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Anticandidal activity of some Zn(II) and Pb(II) complexes

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Abstract

The reactions of zinc and lead acetate with ligands HON=C$(CH_2)_5$, PhN=C(Ph)C(OH)Ph resulted in complexes of the type $[M(ac)_2L_2]$ (M = Zn (Complexes **A** and **C**); Pb (complexes **B and D**) and L = HON=C$(CH_2)_5$, PhN=C(Ph)C(OH)Ph). Ligands were prepared by green methods. Complexes were characterized by ^{1}H-NMR, IR spectral studies and these spectra were compared with that of free ligands. Antifungal activity of the complexes demonstrated that the complexes $[Zn^{II}(ac)_2\{N(OH)=C(CH_2)_5\}_2]$, $[Pb^{II}(ac)_2\{N(OH)=C(CH_2)_5\}_2]$ and $[Zn^{II}(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$ are active against *Candida albicans*.

Keywords: *Antifungal activity, Zinc(II) complexes, Lead(II) complexes.*

1.Introduction

Metal complexes are believed to show better biological significance than free ligand systems [1]. Varied metal-oxime complexes depict cytotoxicity in murines and human tissue cultured cell lines [2]. Different metals oxime complexes are found to be useful as antitubercular [3], antimalarial [4], antiviral [5], antilepral [6] and active against certain kinds of tumors. Oximes and their derivatives also claim anticancer activities [7]. Schiff base complexes have appreciable advantage in many organic reactions as different catalysts [8], for instance as in functional group conversion of >C=O to -OH [9] and alkylation reactions [10-12]. Their feasible synthetic route and thermal stability have been a major reason for their use as metal complexes in possible catalytic applications [8]. Zinc is the one of the most abundant trace element in humans, has an impact role in the metabolism of cells [13] and enhances beneficial effects to human health, while changes in its metabolic activity trafficking are related to few diseases [14, 15]. Lead salts are efficiently absorbed by the body [16]. It is an important constituent in insecticides, waterproofing and varnishes, *etc*. As an effort in succession to our earlier research work [17] and to study the antifungal behavior of metal complexes over a greater expanse; we herein report zinc and lead complexes with cyclohexanone oxime $HON=C(CH_2)_5$ and benzoin-aniline schiff base PhN=C(Ph)C(OH)Ph.

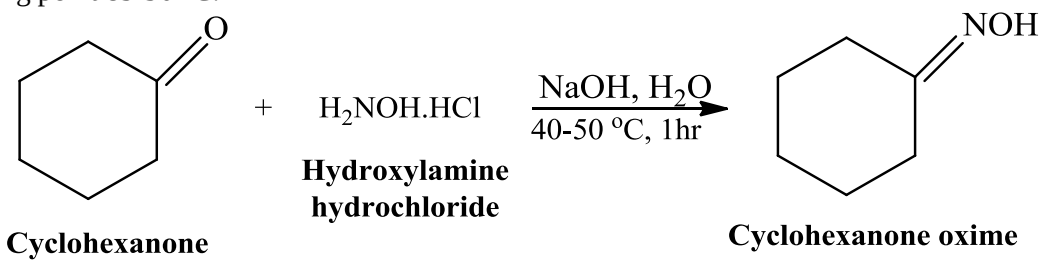
2. Experimental

2.1Materials and Methods

Zinc acetate, lead acetate, cyclohexanone, benzoin and aniline (from Merck) were used without any futher purification. Dry ethanol was used for synthesis of complexes. Ligands were prepared by green methods in aqueous media only. Lead and zinc were estimated gravimetrically as lead chromate and zinc pyrophosphate, respectively. Carbon and hydrogen were examined on Perkin-Elmer 2100 analyzer. Infra-red spectra were noted on Perkin-Elmer spectrophotometer (10.4.00 Version) using Potassium bromide. ^{1}H-NMR was noted on a Bruker-Ascend 300 MHz system in DMSO-d_6 with Tetramethylsilane as reference. The complexes were handled in inert atmosphere only as they were expected to be moisture and air sensitive.

2.2.Synthesis of ligand $HON=C(CH_2)_5$

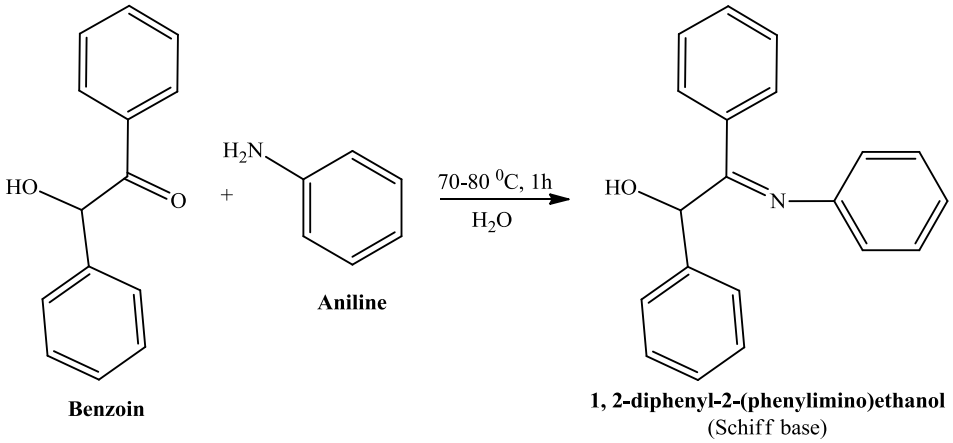
Cyclohexanone (9.81g, 100.03mmol) and hydroxylamine hydrochloride (6.95g, 100.03mmol) mixed in 20ml water were heated to 40-50 °C for 0.5 hrs. NaOH (4.0g, 100.03mmol) was added in fractions, with constant stirring and reaction was continued for 0.5 hrs (Scheme 1). On cooling down, product was filtered off; washed with H_2O and dried under pressure. Cyclohexanone oxime $HON=C(CH_2)_5$ (11.0 g) was obtained as crystalline white solid; recorded melting point 89-90 °C.



Scheme 1: Green synthesis of Cyclohexanone oxime

2.3.*Synthesis of ligand PhN=C(Ph)C(OH)Ph*

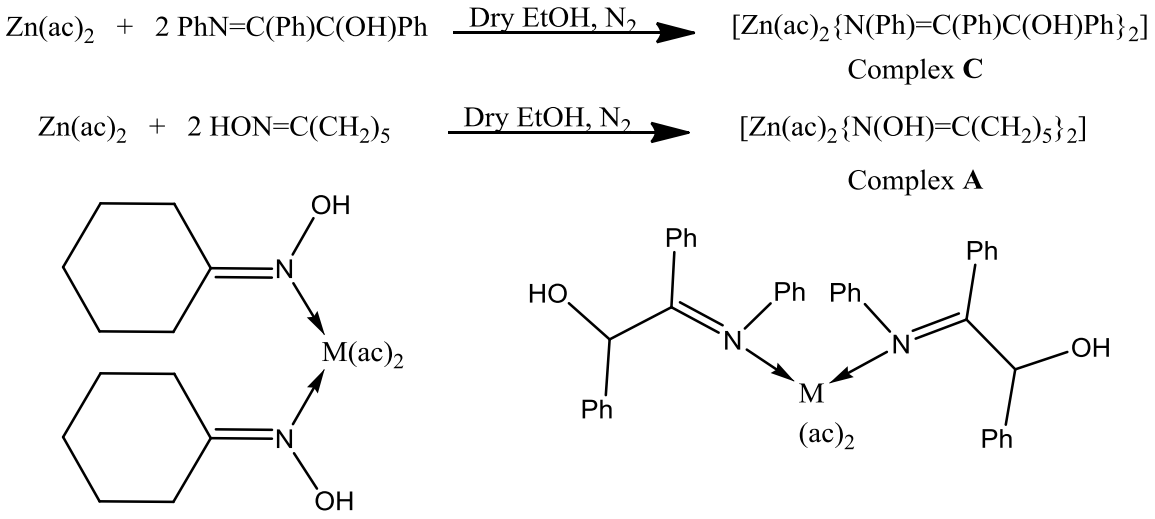
Benzoin (3.27g, 15.41mmol) and aniline (1.43g, 15.41mmol) in 5ml of water were stirred at 70-80 ^{0}C for an hour (Scheme 2). Contents were cooled; filtered, washed under pressured and dried in an electric oven. Benzoin-aniline Schiff base PhN=C(Ph)C(OH)Ph (3.66g) was obtained; recorded melting point 123-124 ^{0}C.



Scheme 2: Green synthesis of Benzoin-Aniline Schiff base

*2.4.**Synthesis of [Zn(ac)$_2${N(Ph)=C(Ph)C(OH)Ph}$_2$] (C)***

Zinc acetate (0.47g, 2.56mmol) and 1, 2-diphenyl-2-(phenylimino)ethanol (0.57g, 5.12mmol) mixed in dry ethanol were stirred for 4 hours in an inert atmosphere. Solvent was stripped off under pressure to obtain solid white product (Scheme 3).



where, M = Zn (in Complexes **A** & **C**) or Pb (in Complexes **B** & **D**)

Scheme 3: Synthesis of complexes of the type [M(ac)$_2${N(OH)=C(CH$_2$)$_5$}$_2$] and [M(ac)$_2${N(Ph)=C(Ph)C(OH)Ph}$_2$]

Similarly, [Zn(ac)$_2${N(OH)=C(CH$_2$)$_5$}$_2$] (**A**), [Pb(ac)$_2${N(OH)=C(CH$_2$)$_5$}$_2$] (**B**) and [Pb(ac)$_2${N(Ph)=C(Ph)C(OH)Ph}$_2$] (**D**), were synthesized.

4.Results and Discussion

The metal acetate complexation with ligands HON=C(CH$_2$)$_5$ and PhN=C(Ph)C(OH)Ph in 1:2 molar ratio resulted in zinc(II) and lead(II) complexes (Scheme 1) of the type [M(ac)$_2${N(OH)=C(CH$_2$)$_5$}$_2$] and [M(ac)$_2${N(Ph)=C(Ph)C(OH)Ph}$_2$] (where M= Zn, Pb). Since, the synthesized complexes were expected to be moisture and air sensitive; they were cautiously handled and stored in N$_2$ atmosphere only. All these products are

white (colorless) solids and are soluble in non-polar solvents like n-hexane, cyclohexane, DMSO, etc. Table 1 lists the melting point and elemental analysis of all the complexes.

Table 1: Melting point and elemental analysis of $[M(ac)_2\{N(OH)=C(CH_2)_5\}_2]$ and $[M(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$

S.N.	Complexes	Elemental Analysis (%) Recorded (Calc.)				Melting point (°C)
		H	C	Zn	Pb	
1	$[Zn(ac)_2\{N(OH)=C(CH_2)_5\}_2]$	6.83 (6.89)	46.80 (46.90)	15.85 (15.95)	---	154-156
2	$[Pb(ac)_2\{N(OH)=C(CH_2)_5\}_2]$	5.13 (5.12)	34.81 (34.84)	---	37.52 (37.56)	178-180
3	$[Zn(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$	5.22 (5.32)	69.64 (69.70)	8.56 (8.62)	---	214-216
4	$[Pb(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$	4.41 (4.48)	58.67 (58.72)	---	22.99 (23.02)	184-186

IR Spectra

Table 2 summarizes some valuable IR spectral bands of complexes. The presence of a signal in the spectra of the complexes $[M(ac)_2\{N(OH)=C(CH_2)_5\}_2]$ and $[M(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$ in the 3600-3100 cm^{-1} region due to υ(OH) suggests that neither of the ligands formed a covalent M-O bond *via* cleavage of O-H bond. The band recorded at 1668 cm^{-1} in the cyclohexanone oxime [18, 19] indicative of (>C=N) group has moved down (1660-1655 cm^{-1}) in complexes $[M(ac)_2\{N(OH)=C(CH_2)_5\}_2]$. It reveals the role of this group in a coordinate bond formation through nitrogen to metal atom. The band in region 940-900 cm^{-1} can be attributed to υ(N-O) in the spectra of complexes. Appearance of bands in the regions 460-425 cm^{-1} and 480-460 cm^{-1} can be assigned to υ(Pb–N) and υ (Zn–N) respectively. The υ(C=N) bands recorded around 1670-1665 cm^{-1} in the spectra of the complexes $[M(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$ depicts formation of a M←N bond [20], since these bands have shifted below compared to respective free schiff base at 1680 cm^{-1}; representing (>C=N) group [21]. Moreover, signals recorded around 1410-1405 cm^{-1} can be assigned to C=C of the arene moiety in the respective complexes; which are below in range compared to respective free Schiff base (1440 cm^{-1}).

Table 2: IR spectral data (in cm^{-1}) for synthesized complexes

S.N.	Complexes	υ(C=N)	υ(O-H)	υ(Zn-N) or υ(Pb-N)	υ(N-O, oxime) or υ(C=C; arene)
1	$[Zn(ac)_2\{N(OH)=C(CH_2)_5\}_2]$	1660	3190	465	900
2	$[Pb(ac)_2\{N(OH)=C(CH_2)_5\}_2]$	1655	3235	425	940
3	$[Zn(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$	1665	3115	480	1410
4	$[Pb(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$	1670	3440	460	1405

^{1}H-NMR Spectra

Table 3 summarizes the ^{1}H-NMR shifts of all the complexes. Since O-H signals were recorded in spectra of all complexes, it suggested that there was no cleavage of O-H bond while formation of the complexes. Complexes showed a high field shift in signal positions as compared to that of their respective free ligands [20, 22-24]; suggesting

the M←L bonding. ^{1}H-NMR of a representative complex $[Zn(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$ (**C**) is provided as supplementary data (Fig. S1 in supplementary file).

Table 3: ^{1}H-NMR data for synthesized complexes recorded at 300MHz in DMSO-d_6

S.N.	Complexes	Proton Chemical Shift (in δ ppm)
1	$[Zn(ac)_2\{N(OH)=C(CH_2)_5\}_2]$	6.71 (s, OH), 2.36 (t, CH_2), 2.10 (t, CH_2), 1.82 (s, CH_2), 1.51 (qt, CH_3).
2	$[Pb(ac)_2\{N(OH)=C(CH_2)_5\}_2]$	6.67 (s, OH), 2.36 (dd, CH_2), 2.18 – 2.01 (m, CH_2), 1.69 (s, CH_2), 1.64 – 1.42 (m, CH_3).
3	$[Zn(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$	10.30 (s, OH), 7.99–7.87 (m, C_6H_5), 7.86–7.72 (m, C_6H_5), 7.72-7.56 (m, C_6H_5), 1.83 (s, CH_3).
4	$[Pb(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$	10.31 (s, OH), 8.01–7.74 (m, C_6H_5), 7.72–7.56 (m, C_6H_5), 7.56–7.34 (m, C_6H_5), 1.69 (s, CH_3).

Anticandidal Activity

Antifungal activity of these complexes clearly reveals that the complexes $[Zn(ac)_2\{N(OH)=C(CH_2)_5\}_2]$, $[Pb(ac)_2\{N(OH)=C(CH_2)_5\}_2]$ and $[Zn(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$ are active against *Candida albicans* in contrast to $[Pb(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$ which showed no activity (Table 4). The *in vitro* experiments were performed on *Candida albicans* nurtured on Sabouraud's Dextrose Agar involving Kirby-Bauer well diffusion method [25]. Complexes were taken at concentrations K1 = 10 mg/ml and K2 = 100 mg/ml in solvent Dimethyl sulfoxide. Itraconazole was taken as positive control (PC) at concentration 5000 µg/ml (Fig.1), whereas Dimethyl sulfoxide DMSO was taken as negative control (NC). A full disc view of the anticandidal activity is provided in supplementary file (Fig. S2)

Table 4: Anticadidal activity of synthesized complexes

S.N.	Complexes	Organism	Positive Control	Negative Control	At conc. K2	At conc. K1
1	$[Zn(ac)_2\{N(OH)=C(CH_2)_5\}_2]$	*Candida albicans*	3.25 mm	No Zone of Inhibition	4.0 mm	1.75 mm
2	$[Pb(ac)_2\{N(OH)=C(CH_2)_5\}_2]$				3.62 mm	1.75 mm
3	$[Zn(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$				3.25 mm	1.62 mm
4	$[Pb(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$				No Zone of Inhibition	

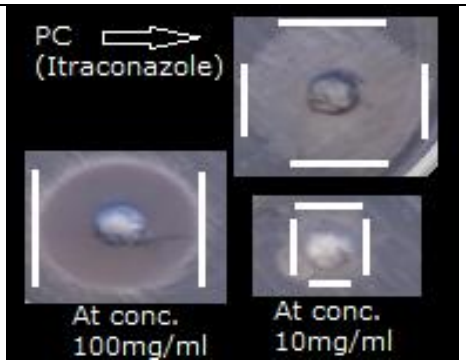


Fig.1: Anticandidal activity of $[Zn(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$

4.Conclusion

The spectral analysis and elemental studies suggestes the general representation of these complexes as $[M(ac)_2L_2]$ (where M = Zn/Pb, L = corresponding ligand; oxime/schiff base). Antifungal activity results showed that except $[Pb(ac)_2\{N(Ph)=C(Ph)C(OH)Ph\}_2]$, all the three other synthesized complexes are active against *Candida albicans*.

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