METAL COMPLEXES OF NITROGEN-OXYGEN DONOR LIGANDS AS POTENTIAL DRUGS

Said A. IBRAHIM, Sahar A. EL-GYAR and Mohamed A. EL-GAHAMI

Department of Chemistry, Faculty of Science, Assiut University, Assiut, Egypt

Received September 3, 1990
Accepted October 30, 1990

Twelve new complexes of Cu(II), Ni(II), Co(II) and Cd(II) with 5-phenyl, 5-*p*-tolyl and 5-aminothioacetimide-azo-8-hydroxyquinoline have been synthesized. The ligands act as bidentate (NO) chelating agents forming the bis-chelate complexes. Analytical, conductivity, spectral and thermal data are consistent with six coordinated structure in the case of Cu(II), Ni(II), Co(II) and four coordinate structure in the case of the analogues Cd(II). It is identified that the metal chelates possess enhanced antibacterial and antifungal activities relative to the free ligands.

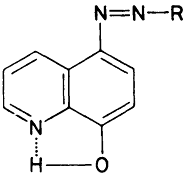
In general, metal ions bind to 8-hydroxyquinoline containing ligand through quinolinol moiety, where the bonding sites are the quinoline ring–nitrogen and the phenolic oxygen atoms[1-3]. It has recently been reported that some drugs have increased activity when administered as metal complexes, and more so as metal chelates[4-8]. Furthermore oxine and its analogues have been established to act as antibacterial, antifungal and antiprotozoal agents by complexing with some metal ions[9].

So, it is thought that complexes of ligands containing 8-hydroxyquinoline-5-azo derivatives are worth studying. In this context, the coordination chemistry and biological activity of the chelates Cu(II), Ni(II), Co(II), Cd(II)-8-hydroxyquinoline-5-azo derivatives are aimed to be investigated. The ligands used are 5-phenyl-, 5-(*p*-tolyl-, and 5-aminothioacetimide-azo-8-hydroxyquinoline (L_1 – L_3, respectively).

EXPERIMENTAL

Solvents used in this study were of a.r. grade. All other materials were of g.r. grade. The IR spectra were recorded on a Perkin Elmer 599 B spectrophotometer as KBr discs. UV-visible spectra were recorded on a CECIL 599 spectrophotometer using 1 cm matched silica cells. Conductivity measurements were carried out using an LF Digi conductance bridge and an immersion cell at room temperature ($\approx 25°C$).

Azo-8-hydroxyquinoline derivatives under investigation were synthesized from reagent grade chemicals by the method given before[10]. The azo-8-hydroxyquinoline used has the following structure:



R = C_6H_5, L_1 = p-CH_3 phenyl, L_2 = aminothioacetimide, L_3

General Method for Synthesis of the Complexes

A solution of metal(II) chloride (1 mmol) in absolute ethanol (40 ml) was mixed with a solution of the appropriate ligand (2 mmol) in absolute ethanol (50 ml) and heated on a water bath for 30 min. The reaction mixture was cooled slowly and the solid product formed was filtered, washed several times with ethanol and dried in a desiccator over P_4O_{10}.

Biological Screening

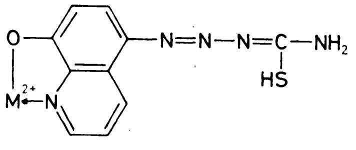
The biological activity of the ligands and their metal chelates were studied by the usual cup-plate agar diffusion technique[11,12]. Solutions (1·0 wt. %) of the compounds prepared in sterile polyethylene glycol were used.

RESULTS AND DISCUSSION

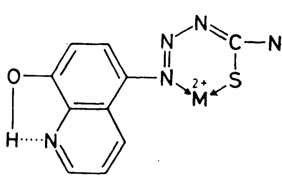
Analytical data (Table I) of the complexes show that they have the composition $[M(H_2O)_2(L)_2]$ and $[Cd(H_2O)LCl]$, where $L = L_1 - L_3$ and M = Cu(II), Ni(II) or Co(II). All the chelates are colored and insoluble or very little soluble in water and common organic solvents. They are, however appreciably soluble in solvents like DMF, acetonitrile and nitrobenzene.

The molar conductance values of the complexes in nitrobenzene (Table I) indicate that all the complexes behave as nonelectrolytes[13].

One of azo compound ligands used in this study, namely 5-amino-thioacetimide-azo-8-hydroxyquinoline (L_3) is ambidentate where it can bind to the metal ion as monobasic bidentate ligand either as NO donor (*I*), or as NS (*II*) donor. However, IR and electronic spectra provide ample evidence in favor of the coordination of the ligand through the monobasic bidentate mode *I*, as it is given hereafter.



I



II

TABLE I

Analytical data, color, decomposition temperature and molar conductance values of the metal chelates

Compound	Color	Decomp. °C	Calculated (Found)				$\Lambda_m \Omega^{-1} . cm^2 mol^{-1}$
			% C	% H	% N	% M	nitrobenzene
Complexes of (L_1)							
[$Cu(C_{15}H_{10}N_3O)_2 2 H_2O$]	green	270	60·44(60·30)	4·05(4·10)	14·09(14·10)	10·65(10·90)	6·55
[$Ni(C_{15}H_{10}N_3O)_2 2 H_2O$]	yellow	290	60·94(61·20)	4·09(4·00)	14·21(14·30)	9·92(10·20)	7·00
[$Co(C_{15}H_{10}N_3O)_2 2 H_2O$]	brown	310	60·91(60·70)	4·00(4·00)	14·20(14·00)	9·96(9·70)	3·19
[$CdCl(C_{15}H_{10}N_3O)H_2O$]	yellowish green	300	43·39(43·50)	2·92(3·20)	10·12(10·30)	27·07(27·30)	4·50
Complexes of (L_2)							
[$Cu(C_{16}H_{12}N_3O)_2 2 H_2O$]	reddish brown	290	61·58(61·50)	4·52(4·60)	13·46(13·60)	10·18(10·40)	2·61
[$Ni(C_{16}H_{12}N_3O)_2 2 H_2O$]	greenish yellow	300	62·06(62·20)	4·55(4·50)	13·56(13·50)	9·47(9·60)	8·15
[$Co(C_{16}H_{12}N_3O)_2 2 H_2O$]	brown	305	62·03(61·80)	4·55(4·70)	13·56(13·30)	9·51(9·50)	6·30
[$CdCl(C_{16}H_{12}N_3O)H_2O]H_2O$	yellow	295	43·07(43·20)	3·61(3·40)	9·41(9·60)	25·19(25·30)	3·41
Complexes of (L_3)							
[$Cu(C_{16}H_8N_5SO)_2 2 H_2O]H_2O$	green	285	39·37(39·50)	3·63(3·80)	22·95(22·10)	10·41(10·60)	7·61
[$Ni(C_{16}H_8N_5SO)_2 2 H_2O$]	green	270	40·90(41·20)	3·43(3·60)	23·84(24·00)	9·99(10·20)	5·60
[$Co(C_{16}H_8N_5SO)_2 2 H_2O]H_2O$	reddish brown	290	36·67(35·60)	3·66(3·80)	23·12(23·10)	9·73(9·40)	3·70
[$CdCl(C_{16}H_8N_5SO)2H_2O]H_2O$	yellow	300	27·92(27·70)	2·81(2·90)	16·27(15·70)	26·12(26·40)	6·00

Thermogravimetric analysis of some representative compounds reveal an initial loss of water molecules on heating around 110 ± 5°C owing to the dehydration of the chelates. The observed slow weight loss above 150°C can be ascribed to the loss of the coordinated water molecules. This weight loss is in accordance with the elimination of two water molecules in the case of Cu(II), Ni(II), Co(II) chelates and one water molecule in the case of Cd(II) chelates.

Infrared Spectra

The IR spectra of the ligands and their metal chelates were recorded in the range 4 000 – 600 cm^{-1} (Table II). Generally the ligands (L_1 – L_3) display a broad band in the high wavenumber region due to the stretching vibration of the H bonded OH group at 3 200 – 3 350 cm^{-1}. This band disappears in the IR spectra of the resultant complexes. In all cases a new broad band appeared at higher wavenumber (3 420 to 3 490 cm^{-1}). This behaviour can be likely ascribed to the presence of water molecules in the prepared complexes. The existence of water molecules is further substantiated from the results of elemental and thermogravimetric analysis. The appearance of a strong band at ≈850 cm^{-1} in the IR spectra of the complexes suggests the presence of water molecule[14] in the complexes as coordinated water.

TABLE II

Selected IR spectra bands (cm^{-1}) of the ligands and their metal chelates

Compound	Assignment				
	ν_{OH}	$\nu_{N=N}$	$\nu_{C=N}$	$\nu_{O=Ph}$	ν_{SH}
L_1	3 200	1 470	1 630	1 280	—
Cu(II)-L_1	3 420	1 460	1 600	1 245	—
Ni(II)-L_1	3 450	1 465	1 605	1 240	—
Co(II)-L_1	3 490	1 460	1 580	1 250	—
Cd(II)-L_1	3 490	1 460	1 610	1 250	—
L_2	3 350	1 470	1 600	1 280	—
Cu(II)-L_2	3 460	1 470	1 570	1 245	—
Ni(II)-L_2	3 460	1 470	1 580	1 250	—
Co(II)-L_2	3 450	1 460	1 580	1 240	—
Cd(II)-L_2	3 470	1 460	1 560	1 250	—
L_3	3 300	1 455	1 615	1 270	2 600
Cu(II)-L_3	3 450	1 450	1 590	1 230	2 600
Ni(II)-L_3	3 450	1 450	1 590	1 240	2 600
Co(II)-L_3	3 450	1 455	1 600	1 245	2 600
Cd(II)-L_3	3 450	1 450	1 605	1 250	2 600

The band due to $\nu_{O-phenyl}$ (ref.[15]) found at 1 280 cm^{-1} for L_1 or L_2 and at 1 270 cm^{-1} for L_3 is shifted to lower values on complexation. This shift illustrates the participation of the quinolinol oxygen in the complex formation. The strong band at 1 630 cm^{-1} for L_1, 1 600 cm^{-1} for L_2 and 1 615 cm^{-1} for L_3 is characteristic of the quinoline $\nu_{C=N}$ (ref.[16]). This band shifts to lower frequency in the spectra of the complexes. This behaviour reflects a decrease in the bond order due to its involvement in coordination to the metal ion. So, the disappearance of the H bonded OH broad band as well as the observed shifts in $\nu_{C=N}$ and $\nu_{O-phenyl}$ on complexation suggest that the complexes are formed by coordination of the ligands to the metal ions through the quinolinol moiety where the bonding sites are the quinoline ring-nitrogen and the phenolic oxygen atoms.

The two bands appearing at 2 600 and 1 470 cm^{-1} in the IR-spectra of L_3 are assignable to ν_{SH} and $\nu_{N=N}$ respectively[17,18]. These two bands were found to be uninfluenced by coordination of this ligand to metal ion. This indicates that the aminothioacetamide moiety did not participate in complex formation.

Electronic Spectra

The electronic absorption spectra of the nitrobenzene Cu(II), Ni(II), Co(II)complex solutions were recorded and the data are given Table III. Generally for all complexes the two absorption bands 28,500 – 32,600 cm^{-1}) and (32,200 – 36,500 cm^{-1}) which can be ascribed to π–π^* and intraligand transitions within the complexed ligands $L_1 - L_3$ exhibit lower excitation energies compared to the corresponding ones of the free ligands. This is reasonably ascribed to the expected easier intramolecular CT transition within the complexed ligand owing to the positive charge of the coordinated metal ion.

In addition to the above transitions, copper(II) complexes show absorptions around 15,000 – 16,600 cm^{-1} characteristic of distorted octahedral geometry[19]. These transitions may be assigned to the combination $^2E_{2g} \rightarrow {}^2T_{2g}$.

Ni(II) and Co(II) complexes show bands around 13,300 and 16,400 cm^{-1} in the visible region, respectively. In the case of Ni(II) complexes the observed band at 13,300 cm^{-1} is assigned to the transition $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ which is suggestive for octahedral Ni(II) complexes[20]. In the case of the Co(II) complexes the band that appeared at 16,500 cm^{-1} is assigned to $^4T_{1g}(F) \rightarrow {}^4A_{2g}$ transition. Such transition is usually found for the distored octahedral Co(II) complexes[20].

The Biological Properties

The bacteriostatic and fungicidal properties of the ligands and their metal chelates against four bacteria and four fungi are given in Table IV. The ligands material showed antimicrobial activity against all the bacteria except *Bacillus cereus* or

Escherichia coli in case of L_2 and L_1, respectively. But activity against the fungi used appeared weak. However, transformation of ligands to metal chelates exerted

TABLE III

Electronic spectral data of Cu(II), Ni(II) and Co(II) complexes

Complex	ν, cm^{-1} ($\varepsilon_{\max}$, l^{-1} mol^{-1} cm^{-1})
Cu(II)-L_1	15,000(560); 28,600(1 300); 35,000(3 400)
Ni(II)-L_1	13,300(210); 29,700(2 300); 35,600(3 600)
Co(II)-L_1	16,400(180); 29,700(3 100); 34,000(6 700)
Cu(II)-L_2	16,200(260); 30,200(2 000); 34,500(5 200)
Ni(II)-L_2	13,300(180); 32,600(3 100); 34,000(3 500)
Co(II)-L_2	16,400(430); 28,500(1 200); 36,200(4 500)
Cu(II)-L_3	17,600(360); 29,700(2 300); 33,200(5 000)
Ni(II)-L_3	13,300(280); 29,500(2 400); 35,100(7 100)
Co(II)-L_3	16,400(250); 31,600(1 800); 36,500(8 200)

TABLE IV

Biological screening of compounds L_1-L_3 and their metal complexes (inhibition zones in mm)

Compound	Bacteria				Fungi			
	Gram +ve		Gram −ve					
	1	2	3	4	5	6	7	8
(L_1)	7	10	10	−ve	10	−ve	8	−ve
(L_2)	−ve	8	9	12	−ve	−ve	−ve	−ve
(L_3)	8	9	9	10	−ve	7	−ve	8
Cu(II)-L_1	17	15	20	8	−ve	−ve	10	−ve
Co(II)-L_1	15	18	15	7	−ve	−ve	10	−ve
Ni(II)-L_1	20	25	20	10	−ve	−ve	−ve	−ve
Cu(II)-L_2	16	18	12	17	−ve	−ve	J	−ve
Co(II)-L_2	−ve	15	15	15	−ve	−ve	−ve	−ve
Cd(II)-L_2	20	18	25	20	−ve	−ve	7	−ve
Cu(II)-L_3	10	15	10	15	−ve	−ve	−ve	−ve
Ni(II)-L_3	15	20	15	15	−ve	8	−ve	10
Cd(II)-L_3	18	25	15	18	−ve	10	−ve	15

1 — *Bacillus cereus*, 2 — *Staphylococcus aureus*, 3 — *Serratia*, 4 — *Escherichia coli*, 5 — *Aspergillus flavus*, 6 — *Penicillium oxalicum*, 7 — *Penicillium variabile*, 8 — *Chrysosporium tropicum*.

predominant activity the majority of the bacteria and some of the fungi used. In spite of the predominant potency of the chelates, the more potent complexes are those with Cd(II) and Ni(II) which exhibit good activity against most of the used bacteria.

REFERENCES

1. Ibrahim S. A., El-Gahami M. A., Mahfouz R. M., Farghali K. A.: Z. Naturforsch. *44*, 1488 (1989).
2. Kamal M. M., Aly A. A. M., El-Meligy M. S., El-Said A. I.: Synth. React. Inorg. Met.-Org. Chem. *19*, 557 (1989).
3. Tiwari G. P., Mishra M. N.: J. Indian Chem. Soc. *60*, 689 (1983).
4. Williams D. R.: Chem. Rev. *72*, 203 (1972).
5. Furst A., Haro R. T.: Prog. Exp. Tumor Res. *12*, 102 (1969).
6. Ibrahim S. A., Makhlouf M. Th., Abdel-Hafez A. A., Moharram A. M.: J. Inorg. Biochem. *28*, 57 (1986).
7. Abdel-Hafez A. A., Awad I. M. A., Hassan K. M.: Collect. Czech. Chem. Commun. *52*, 2753 (1987).
8. Long P. H., Bliss E. A.: J. Am. Med. Assoc. *32*, 108 (1937).
9. Albert A., Rubbo S., Goldacre R., Balfour B.: Br. J. Exp. Path. *28*, 69 (1947).
10. Zakemato S., Fernando Q., Freiser H.: Anal. Chem. *37*, 1249 (1965).
11. *British Pharmacopeia*, p. 796. Pharmaceutical Press, London 1953.
12. Chaturvedi K. K., Jain N. K., Prabuddha Jain, Kaushal R.: Indian Drugs *15*, 57 (1978).
13. Geary W. J.: Coord. Chem. Rev. *7*, 81 (1971).
14. Nakamoto K.: *Infrared Spectra of Inorganic Coordination Compounds*, p. 156. Wiley, New York 1963.
15. Kovacic J. E.: Spectrochim. Acta *23*, 183 (1967).
16. Lambert J. B., Shurvell H. F., Verbit L., Cooks R. G., Stout H. G.: *Organic Structural Analysis*, p. 275. Macmillan, New York 1976.
17. Morelli N.: Analyst *109*, 47 (1984).
18. Gopalakrishnannair M. R., Prabhakaran C. P.: J. Inorg. Nucl. Chem. *43*, 12 (1981).
19. Day M. C., Selbin J.: *Theoretical Inorganic Chemistry*, p. 492. Reinhold, New York 1969.
20. Lever A. B. P.: *Inorganic Electronic Spectroscopy*, 2nd ed., p. 481. Elsevier, Amsterdam 1984.