PHYSICO-CHEMICAL CHARACTERISATION AND BIOLOGICAL ACTIVITY OF ZINC (II) COMPLEXES WITH 2-AMINO AND 2-METHYLBENZIMIDAZOLE DERIVATIVES

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Abstract: *The preparation and characteristics of some zinc(II) complexes with 2-amino and 2-methylbenzimidazole derivatives are reported. The synthesized complexes are of the general formula: $[ZnL_2Cl_2]\cdot nH_2O$; (L=2-aminobenzimidazole, 1-benzyl-2-aminobenzimidazole, 1-(4-methylbenzyl)-2-aminobenzimidazole, 2-methylbenzimidazole, 1-benzyl-2-methylbenzimidazole or 1-(4-methylbenzyl)-2-methylbenzimidazole; n=0, 0.5 or 1). The complexes were characterized by elemental analysis, molar conductivity and IR spectra. The antimicrobial activity of the benzimidazoles and their complexes were evaluated against Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus sp., Saccharomyces cerevisiae and Sarcina lutea. It is found that amino group at position 2 of the benzimidazole ring increases the general antibacterial activity of the relevant benzimidazoles.*

Keywords: benzimidazole, complexes, zinc(II), biological activity.

1. INTRODUCTION

Benzimidazole and its derivatives have received much attention because of their biological activity and commercial application. They are present in many naturally occuring products and various drugs. Some of these compounds have antibacterial, antifungal, antiviral, antiinflammatory, antihypertensive, arteriosclerosis and anti-HIV activities [3-6,8-11]. Recently, a class of compounds which have a benzimidazole nucleus were reported as a new group of antitumor agents [2].

Considerable attention is being paid in recent years to the study of transition metal complexes of benzimidazoles and related ligands because of their biological significance and interesting spectral, magnetic and structural aspects. We have reported earlier the isolation and

characterisation of different metal ion complexes with 2-substituted benzimidazoles [8-11]. A similar study of physico-chemical characteristics and antimicrobial activities of zinc(II) complexes with 2-amino and 2-methylbenzimidazole derivatives is being report here.

2. EXPERIMENTAL

All chemicals used to prepare the complexes were of analytical reagent grade, commercially available from different sources.

Synthesis of complexes

All the complexes were prepared following the same procedure. A solution of 2.5mmol $ZnCl_2$ in 10cm^3 of EtOH was added into a solution of 5mmol of the ligand (L) (L^1=2-aminobenzimidazole, L^2=1-benzyl-2-aminobenzimidazole, L^3=1-(4-methylbenzyl)-2-aminobenzimidazole, 2-methylbenzimidazole, L^4=2-methylbenzimidazole, L^5=1-benzyl-2-methylbenzimidazole or L^6=1-(4-methylbenzyl)-2-methylbenzimidazole) in 10cm^3 EtOH. The resulting mixture was boiled under reflux on a water bath for about 2h and then cooled. The complexes were separated from the reaction mixture by filtration, washed with EtOH and dried *in vacuo* over $CaCl_2$. The yield of the complexes varied in the range 45-50%.

Measurement methods

Elemental analysis was carried out by standard micromethods. Molar conductivies of freshly prepared $1 \cdot 10^{-3}$ moldm^{-3} solutions (DMF) were measured on a Jenway 4010 conductivity meter. Infrared spectra (KBr pellets) were recorded on an Infrared 457 Perkin-Elmer spectrophotometer.

Antimicrobial investigations

For these investigations the filter paper disc method was applied. Each of the investigated isolates of bacteria were seeded in the tubes with nutrient broth (NB). The seeded NB (1cm^3) were homogenized in the tubes with 9cm^3 of melted (45^{o}C) nutrient agar (NA). The homogenous suspension was poured into Petri dishes.

The discs of filter paper (diameter 5mm) were ranged on cool. After cooling on the formed solid medium, $2 \cdot 10^{-5}$dm^3 of the investigated compounds were placed with micropipette. After incubation for 24 hours in thermostat at 25-27^{o}C, inhibition (sterile) zone diameters (including disc) were measured and expressed in mm. Inhibition zone diameter over 8mm indicates the tested compound is active against bacteria under investigation. Every test was done in three replications.

The antimicrobial activities of the investigated compounds were tested against four strains of bacteria (*Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus sp., Saccharomyces cerevisiae and Sarcina lutea*). In parallel with antimicrobial investigations of Zn(II) complexes, all ligands were tested too, as well as the pure solvent. The concentration of each solution was $5 \cdot 10^{-2}$moldm^{-3}. Commercial DMF was employed to dissolve the tested samples.

3. RESULTS AND DISCUSSION

The elemental analysis of complexes and molar conductance data are summarized in Table1.

Table 1. *Some physical characteristics and analytical data of the complexes*

Complex	Mr	Colour	M.p. (°C)	λ_M *	Metal Found (Calcd.) %
$[Zn(L^1)_2Cl_2]$	402.28	white	199	5.4	15.98 (16.25)
$[Zn(L^2)_2Cl_2]$	582.28	rose	195	34.2	10.97 (11.23)
$[Zn(L^3)_2Cl_2]$	610.28	white	210	5.6	10.08 (10.71)
$[Zn(L^4)_2Cl_2]$	400.28	white	220	4.4	15.87 (16.33)
$[Zn(L^5)_2Cl_2]\cdot 0.5H_2O$	589.28	white	212	37.5	10.57 (11.09)
$[Zn(L^6)_2Cl_2]\cdot H_2O$	626.28	white	218	14.4	9.96 (10.44)

* In DMF, 1 mmoldm^{-3} solution at 25° C; in Scm^{2}mol^{-1}

All the complexes are sparingly soluble in common organic solvents such as alcohols or acetone, but highly soluble in dimethylformamide and dimethylsulphoxide. The complexes were synthesized in the reaction of warm ethanolic solution of the $ZnCl_2$ with L^1, L^2, L^3, L^4, L^5 or L^6 in a mole ratio 1:2. It should be noticed that the reaction of all the ligands yielded bis(ligand) complexes.

The molar conductances values of L^1, L^3 ,L^4 and L^6 complexes in DMF solutions fall in the range 4.4-14.4Scm^{2}mol^{-1} (Table 1). The values indicate that the complexes behave as non-electrolytes in DMF [11]. The molar conductances of $[Zn(L^2)_2Cl_2]$ and $[Zn(L^5)_2Cl_2]\cdot 0.5H_2O$ in DMF solutions, compared with the values of non-electrolytes are increased. The same values are considerably less compared with the molar conductances of the 1:1 type electrolytes (λ_M=65-90 Scm^{2}mol^{-1}) [11], which indicates the partial substitution of coordinated anions with solvent molecules.

Infrared spectra

The infrared spectra of some ligands (L^1, L^2 and L^3) exhibit band at 3450-3330cm^{-1} and ca. 1650cm^{-1}, assigned to $\nu(NH_2)$ and $\delta(NH_2)$ of the benzimidazole ring, respectively [7]. The band appearing at about 1550cm^{-1}, for all the ligands, may be assigned to $\nu(C=N)$ vibrations [7]. Substituted phenyl group shows ring vibrations at 1485 and 740 cm^{-1} . The infrared spectra of the complexes investigated are similar to those of the corresponding ligands.

An upward shift (5-15cm^{-1}) of $\nu(C=N)$ in the IR spectra of the complexes as compared to theirs values in the free ligands, suggests coordination through pyridine nitrogen of benzimidazoles [1]. The bands due to $\nu(NH_2)$ and $\delta(NH_2)$ in the complexes are shifted to lower frequency in all the complexes. These shifts may be indicative of present hydrogen bonding [1]. The other bands in the spectrum of each complex are similar to those in the corresponding ligand spectrum except for slight shifts in their positions and changes in their intensities due to coordination.

The presented results (molar conductivity and IR spectra) suggest that all the complexes are tetrahedral which is realized by participation of the pyridine nitrogen of two organic ligand molecules and two chloride anions.

Antimicrobial investigations

All the complexes were screened for their antimicrobial activities against *Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus sp., Saccharomyces cerevisiae* and *Sarcina lutea..* The relevant data are presented in Table 2.

From the data, it is evident that the most active ligand is 1-(4-methylbenzyl)-2-aminobenzimidazole (L^3), as well as its zinc(II) complex ($[Zn(L^3)_2Cl_2]$). In the case of the 2-methylbenzimidazole derivatives all the compounds are not antimicrobial active, except 1-(4-methylbenzyl)-2-methylbenzimidazole (L^6) and its zinc(II) complex. On comparing the biological activity of the ligands and theirs complexes, it was found that some complexes are more effective against the bacteria. The higher activity of the complexes, as compared to the free ligands, can be understood in terms of the chelation theory. This theory explains that a decrease in the polarizability of the metal could enhance the lipophilicity of the complexes.

From the results, it can be concluded that amino group at position 2 of the benzimidazole ring, as well as methyl group at position 4 of the benzyl substituent increase the general antibacterial activity of the relevant benzimidazoles.

Table 2. *Antimicrobial activity of the benzimidazole derivatives and their complexes*

Compound	*Pseud. aerugin.*	*Staph. aureus.*	*Bacillus sp.*	*Sacch. cerevis*	*Sarcina lutea*
L^1	+	Ø	Ø	Ø	Ø
$[Zn(L^1)_2Cl_2]$	+++	+++	+++	+++	++
L^2	+/-	++	++	+/-	+/-
$[Zn(L^2)_2Cl_2]$	+++	+++	+++	Ø	++
L^3	+++	+++	+++	+/-	+++
$[Zn(L^3)_2Cl_2]$	+++	+++	++++	+++	++++
L^4	+/-	Ø	Ø	Ø	Ø
$[Zn(L^4)_2Cl_2]$	+	Ø	Ø	Ø	Ø
L^5	+/-	Ø	Ø	Ø	Ø
$[Zn(L^5)_2Cl_2]\cdot 0.5H_2O$	+/-	Ø	Ø	Ø	Ø
L^6	++	++	++	Ø	+++
$[Zn(L^6)_2Cl_2]\cdot H_2O$	+++	+++	++	Ø	+++

Ø - no activity
\+ - low inhibitory activity
++ - middle inhibitory activity
+++ - high inhibitory activity
++++ - very high inhibitory activity

4. CONCLUSION

Zinc(II) with 2-aminobenzimidazole, 1-benzyl-2-aminobenzimidazole, 1-(4-methylbenzyl)-2-aminobenzimidazole, 2-methylbenzimidazole, 1-benzyl-2-methylbenzimidazole and 1-(4-methylbenzyl)-2-methylbenzimidazole formed complexes of the general formula $[ZnL_2Cl_2]\cdot nH_2O$; n=0, 0.5 or 1). All the complexes have a tetrahedral configuration, which is realized by coordination through pyridine nitrogen of one or two organic ligands and two chloride anions.

The results of antimicrobial investigations indicate that the most active ligand is 1-(4-methylbenzyl)-2-aminobenzimidazole (L^3), as well as its zinc(II) complex. On comparing the biological activity of the ligands and theirs complexes, it was found that some complexes are more effective against the bacteria. From the results, it can be concluded that amino group at position 2 of the benzimidazole ring, as well as methyl group at position 4 of the benzyl substituent increase the general antibacterial activity of the relevant benzimidazoles.

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