reaction (n = 0.97 to1.51) and the energy of activation (E_a = 3.76 to 88.40 kJmol^{-1}) have been reported using Freeman-Carroll method. The pre-exponential factor (A), the activation entropy (S^* = -175 to -283 JK^{-1}mol^{-1}), the activation enthalpy (H^* = 0.856 to 80.97 kJmol^{-1}) and the free energy of activation (G^* = 97.6 to 251 kJmol^{-1}) have been calculated.

Keywords: Ni(II)–Clioquinol complexes, spectroscopic, Freeman-Carroll method, TG/DTG, DSC analysis, antibacterial activity.

INTRODUCTION

Coumarin-containing compounds have found important uses as ligands for the synthesis of coordination compounds. The coumarin group can participate in monodentate, didentate or □^{6}-arene binding modes to a metal centre based upon the coumarin/donor atoms present. Coumarins and/or their metal complexes have been shown to display interesting biological [I], cation/anion sensor [II], phosgene detection , and luminescent properties. Coumarin (2*H*-1-benzopyran-2-one), a naturally occurring plant constituent, has been used in the treatment of cancer, and edemas, many of its derivatives shows biological activity.

In addition to that 5-chloro-7-iodo-8-hydroxyquinoline (clioquinol, CQ) have promising for its therapeutical action to the chelation of metal ion in the brain. Recently Nguyen *et al.* [III] reported the Clioquinol down-regulates mutant huntingtin expression *in vitro* and mitigates pathology in a Huntington's disease in mouse. These results suggest a broader clinical potential of CQ in the treatment of neurodegenerative diseases.

The importance and application of coumarin and CQ are the promising candidates for biological application. Many reports are available on its credited [IV]. Our interest in this area is focused for a considerable time on the investigation of coordination chemistry of transition metal with using coumarin and CQ based complexes [V-VIII]. We herein report the novel mixed ligand complexes of Ni(II) derived from coumarin and CQ and its synthesis, thermal, spectroscopic and anti-bacterial activity.

EXPERIMENTAL

All the chemicals used were of analytical grade. Salicylaldehyde, ethyl acetoacetate, piperidine, chloroform, hexane, bromine, pyridine, toluene, cyclopentanone, cyclohexanone, □-tetralone, dimethyl formamide and nickel nitrate was purchased from the E. Merck (India) Limited, Mumbai. Clioquinol was purchased from Atul Ltd., Agro Chemical Division, Atul, Valsad (India). Luria broth and agar-agar were purchased from SRL, India. Acetic acid and EDTA were purchased from Sigma Chemical Co., India. The organic solvents were purified by recommended method [IX]. The metal content of the complexes were determined by the EDTA titration technique [X] after decomposing the organic matter with a mixture of $HClO_4$, H_2SO_4 and HNO_3 (1:1.5:2.5). Carbon, hydrogen and nitrogen were analyzed with the Perkin Elmer, USA 2400-II CHN analyzer. The magnetic moments were obtained by the Gouy's method using mercury tetrathiocyanatocobaltate(II) as a calibrant ($\chi_g=16.44\times10^{-6}$ c.g.s. units at 20 ^oC). Diamagnetic corrections were made using Pascal's constant [XI]. A simultaneous TG/DTG had been obtained by a model 5000/2960 SDT, TA Instruments, USA. The experiments were performed in N_2 atmosphere at a heating rate of 10 ^oC min^{-1} in the temperature range 50-800 ^oC, using Al_2O_3 crucible. The sample sizes are ranged in mass from 4.5-10 mg. The IR spectra were recorded on a FT-IR Nicolet 400D Spectrophotometer using KBr pellets. NMR spectra were recorded on a model Avance 400 Bruker FT-NMR instrument and $CDCl_3$ used as solvent. The FAB mass spectrum of the complexes was recorded at SAIF, CDRI, Lucknow with JEOL SX-102/DA-6000 mass spectrometer.

Microbiological studies

Preparation of stock solution

A stock solution of 10 mg/mL was made by dissolving compound in minimum amount of DMSO and making it up with D.D.Water.

Preparation of agar plates

The media was made up by dissolving bacteriological agar (20 gm) and Luria broth (20 gm) (SRL, India) in 1 L distilled water. The mixture was autoclave for 15 minutes at 120 ^oC and then dispended into sterilized Petri dishes, allowed to solidify, and then used for inoculation.

Procedure of inoculation

The target microorganism cultures were prepared separately in 15 mL of liquid Luria broth medium for activation. Inoculation was done with the help of micropipette with sterilized tips; 100μL of activated strain is placed onto the surface of an agar plate, and spread evenly over the surface by means of a sterile, bent glass rod. Then two well having diameter of 10 mm is done with the help of sterilized borer in each plate.

Application of discs

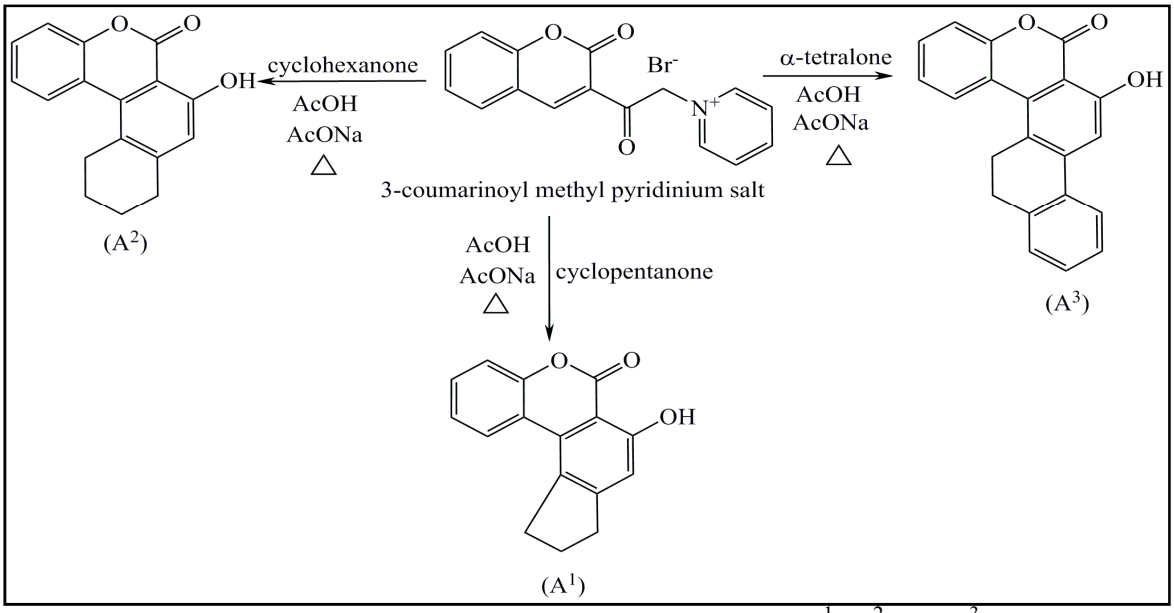
Sterilized stock solutions (10 mg/mL) were used for the application in the well of earlier inoculated agar plates. When the discs were applied, they were incubated at 30 ^{o}C (gram-positive) and 37 ^{o}C (gram-negative) for 24 h. The zone of inhibition was then measured (in mm) around the disc. The control experiments were performed where only equivalent volume of solvents without added test compounds and measured the zone of inhibitions (in mm). All experiments were performed and clioquinol was used as standard drugs. The growth was compared with solvent as the control and is expressed as zone of inhibition (in mm).

Synthesis of ligands

The monobasic bidentate ligands were synthesized according to methods. Structures of ligands A^1-A^3 are shown in Scheme 1.

Preparation of 5-hydroxy-indano [5,4-C] coumarin (A^1)

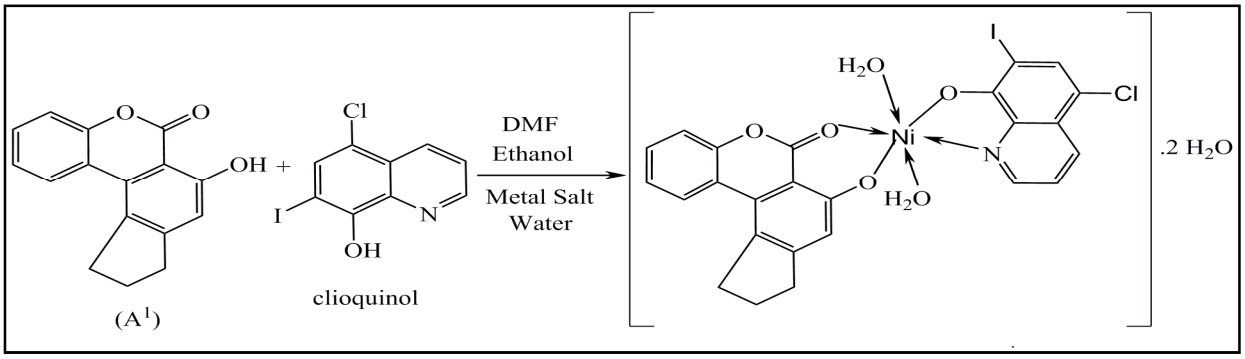
The condensation of various 3-coumarinoyl methyl pyridinium salts (0.004 mol) [XII], with cyclopentanone (0.004 mol), in the presence of sodium acetate (0.020 mol) and acetic acid (40 mL). The reaction mixture was stirred for 10 minutes and then refluxed for 8 h. It was then allowed to cool to room temperature, and poured into cold water (75 mL), the crude solid was extract with chloroform (3 × 30 mL). The combined chloroform extract was washed with water (3 × 20 mL). It was dried over anhydrous sodium sulphate. The removal of chloroform under reduced pressure gave a solid product. It was recrystallized from chloroform-hexane to give white crystalline products. Yield 65%, m.p: 180-182 ^{o}C. Anal. Calcd. for $C_{16}H_{12}O_3$(%): C, 76.18; H, 4.79. Found: C, 76.24; H, 4.80. FT-IR (KBr, cm^{-1}): 3420 ν(O-H), 3045 ν(C-H), 2955 ν(aliphatic C-H), 1670 ν(C=O), 1610 ν(C=C), ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 11.69 (1H, s, protons -OH); 8.11 (1H, d, protons at C_{11}); 7.31-7.48 (3H, m, protons at C_8-H, C_9-H,C_{10}-H); 6.96 (1H, s, protons at C_4); 3.31 (2H, t, protons at C_3); 3.01 (2H, t, protons at C_1); 2.21 (2H, m, protons at C_2). ^{13}C NMR (400MHz, DMSO-d_6): δ (ppm) = 166.00 (CO of coumarin), 161.98 (C_5), 157.00 (C), 150.60 (C), 130.73 (C), 129.84 (C), 129.71 (CH), 126.55 (CH), 124.65 (CH), 119.89 (C), 117.49 (CH), 112.80 (CH), 104.30 (C), 34.66 (C_3), 33.47 (C_1), 25.12 (C_2). GC-Mass M^+ peak at 252 (100%) (m/z %) along with M-1 peak at 251 (54%) and some other fragment peaks at 223 (30%), 207 (17%), 178 (16%), 165 (18%), 152 (16%), 139 (114%), 115 (11%), 103 (6%), 89 (12%), 76 (16%), 63 (13%). A^2 and A^3 was synthesized by same method used for A^1 by using cyclohexanone and α-tetralone instead of cyclopentanone respectvely.



Scheme 1. Synthesis and structure of the ligand (A^1, A^2 and A^3)

Synthesis of metal complexes

A water solution (100 mL) of Ni(II) nitrate (10 mmol) was added to dimethyl formamide solution (100 mL) of ligand (A^n) (10 mmol), followed by addition of clioquinol (10 mmol) in ethanol; the pH was adjusted to 4.5-6.0 with diluted NaOH solution. The resulting solution was refluxed for 7 h and then heated over a steam bath to evaporate up to half of the volume. The reaction mixture was kept overnight at room temperature. A darkbrown colored product was obtained.



Scheme 2. Synthesis of $[Ni(A^1)(CQ)(H_2O)_2].2H_2O$

RESULTS AND DISCUSSION

The analytical and physical properties of the complexes are listed in Table 1. The following reaction describes the formation of the complexes:

$$Ni(NO_3)_2.6H_2O + A^1 + CQ \longrightarrow [Ni(A^1)(CQ)(H_2O)_2].2H_2O + 2HNO_3 + 4H_2O$$

$$Ni(NO_3)_2.6H_2O + A^2 + CQ \longrightarrow [Ni(A^2)(CQ)(H_2O)_2].H_2O + 2HNO_3 + 5H_2O$$

$$Ni(NO_3)_2.6H_2O + A^3 + CQ \longrightarrow [Ni(A^3)(CQ)(H_2O)_2].H_2O + 2HNO_3 + 5H_2O$$

All the complexes are insoluble in all common organic solvents such as acetone, ethanol, chloroform, methanol, benzene, dimethyl formamide etc., but least soluble in DMSO.

Table 1 Analytical and physical data of complexes

Empirical formula of complexes	Formula weight	Colour (Yield %)	M.P. (^oC)	Found (calcd.) (%)				μ_{eff} (B.M.)
				C	H	N	M	
Ni(II)-A^1 $C_{25}H_{23}O_8ClNINi$	684.95	Yellowish green (63)	>300	43.72 (43.74)	3.31 (3.38)	2.00 (2.04)	8.41 (8.55)	3.01
Ni(II)-A^2 $C_{26}H_{23}O_7ClNINi$	664.50	Yellowish green (65)	>300	46.56 (46.99)	3.03 (3.19)	2.10 (2.11)	8.73 (8.83)	2.98
Ni(II)-A^3 $C_{30}H_{23}O_7ClNINi$	730.56	Yellowish green (62)	>300	49.27 (49.32)	3.16 (3.17)	1.91 (1.92)	7.99 (8.03)	2.99

Infrared spectra

The important infrared spectral bands and their tentative assignments for the synthesized complexes were recorded as KBr disks and are summarized in Table 2.

In the 8-hydroxyquinoline complexes of divalent metals, the ν (C-O), appeared at 1120 cm^{-1} region and the position of the band slightly varies with the metal [XIII]. The ν (C-O), observed in the free oxine molecule at 1090 cm^{-1} , shifted to higher frequencies in all the mixed ligand complexes giving a strong absorption band at 1110 cm^{-1} . This clearly indicates the coordination of 8-hydroxyquinoline in these complexes. In the investigated complexes, the band observed in the region 3400-3500, 1295-1300, 860-870 and 715-717 cm^{-1} are attributed to –OH stretching, bending, rocking and wagging vibrations, respectively due to the presence of water molecules [XIV]. The presence of later band indicates the coordination nature of the water molecule. The IR spectra of the coumarin derivatives show 1670 cm^{-1} corresponding to (lactone carbonyl ketone) respectively; on complexation these peaks shifted to a lower frequency 1656 cm^{-1} due to complex formation. The weak band around 510 cm^{-1} and 540 cm^{-1} are attributed to the M-O and M-N stretching frequency.

Table 2 The characteristic IR bands of complexes

Complexes	ν (O-H) cm^{-1}	ν (C=N) cm^{-1}	ν (C=C) cm^{-1} (aromatic)	ν (C=O) cm^{-1} [A^n]	ν (M-O) cm^{-1} [A^n]	ν (M-N) cm^{-1} [CQ]
Clioquinol (CQ)	3415 (br)	1595 (w)	1510 (s)	-	-	-
Ni(II)-A^1	3445 (br)	1585 (w)	1520 (s)	1655 (s)	510	540
Ni(II)-A^2	3450 (br)	1589 (w)	1515 (s)	1645 (s)	512	536
Ni(II)-A^3	3425 (br)	1599 (w)	1518 (s)	1650 (s)	507	539

s = strong, w = weak, br = broad.

^{1}H NMR spectra of ligands

The ^{1}H NMR studies of all the coumarin base ligands (A^n) were carried out in a polar solvent such as DMSO-d_6 at room temperature and the data are given in the experimental section. A broad singlet corresponding to one proton for all the coumarin base ligands (A^n) is observed in the range δ 11.60 – 11.69 ppm. This signal disappeared when a D_2O exchange experiment was carried out. It can be assigned either to OH or NH, in either case it is strongly deshielded because of hydrogen bonding with the other atom (N/O) (Scheme 1). The ^{1}H NMR spectrum of ligand A^1 showed a multiple integrating for two protons and centered at 2.21 δ. This is due to two protons attached at C_2. A triplet centered at 3.01 δ (2H) is due to two protons attached at C_1. A triplet centered at 3.31 δ (2H) is due to two protons attached at C_3. A singlet at 6.96 δ (1H) is due to one proton attached at C_4. The multiplet observed between 7.31-7.48 δ (3H) is due to C_8-H, C_9-H and C_{10}-H. A poorly resolved doublet of a doublet observed at 8.11 δ (1H) is due to C_{11}-H. The ^{1}H NMR spectrum of ligand A^2 showed a multiple integrating for four protons and centered at 1.88 δ. This is due to four protons attached at C_2 and C_3. A triplet centered at 2.99 δ (2H) is due to two protons attached at C_1. A triplet centered at 3.19 δ (2H) is due to two protons attached at C_4. A singlet at 6.91 δ (1H) is due to one proton attached at C_5. The multiplet observed between 7.32-7.51 δ (3H) is due to C_9-H, C_{10}-H and C_{11}-H. A poorly resolved doublet of a doublet observed at 8.29 δ (1H) is due to C_{12}-H. The ^{1}H NMR spectrum of ligand A^3 showed a triplet integrating for two protons and centered at 2.83 δ. This is due to two protons attached at C_{13}. A triplet centered at 3.34 δ (2H) is due to two protons attached at C_{14}. The multiplet observed between 7.31-7.75 δ (8H) is due to C_1-H, C_2-H, C_3-H, C_4-H, C_5-H, C_9-H, C_{10}-H, and C_{11}-H. A poorly resolved doublet of a doublet observed at 8.02 δ (1H) is due to one proton attached at C_{12}.

Magnetic moments and electronic spectra

The information regarding geometry of the mixed-ligand complexes are obtained from their electronic spectral data and magnetic moments.

The electronic spectra of the Ni(II) mixed-ligand complexes exhibit absorption bands at ~ 10,500 (ν_1), ~ 17,500 (ν_2), and ~ 24,200 (ν_3) cm^{-1} attributed to $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$, and $^3A_{2g}(F) \rightarrow {}^3T_{2g}(P)$ transitions, respectively, in an octahedral geometry. The magnetic moment

values of Ni(II)-A^1, Ni(II)-A^2 and Ni(II)-A^3 complexes are 3.01, 2.98 and 2.99 B.M. respectively may be taken as additional evidence for their octahedral structure [XV].

Thermodynamic studies

The thermodynamic activation parameters of the decomposition process of the complexes such as energy of activation (E_a) and order of reaction (n) were evaluated graphically by employing the Freeman-Carroll [XVI] method using the following relation:

$$[(-Ea/2.303R)\,\Delta\,(1/T)] / \Delta \log w_r = -n + \Delta \log (dw/dt) / \Delta \log w_r$$

Where T is the temperature in K, R is gas constant, $w_r = w_c - w$; w_c is the weight loss at the completion of the reaction and w is the total mass loss up to time t. E_a and n are the energy of activation and order of reaction, respectively. A typical curve of [Δ log (dw/dt) / Δlog w_r] vs. [Δ ($1/T$) / Δ log w_r] for the Ni(II) complex is shown in Fig. 1. The slope of the plot gave the value of E_a / 2.303R and the order of reaction (n) was determined from the intercept.

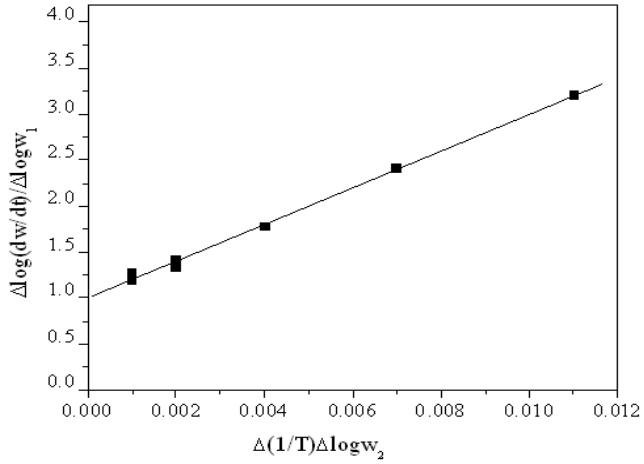


Figure 1. Freeman-Carroll plot for thermal degradation of [Ni(A^1)(CQ)(H_2O)$_2$].2H_2O

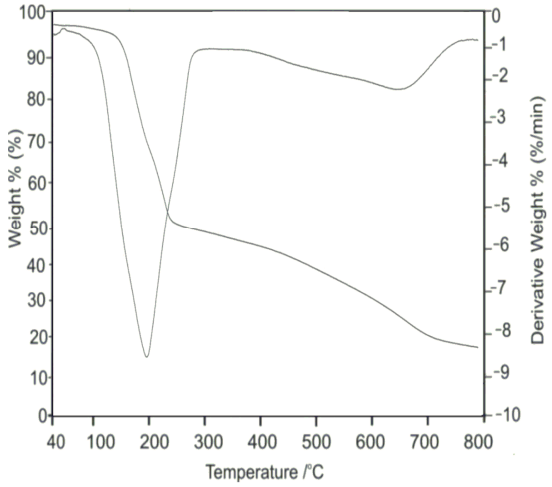
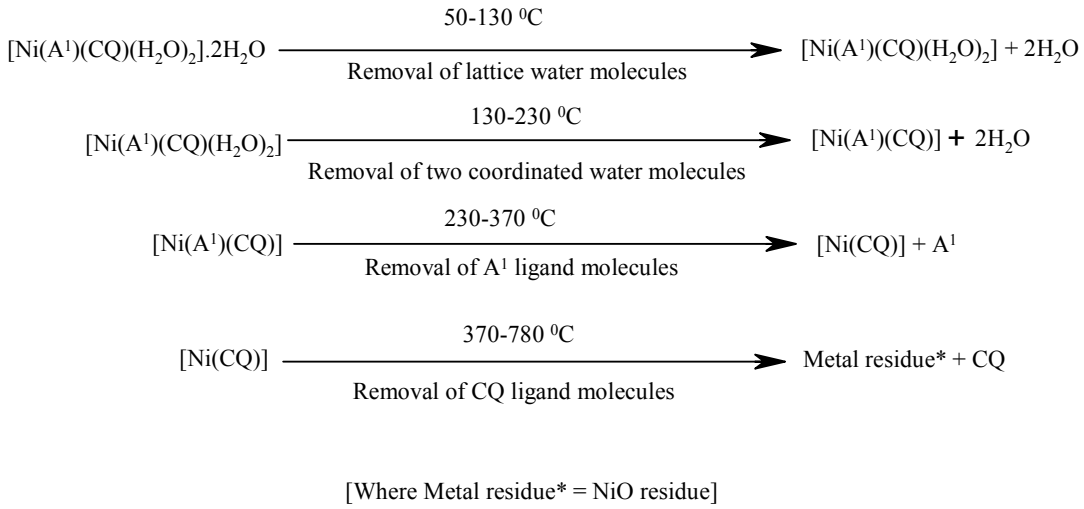


Figure 2. TGA/DTG curve of [Ni(A^1)(CQ)(H_2O)$_2$].2H_2O

The thermal behavior of the prepared complexes

Thermal data and kinetic parameters of the complexes are given in Table 3, respectively. The typical TG/DTG, DTA curves of the complexes Ni(II)-A^1 are represented in Fig. 2. The thermal fragmentation scheme for Ni(II)-A^1 complexes is shown below:



[Where Metal residue* = NiO residue]

Table 3 Kinetic parameters of complexes

Complexes	TG range (°C)	E_a (kJ mol^{-1})	n	A (s^{-1})	S^* (JK^{-1} mol^{-1})	H^* (kJ mol^{-1})	G^* (kJ mol^{-1})
Ni(II)-A^1	50-130	3.89	1.00	0.009	-283	1.051	98.4
	130-230	5.11	1.00	0.111	-266	1.307	123
	230-370	10.54	1.39	0.451	-256	6.051	144
	370-780	55.80	0.97	1.02×10^3	-195	49.06	191
Ni(II)-A^2	50-140	3.84	1.51	0.010	-283	1.005	98.1
	140-280	4.91	0.98	0.082	-269	0.856	132
	280-400	13.05	1.00	0.411	-258	7.645	176
	400-780	59.73	1.00	1.66×10^2	-211	51.90	251
Ni(II)-A^3	50-130	3.76	1.10	0.010	-283	0.947	97.6
	130-250	4.80	0.97	0.092	-268	0.928	125
	250-520	8.09	1.49	0.113	-268	2.828	173
	520-650	88.40	1.00	1.95×10^4	-171	80.97	234

The thermodynamic activation parameters of decomposition process of dehydrated complexes such as activation entropy (S^*), pre-exponential factor (A), activation enthalpy (H^*) and the free energy of activation (G^*) were calculated using the reported equations [XVII]. According to kinetic data obtained from DTG curves, all the complexes have negative entropy, which indicates that the studied complexes have more ordered systems than reactants [VIII]. The kinetic parameters, especially energy of activation (E_a) is helpful in assigning the strength of the complexes.

Mass spectral studies

The mass spectra of the Ni(II)-A^1 is shown in Fig. 3. Here the peak at m/z = 648 stands for the molecular ion peak of complex (without water of crystallization).

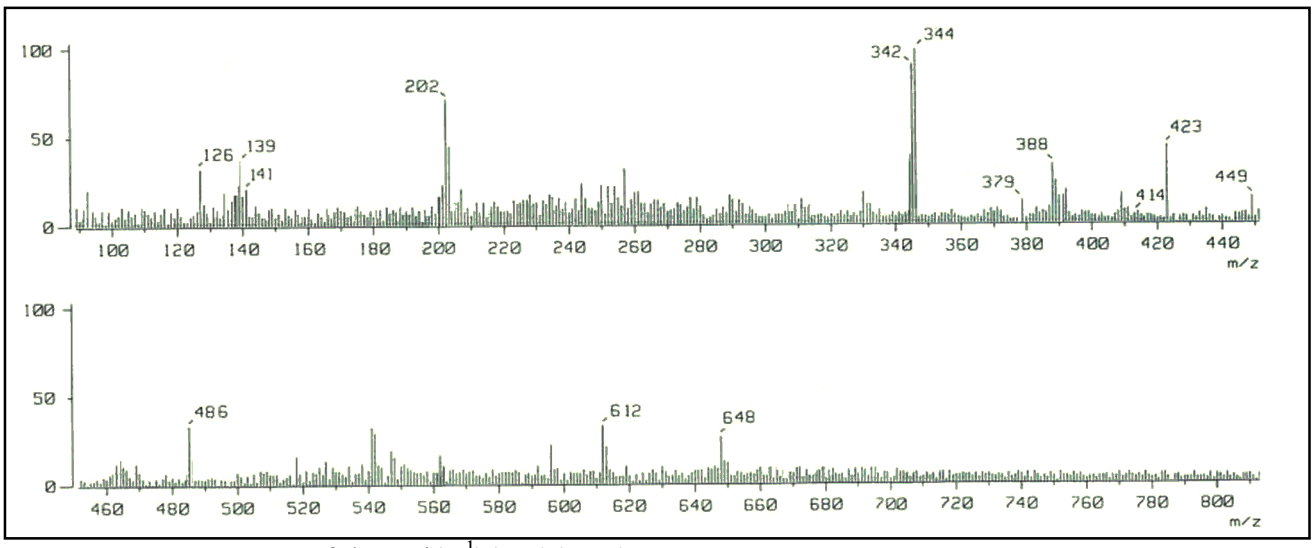


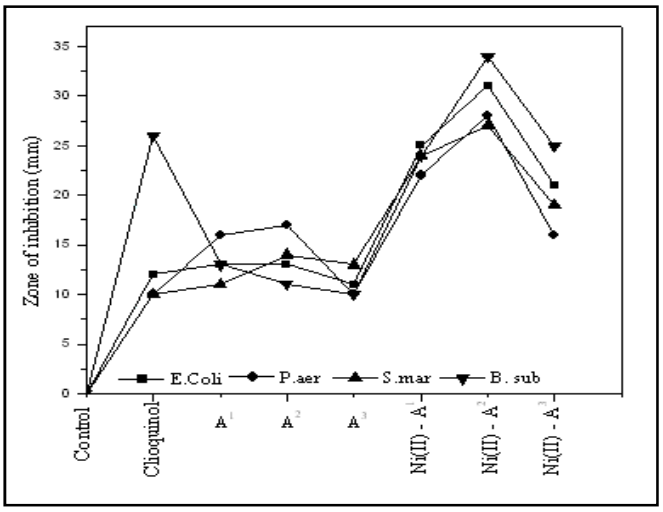
Figure 3. Mass spectra of the $[Ni(A^1)(CQ)(H_2O)_2].2H_2O$

Table 4 Agar plate technique.

Compound	Zone of inhibition (mm)			
	Escherichia coli	*Pseudomonas aeruginosa*	*Serratia marcescens*	*Bacillus substilis*
Control (DMSO)	0	0	0	0
Clioquinol (CQ)	12	10	10	26
A^1	13	16	11	13
A^2	13	17	14	11
A^3	11	10	13	10
Ni(II)-A^1	25	22	24	24
Ni(II)-A^2	31	28	27	34
Ni(II)-A^3	21	16	19	25

Biological activity of complexes

Coordination compounds have promising character for biological application. Many metal complexes are reported biological study and compared with ligands itself [XIX]. Metal complexes exhibit higher biocidal activity as compared to the free ligands, metal salts, control (DMSO) where as are in competition with clioquinol. From comparative analysis as shown in Fig. 4. it is observed that all the metal complexes are more potent biocidal than the ligands A^1-A^3. The zone of inhibition was measured (in mm) around the disc and the results are represented in Table 4. From the graph it is clear that Ni(II)-A^2 is highly active among the complexes of the respective metal.



Conclusion

The results obtained in this study allow the following conclusions:

1. All the synthesized compounds were screened for their bioassay. The complexes exhibited strong activities against gram-negative and gram-positive microorganisms. In comparison with both the ligands and metal salt, the Ni(II)-A^2 heterochelates were more active against one or more bacterial strains, thus introducing novel class of metal-based bactericidal agents.
2. The information regarding geometry of the complexes was obtained from their magnetic moment values. Magnetic moment values indicate that Ni(II) complexes are high spin, lacking exchange interactions. The study reveals that octahedral geometry around the central metal ion as shown in Scheme 2.
3. The kinetic parameters, especially energy of activation (*E*a), are helpful in assigning the strength of the complexes. The calculated *E*a values of the investigated complexes for the first dehydration step were in the range 3.76-3.84 $kJmol^{-1}$ (Table 3). Based on the activation energy values the thermal stabilities of complexes in the decreasing order are: Ni(II)-A^1 > [Ni(II)-A^2 > Ni(II)-A^3

ACKNOWLEDGEMENTS

The authors are grateful to Principal, Navjivan Science College , Gujarat University, Jhalod Road , Dahod-389151, Gujarat, INDIA, for providing the necessary laboratory facilities. Analytical facilities provided by the SAIF, Central Drug Research Institute, Lucknow, India and the Sophisticated Instrumentation Centre for Applied Research & Testing (SICART), Vallabh Vidyanagar, Gujarat, India is gratefully acknowledged.

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Received on August 19, 2013